# Photo-induced Transformations. Part 51.[1] Photo- and Thermally-induced Rearrangements of Hypoiodites of Steroidal Homoallyl Alcohols. The Formation of Some Oxygen Heterocycles *via* Photo- and Thermally-induced Rearrangements of 3-Hydroxy-$\Delta^5$-steroid Hypoiodites in the Presence of Mercury(II) Oxide and Iodine [2]

By **Hiroshi Suginome,* Akio Furusaki, Kimitoshi Kato, Norio Maeda,** and **Fumihiko Yonebayashi,**
Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060, Japan

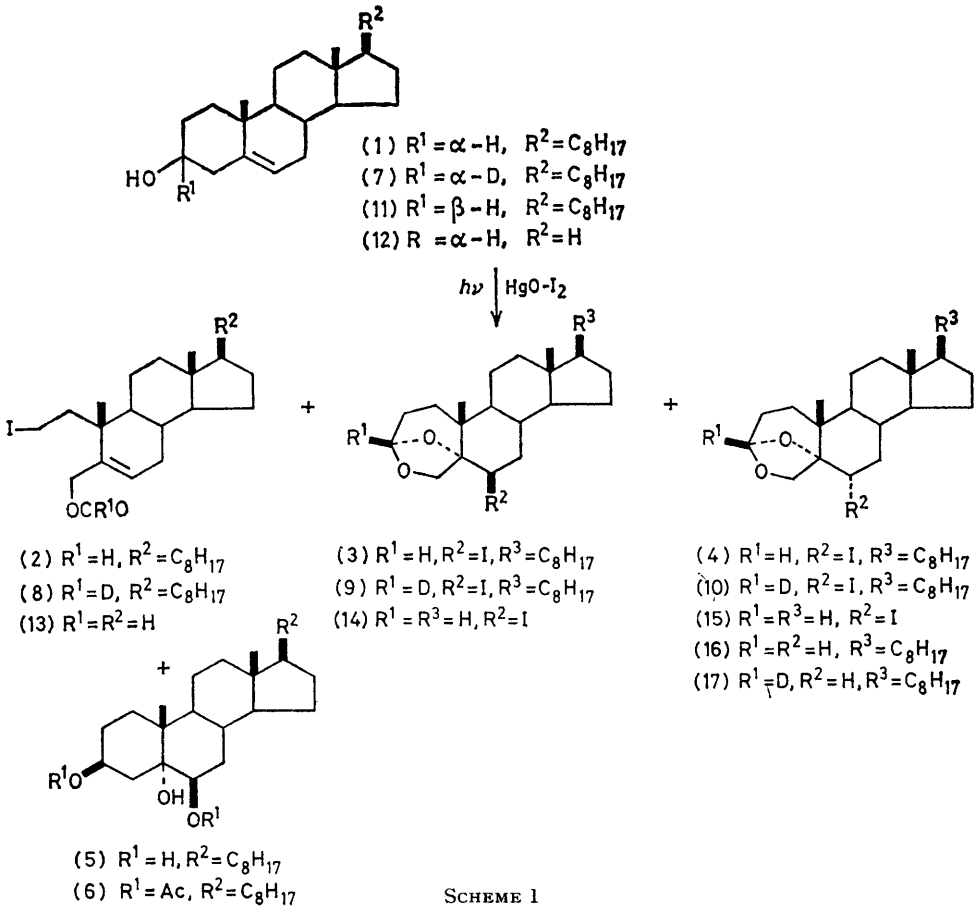
Hypoiodites of cholesterol and epicholesterol in benzene containing mercury(II) oxide and iodine underwent photo-induced rearrangement to give 3α,5-epoxy-6β- and -6α-iodo-A-homo-4-oxa-5α-cholestanes (3) and (4), together with 3-formyloxy-2-iodo-A-nor-2,3-secocholest-5-ene (2). Stereochemistry of the epoxide (3) was established by an *X*-ray crystallographic analysis. When the reaction of cholesterol hypoiodite was induced thermally at 55—60 °C, only the 6β-isomer, accompanied by cholest-5-en-3α-yl A-homo-4-oxacholest-5-en-3α-yl ether (20) and A-homo-4-oxacholest-5-en-3α-ol (21), is formed. Catalytic hydrogenolysis of iodo-epoxide (3) or (4) gave 3α,5-epoxy-A-homo-4-oxa-5β-cholestane (16) which was transformed into 2-acetyl-5-acetoxymethyl-4-oxa-5β-cholest-2-ene (29) upon treatment with boron trifluoride–ether–acetic anhydride in benzene.

In contrast, the newly synthesized hypoiodite of 3α,4,4-trimethylcholest-5-en-3β-ol, in benzene containing mercury(II) oxide and iodine, gave 2-acetyl-3-oxacholest-5-enes (26) and (27) together with 3α,5α-epoxy-A-homo-4-oxasteroids (24) and (25) on irradiation or thermolysis. The formation of the products (26) and (27) indicates the intervention of a common oxyl radical (E) in the rearrangements of 3-hydroxy-$\Delta^5$-steroid hypoiodites to products (3), (4), (24), (25), (26), and (27). The pathways of the rearrangements and the stereoselectivity of the reactions are discussed.



It is well known that oxyl radicals derived from cyclic homoallyl alcohols rearrange readily to allyl radicals and they then react with species present in the solution to give novel heterocyclic compounds.[3]

In this paper we describe the results of photo-induced and thermal reactions of hypoiodites of cholesterol, epicholesterol, and 3α,4,4-trimethylcholest-5-en-3β-ol as steroidal homoallyl alcohols in the presence of mercury(II) oxide–iodine.[4,5]

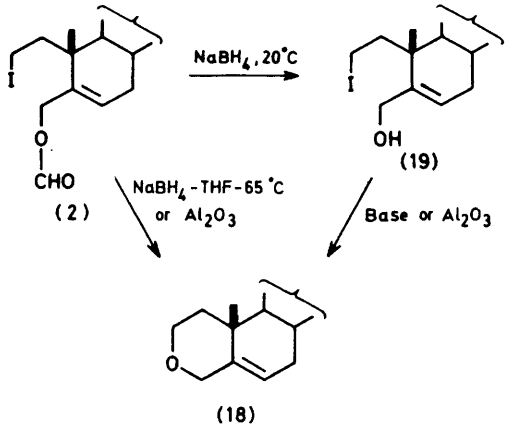



SCHEME 1

RESULTS

Irradiation of cholesterol (1) in dry benzene containing 3 mol equiv. of mercury(II) oxide and iodine gave three major products, (2) (27%), (3) (8%), and (4) (11%) in order of increasing polarity. A further more polar substance (5), m.p. 239—241 °C, was isolated in 2—4% yield (Scheme 1) and shown to be 3β,5α,6β-trihydroxy-5α-cholestane [6a-c] by direct comparison and formation of its diacetate (6).[6a-b, 7] Epicholesterol [8] gave virtually the same mixture of the products as indicated by t.l.c. in the reaction under the same conditions as cholesterol. Moreover, as would be expected, androst-5-en-3β-ol reacted in a manner exactly analogous to cholesterol and afforded three products (13), (14), and (15) corresponding to compounds (2), (3), and (4). Products (3) and (4), adsorbed for 22 h on silica gel, were stable and were recovered unchanged.

The structure of product (2) was confirmed to be 3-formyloxy-2-iodo-A-nor-2,3-secocholest-5-ene on the basis of the analysis of spectra and its transformation into 3-oxacholest-5-ene (18).[9] The mass spectrum of (2) showed the molecular-ion peak at *m/e* 527, and the i.r. spectrum showed two strong bands at 1 731 and 1 166 $cm^{-1}$, arising from carbonyl and C–O stretchings of formate. The $^1H$ n.m.r. spectrum of (2) showed a 1H singlet at τ 1.90 (OC*H*O),[10] an AB quartet at τ 5.36 and 5.51 (*J* 12.0 Hz) (–C=C–C$H_2$–OCOR),[11] and a 2H multiplet at τ 6.80—7.23 (R–C$H_2$C$H_2$I).[11] When the formate (2) was reduced with sodium borohydride in boiling THF, a crystalline product (18), m.p. 75—77 °C, was obtained [12] as virtually the only product, and its structure was confirmed as 3-oxacholest-5-ene (18). Previously we assigned an incorrect structure to this product,[12] which we now wish to retract. The following spectral data (Scheme 2) were found for compound (18). The molecular




SCHEME 2

formula $C_{26}H_{44}O$ was determined by high-resolution mass spectrometry. The $^1H$ n.m.r. spectrum showed two 3H singlets at τ 9.37 and 8.95 assignable to 19-Me and 18-Me, a 2H double doublet at τ 5.88 and 6.21 (*J* 13.5 Hz) assignable to the C-4 methylene protons, a 2H multiplet at τ 6.08—6.49 assignable to the C-2 methylene protons, and a 1H broad doublet at τ 4.60 attributable to C-6-H.

Table 1 shows the assignments of all the signals in the $^{13}C$ n.m.r. spectrum, which were made possible by a comparison with those of cholesterol [13] together with the aid of proton off-resonance studies.

This transformation is readily explained by a reductive hydrolysis of formyl group to 3-hydroxy-2-iodo-A-nor-2,3-secocholest-5-ene (19) followed by an intramolecular nucleophilic displacement of iodine. When the reduction was conducted at room temperature, an unstable iodo-alcohol (19) was obtained.[12] The iodo-alcohol was transformed into 3-oxacholest-5-ene with potassium t-butoxide in t-butyl alcohol.[12] Moreover, it was found that when the

TABLE 1

The chemical shifts and assignments for the $^{13}C$ n.m.r. spectrum of 3-oxacholest-5-ene in $CDCl_3$ solution (δ from $SiMe_4$)

| Carbon | | Carbon | |
|---|---|---|---|
| 1 | 39.65 | 15 | 24.22 |
| 2 | 64.75 | 16 | 40.19 |
| 4 | 70.23 | 17 | 56.21 |
| 5 | 139.59 | 18 | 11.94 |
| 6 | 121.54 | 19 | 18.78 |
| 7 | 31.40 | 20 | 35.87 |
| 8 | 31.55 | 21 | 18.64 |
| 9 | 49.99 | 22 | 36.26 |
| 10 | 35.43 | 23 | 23.93 |
| 11 | 20.39 | 24 | 39.65 |
| 12 | 28.25 | 25 | 28.05 |
| 13 | 42.42 | 26 | 22.62 |
| 14 | 56.84 | 27 | 22.86 |

formate (2) or the iodo-alcohol (19) is adsorbed on neutral alumina and then eluted, the eluates contained 3-oxacholest-5-ene as virtually the sole product.[12] It is apparent that hydrolysis of the formate ester and intramolecular nucleophilic displacement took place on the alumina.

The products (3) and (4) were isomeric with regard to the carbon attached to the iodine, since catalytic hydrogenolysis of either (3) or (4) in benzene–ethanol with Pd–C for 36 h led to an identical iodine-free compound (16). Compound (16) was also obtained in low yield by reduction of (4) with sodium–n-butyl alcohol. Although, in low-resolution mass spectra, compounds (3) and (4) did not give significant molecular ion peaks, but only gave $M^+ - I$ at *m/e* 401 as the base peak or the prominent peak, compound (16) exhibited an intense molecular-ion peak at *m/e* 402 (28%) in agreement with the molecular formula, $C_{27}H_{46}O_2$. This together with the elemental analysis and the n.m.r. spectra confirmed that the molecular formula of (3) and (4) is $C_{27}H_{45}O_2I$. The n.m.r. spectra of all the compounds (3), (4), and (16) showed signals due to an AB quartet in the range τ 5.8—τ 6.9 (Table 2). One of the doublets in the AB quartet collapsed to a singlet on irradiation at the resonance frequency of the centre of another doublet and the AB quartet is assigned to a methylene group attached to an oxygen-bearing carbon. There was another 1H broad singlet at τ *ca.* 4.5, assignable to a proton attached to carbon bearing two oxygen atoms, in compounds (3), (4), and (16). This was not present in the n.m.r. spectra of the corresponding products (9) and (10), obtained by the hypoiodite reaction of 3-deuteriocholesterol (7) [14] and the iodine-free compound (17) derived from (9) and (10). $^{13}C$ N.m.r. spectra of products (3) and (4) each exhibited three signals at δ 103.4 and 101.7, 83.8 and 85.2, and 73.3 and 73.8, respectively and these signals were assignable (with proton off-resonance) to an acetal-type carbon bearing one hydrogen atom (–O–C(H)–O–), a carbon bearing one oxygen atom (C–C(O)–C), and to a carbon bearing two hydrogens and an oxygen (–$H_2$C–O–), respectively. All these results together with the reaction of

oxepan (16) (see below) were in accord with the structure 3,5-epoxy-A-homo-4-oxacholestane for the iodine-free compound.

The n.m.r. spectrum of (3) showed a 1H triplet and that of (4) showed a 1H quartet, each assignable to protons attached to the iodine-bearing carbon C-6. On the basis of their coupling constants, together with the results of spin-decoupling, these protons are β and α oriented, respectively.

TABLE 2

N.m.r. parameters (100 MHz) for the products in $CDCl_3$ solution; chemical shifts (τ) (*J* Hz in parentheses)

| Product | 18-Me | 19-Me | 3-H | 4-H | 6-H |
|---|---|---|---|---|---|
| (2) | 9.33s | 9.01s | 1.90s ($W_{\frac{1}{2}}$ 2.4) | 5.36d, 5.51d (*J* 12.0) | 4.12d (*J* 6.0) |
| (3) | 9.28s | 8.67s | 4.40s ($W_{\frac{1}{2}}$ 3.7) | 5.77d, 6.68d (*J* 8.1) | 5.78t [a] |
| (4) | 9.35s | 9.10s | 4.48s ($W_{\frac{1}{2}}$ 4.1) | 5.82d, 6.28d (*J* 7.5) | 5.45q ($J_{6\beta,7\beta}$ 6.0, $J_{6\beta,7\alpha}$ 12.0) |
| (5) [b] | 9.28s | 8.80s | 6.00br | *c* | 6.47t (*J* 3) |
| (5) [d] | 9.30s | 8.45s | 5.35br | *c* | 5.95br,s |
| (6) [e] | 9.32s | 8.83s | 4.84br | *c* | 5.29t (*J* 2) |
| (8) | 9.33s | 9.01s | | 5.36d, 5.51d (*J* 12.0) | 4.12d (*J* 6.0) |
| (9) | 9.28s | 9.10s | | 5.77d, 6.67d (*J* 8.1) | 5.78t [a] |
| (10) | 9.36s | 9.10s | | 5.83d, 6.28d (*J* 7.5) | 5.46q ($J_{6\beta,7\beta}$ 6.0, $J_{6\beta,7\alpha}$ 12.0) |
| (13) | 9.31s | 9.02s | 1.86s ($W_{\frac{1}{2}}$ 2.4) | 5.30d, 5.48 (*J* 12.0) | 4.07d (*J* 4.5) |
| (14) | 9.26s | 8.67s | 4.38s ($W_{\frac{1}{2}}$ 4.2) | 5.74d, 6.67d (*J* 7.5) | 5.75t [a] |
| (15) | 9.33s | 9.11s | 4.45s ($W_{\frac{1}{2}}$ 3.8) | 5.65d, 6.27d (*J* 7.5) | 5.22q ($J_{6\beta,7\beta}$ 5.3, $J_{6\beta,7\alpha}$ 12.0) |
| (16) | 9.36s | 9.13s | 4.53 ($W_{\frac{1}{2}}$ 5.0) | 5.89d, 6.85d (*J* 7.5) | *c* |

[a] Overlapped with one of 4-$H_2$ doublet signal. [b] Data in [$^2H_6$]acetone. [c] Unassignable. [d] Data in [$^2H_5$]pyridine. [e] Two acetyl peaks at τ 7.91 and 7.97.

In accordance with these assignments 19-Me of (3) resonates at considerably lower field than those of the corresponding protons of (4) and (16), due to deshielding by the iodine atom which is in a 1,3-diaxial relationship with it. *X*-Ray crystallographic analysis of oxepan (3) was finally undertaken to confirm the stereochemistry of the epoxide group. The atomic parameters, the interatomic distances and angles, and the torsion angles in the ring system of (3) are listed in Tables 3—5.

Ring A adopts a boat-like conformation and rings B and C adopt distorted chair conformations (Figure). Owing to the occupation of the 1,3-diaxial positions in ring B, the I and C(19) atoms approach each other very closely, the separation being only 3.48(2) Å. The distortion of ring B seems to be caused mainly by the strong steric repulsion between the I atom and the C(19) methyl group. Ring D has a somewhat deformed half-chair conformation with an approximate two-fold rotation axis running through the C(16) atom.

TABLE 3

Fractional co-ordinates with standard deviations in parentheses

| Atom | *x* | *y* | *z* |
|---|---|---|---|
| C(1) | 0.095 5(6) | 0.308(3) | 0.402(1) |
| C(2) | 0.094 5(7) | 0.486(6) | 0.482(2) |
| C(3) | 0.078 8(9) | 0.663(3) | 0.401(2) |
| C(4) | 0.025 6(7) | 0.577(3) | 0.207(2) |
| C(5) | 0.113 0(5) | 0.544(1) | 0.216(1) |
| C(6) | 0.153 8(6) | 0.617(2) | 0.099(2) |
| C(7) | 0.240 6(5) | 0.599(2) | 0.120(1) |
| C(8) | 0.265 1(5) | 0.395(1) | 0.165(1) |
| C(9) | 0.223 9(5) | 0.339(2) | 0.288(1) |
| C(10) | 0.136 7(5) | 0.342(2) | 0.267(1) |
| C(11) | 0.252 8(6) | 0.148(2) | 0.339(1) |
| C(12) | 0.339 8(6) | 0.141(2) | 0.358(1) |
| C(13) | 0.378 1(5) | 0.192(2) | 0.232(1) |
| C(14) | 0.349 1(5) | 0.392(2) | 0.191(1) |
| C(15) | 0.401 4(6) | 0.452(2) | 0.082(1) |
| C(16) | 0.478 6(6) | 0.370(2) | 0.128(1) |
| C(17) | 0.466 0(5) | 0.237(2) | 0.246(1) |
| C(18) | 0.364 4(6) | 0.044(2) | 0.129(1) |
| C(19) | 0.109 8(6) | 0.181(2) | 0.177(2) |
| C(20) | 0.520 8(5) | 0.068(2) | 0.252(1) |
| C(21) | 0.509 1(9) | −0.067(3) | 0.366(2) |
| C(22) | 0.605 4(5) | 0.133(2) | 0.251(1) |
| C(23) | 0.633 3(7) | 0.246(3) | 0.368(1) |
| C(24) | 0.717 1(7) | 0.298(3) | 0.361(1) |
| C(25) | 0.741 7(10) | 0.426(3) | 0.256(2) |
| C(26) | 0.825 6(9) | 0.467(4) | 0.265(3) |
| C(27) | 0.699 8(13) | 0.620(4) | 0.257(3) |
| O(1) | 0.008 4(6) | 0.646(2) | 0.335(1) |
| O(2) | 0.132 5(5) | 0.683(1) | 0.314(1) |
| I | 0.114 76(5) | 0.492 5(4) | −0.086 8(1) |

When 3α,5-epoxy-6α-iodo-A-homo-4-oxa-5α-cholestane (4) in benzene containing 3 mol equiv. of iodine and mercury(II) oxide was irradiated for 14 h, *ca.* 19% was isomerized to the 6β-isomer (3). This isomerization did not take place when the irradiation was conducted in the presence of iodine only (1.5 mol equiv.). Attempted isomeriz-

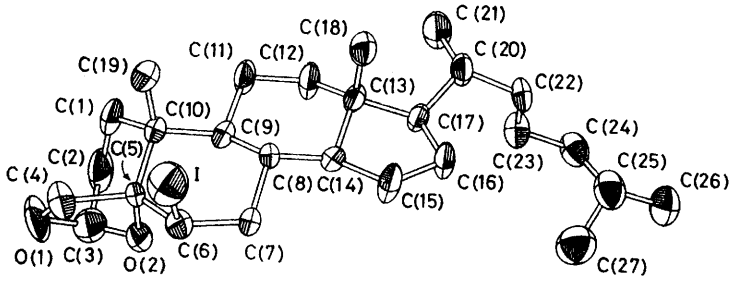



FIGURE Perspective view of (3) and the crystallographic numbering scheme

ation with mercury(II) oxide and iodine was also carried out on the 6β-isomer (3) under the same experimental conditions as for the 6α-isomer (4). However, no isomerization from the 6β-isomer to the 6α-isomer occurred.

Finally, we confirmed that products (3) and (4) are not isomerized when either compound (3) or (4) in benzene containing (*a*) 1.5 mol equiv. of iodine and mercury(II) oxide, or (*b*) 3 mol equiv. of iodine and mercury(II) oxide

TABLE 4

Bond lengths (Å) and angles (°) (standard deviations are referred to the last digits)

| | | | |
|---|---|---|---|
| C(1)–C(2) | 1.50(4) | C(2)–C(1)–C(10) | 111.5(14) |
| C(1)–C(10) | 1.60(2) | C(1)–C(2)–C(3) | 112.6(15) |
| C(2)–C(3) | 1.52(4) | C(2)–C(3)–O(1) | 109.9(15) |
| C(3)–O(1) | 1.40(2) | C(2)–C(3)–O(2) | 109.3(14) |
| C(3)–O(2) | 1.33(2) | C(5)–C(4)–O(1) | 104.1(13) |
| C(4)–C(5) | 1.56(2) | C(4)–C(5)–C(6) | 114.2(12) |
| C(4)–O(1) | 1.44(3) | C(4)–C(5)–C(10) | 113.7(10) |
| C(5)–C(6) | 1.51(2) | C(4)–C(5)–O(2) | 98.7(10) |
| C(5)–C(10) | 1.57(2) | C(6)–C(5)–C(10) | 116.6(9) |
| C(5)–O(2) | 1.44(2) | C(6)–C(5)–O(2) | 102.6(9) |
| C(6)–C(7) | 1.55(1) | C(10)–C(5)–O(2) | 108.6(10) |
| C(6)–I | 2.19(2) | C(5)–C(6)–C(7) | 111.3(11) |
| C(7)–C(8) | 1.56(2) | C(5)–C(6)–I | 114.1(8) |
| C(8)–C(9) | 1.53(2) | C(7)–C(6)–I | 111.4(9) |
| C(8)–C(14) | 1.50(1) | C(6)–C(7)–C(8) | 112.5(9) |
| C(9)–C(10) | 1.55(1) | C(7)–C(8)–C(9) | 110.0(8) |
| C(9)–C(11) | 1.53(2) | C(7)–C(8)–C(14) | 109.3(8) |
| C(10)–C(19) | 1.53(2) | C(8)–C(9)–C(10) | 113.1(9) |
| C(11)–C(12) | 1.55(1) | C(8)–C(9)–C(11) | 110.1(9) |
| C(12)–C(13) | 1.52(2) | C(10)–C(9)–C(11) | 112.0(9) |
| C(13)–C(14) | 1.54(2) | C(1)–C(10)–C(5) | 107.5(10) |
| C(13)–C(17) | 1.59(1) | C(1)–C(10)–C(9) | 111.5(9) |
| C(13)–C(18) | 1.50(2) | C(1)–C(10)–C(19) | 106.0(10) |
| C(14)–C(15) | 1.54(2) | C(5)–C(10)–C(9) | 107.8(9) |
| C(15)–C(16) | 1.54(2) | C(5)–C(10)–C(19) | 112.8(10) |
| C(16)–C(17) | 1.55(2) | C(9)–C(10)–C(19) | 111.1(9) |
| C(17)–C(20) | 1.54(2) | C(9)–C(11)–C(12) | 113.1(11) |
| C(20)–C(21) | 1.52(2) | C(11)–C(12)–C(13) | 111.0(10) |
| C(20)–C(22) | 1.57(1) | C(12)–C(13)–C(14) | 106.9(10) |
| C(22)–C(23) | 1.51(2) | C(12)–C(13)–C(17) | 116.0(9) |
| C(23)–C(24) | 1.53(2) | C(12)–C(13)–C(18) | 111.5(10) |
| C(24)–C(25) | 1.48(3) | C(14)–C(13)–C(17) | 99.2(8) |
| C(25)–C(26) | 1.51(3) | C(14)–C)13)–C(18) | 113.3(9) |
| C(25)–C(27) | 1.55(4) | C(17)–C(13)–C(18) | 109.5(9) |
| | | C(8)–C(14)–C(13) | 112.4(8) |
| | | C(8)–C(14)–C(15) | 119.1(9) |
| | | C(13)–C(14)–C(15) | 104.1(9) |
| | | C(14)–C(15)–C(16) | 103.2(10) |
| | | C(15)–C(16)–C(17) | 108.1(9) |
| | | C(13)–C(17)–C(16) | 102.7(8) |
| | | C(13)–C(17)–C(20) | 117.7(10) |
| | | C(16)–C(17)–C(20) | 113.0(9) |
| | | C(17)–C(20)–C(21) | 114.1(11) |
| | | C(17)–C(20)–C(22) | 112.1(11) |
| | | C(21)–C(20)–C(22) | 110.0(10) |
| | | C(20)–C(22)–C(23) | 115.7(10) |
| | | C(22)–C(23)–C(24) | 112.2(12) |
| | | C(23)–C(24)–C(25) | 119.3(13) |
| | | C(24)–C(25)–C(26) | 112.4(17) |
| | | C(24)–C(25)–C(27) | 112.2(17) |
| | | C(26)–C(25)–C(27) | 107.9(20) |
| | | C(3)–O(1)–C(4) | 104.8(12) |
| | | C(3)–O(2)–C(5) | 104.0(11) |

and 1 mol equiv. of 5α-cholestan-3β-ol or t-butyl alcohol, was heated for 5 h.

*Thermal Decomposition of Cholesterol Hypoiodite in the Presence of Mercury*(II) *Oxide and Iodine.*—We then compared products in the photo-induced reaction of cholesterol hypoiodite with those of the thermal reaction.

Thus cholesterol in dry benzene containing mercury(II) oxide–iodine was decomposed at 55—60 °C in the dark under

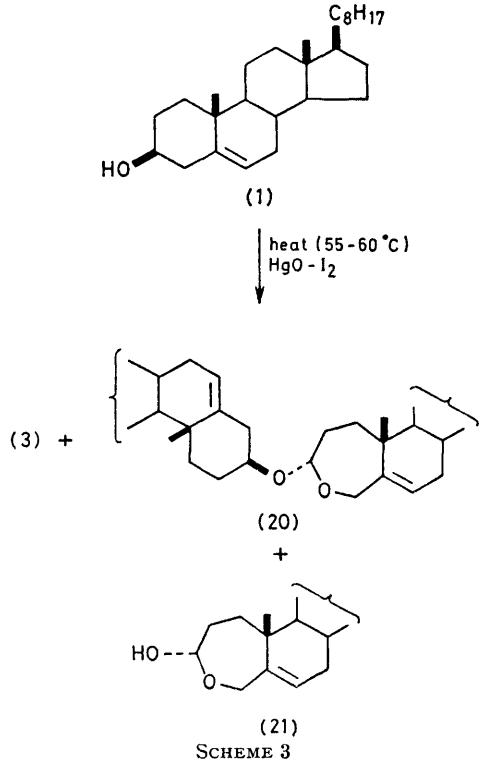
TABLE 5

Torsion angles (°) in the ring system

| | | | |
|---|---|---|---|
| Ring A | | | |
| C(10)–C(1)–C(2)–C(3) | 40 | O(1)–C(4)–C(5)–C(10) | 88 |
| C(1)–C(2)–C(3)–O(1) | 60 | C(4)–C(5)–C(10)–C(1) | −52 |
| C(2)–C(3)–O)1)–C(4) | −96 | C(5)–C(10)–C(1)–C(2) | −39 |
| C(3)–O(1)–C(4)–C(5) | 4 | | |
| Ring B | | | |
| C(10)–C(5)–C(6)–C(7) | −50 | C(7)–C(8)–C(9)–C(10) | 59 |
| C(5)–C(6)–C(7)–C(8) | 50 | C(8)–C(9)–C(10)–C(5) | −55 |
| C(6)–C(7)–C(8)–C(9) | −55 | C(9)–C(10)–C(5)–C(6) | 51 |
| Ring C | | | |
| C(14)–C(8)–C(9)–C(11) | −54 | C(11)–C(12)–C(13)–C(14) | 57 |
| C(8)–C(9)–C(11)–C(12) | 52 | C(12)–C(13)–C(14)–C(8) | −61 |
| C(9)–C(11)–C(12)–C(13) | −56 | C(13)–C(14)–C(8)–C(9) | 61 |
| Ring D | | | |
| C(17)–C(13)–C(14)–C(15) | 48 | C(15)–C(16)–C(17)–C(13) | 19 |
| C(13)–C(14)–C(15)–C(16) | −36 | C(16)–C(17)–C(13)–C(14) | −40 |
| C(14)–C(15)–C(16)–C(17) | 10 | | |

an argon atmosphere for 5 h. Examination of the reaction product by t.l.c. indicated the formation of two mobile major products, (20) and 3α,5-epoxy-6β-iodo-A-homo-4-oxa-5α-cholestane (3). Several less mobile minor products, including compound (21), were also detected. However, 3α,5-epoxy-6α-iodo-A-homo-4-oxa-5α-cholestane (4), one of the major products in photo-induced reactions, was absent in the product. Compound (20), m.p. 218—220 °C, compound (3), and another new product (21), m.p. 210—212 °C, were isolated by chromatography in 7, 11, and 4% yields (Scheme 3).

The structures of products (20) and (21) were confirmed to be cholest-5-en-3β-yl A-homo-4-oxacholest-5-en-3α-yl ether (20), and A-homo-4-oxacholest-5-en-3α-ol (21), on the basis of the following physical and chemical evidence.

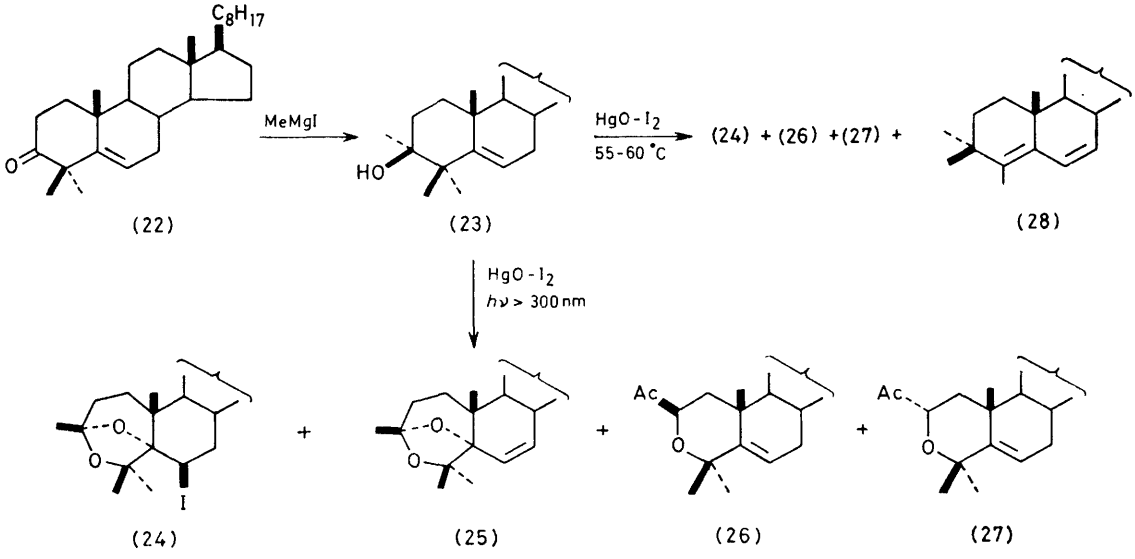



SCHEME 3

High-resolution mass spectrometry indicated that the molecular formula of product (21) was $C_{27}H_{46}O_2$. The mass spectrum exhibited a peak due to $M^+ - H_2O$ at *m/e* 384 (95.6%) and the base peak at *m/e* 95. The i.r. spectrum showed a broad band due to a hydroxy-group. The $^1H$ n.m.r. spectrum showed a broad singlet at τ 4.42 assignable to the olefinic proton at C-6, a triplet at τ 5.18 (*J* 4.5 Hz) assignable to 3β-H, and an AB quartet (τ 5.62 and 5.50, *J* 12.0 Hz) assignable to the methylene group attached to C-4a. There were two singlets (each 3H) at τ 9.32 and 9.05 assignable to 18-Me and 19-Me.

The i.r. spectrum of product (20) showed the absence of hydroxy and carbonyl groups. An acid-catalysed hydrolysis of product (20) at room temperature afforded cholesterol and A-homo-4-oxacholest-5-en-3α-ol (21), proving it to be an ether with cholesterol. It was also found that when (20) is adsorbed on silica gel and then eluted, compound (21) is obtained. Thus, it is certain that at least part of the (21) formed is generated from ether (20) by hydrolysis, either in the course of the reaction or during column chromatography. The $^1H$ n.m.r. spectrum of (20) was consistent with the ether structure and showed six very informative signals (each 1H) at τ 4.44 (broad singlet), 4.68 (broad singlet), 5.12 (triplet, *J* 6.0 Hz), 5.62 (doublet, *J* 12.8 Hz), 6.50 (doublet, *J* 12.8 Hz) and at τ 6.54 (broad singlet overlapped with a doublet at τ 6.50). A comparison of this spectrum with that of (21) (see below) indicated that the spectrum of ether (20) corresponded to a spectrum made by combining the signals of compound (21) and the signals of cholesterol. Thus, two signals at τ 4.68 and 6.54 in the spectrum of ether (20) are assignable to the C-6 olefinic proton and the 3α-H of the cholesterol part of the molecule, since the spectrum of compound (21) lacked signals corresponding to them. Irradiation of the centre of the doublet at τ 5.62 in the spectrum of (20) caused a collapse of the doublet at τ 6.50 to a singlet, and irradiation of the centre of the doublet at τ 6.50 changed the doublet at τ 5.62 to a singlet, without affecting the couplings of the signals at τ 4.40, 4.68, 5.12, and 6.54. This AB quartet is assignable to the C-4a methylene protons. The broad triplet at τ 5.12 was partially decoupled to a broad singlet ($W_{\frac{1}{2}}$ 4 Hz) on irradiation at τ 8.21 and assigned to a proton attached to the C-3 carbon. The broad singlet at τ 4.44 is assigned to the olefinic proton attached to C-6 of the A-homo-4-oxacholest-5-ene portion, and irradiation at τ 8.0 caused collapse of this signal, and a broad singlet due to olefinic protons of the cholesterol portion, into sharper singlets. The spectrum also exhibited a 6H singlet at τ 9.32 and two 3H singlets at τ 9.04 and 8.99. A singlet at τ 9.32 is ascribable to a superimposed signal of the two 18-Me in the A-homo-4-oxacholest-5-ene and cholesterol portions. One of two singlets at τ 9.04 and 8.99 is assignable to 19-Me of the cholesterol unit. All these spectral and chemical results for compound (20) are consistent with the structure depicted.

*Reaction of* 3α,4,4-*Trimethylcholest*-5-*en*-3β-*ol Hypoiodite* (*Scheme* 4).—Since the aforementioned reaction is unprecedented, photo- and thermally-induced reactions of

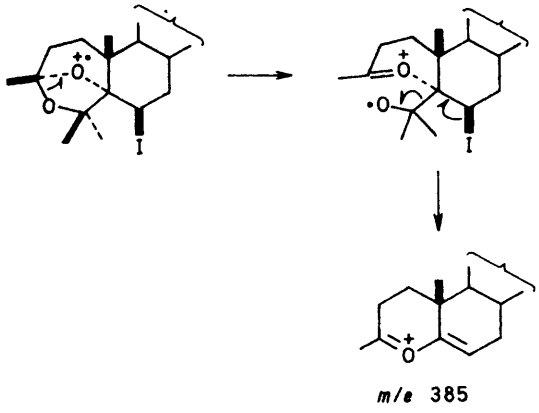



SCHEME 4

3α,4,4-trimethylcholest-5-en-3β-ol hypoiodite were then investigated to examine the effects of alkyl groups attached to both the carbon centre bearing the oxyl radical and the reacting C-4 terminus of the potential allyl radical on the rearrangements. 3α,4,4-Trimethylcholest-5-en-3β-ol (23) was prepared in a 64% yield by the Grignard reaction of 4,4-dimethylcholest-5-en-3-one (22) [15] with methylmagnesium iodide. The hydroxy-group is β-oriented on the basis of the predominant addition of the Grignard reagent at the carbonyl from the less-hindered α-face of ring A in the chair form.[16]

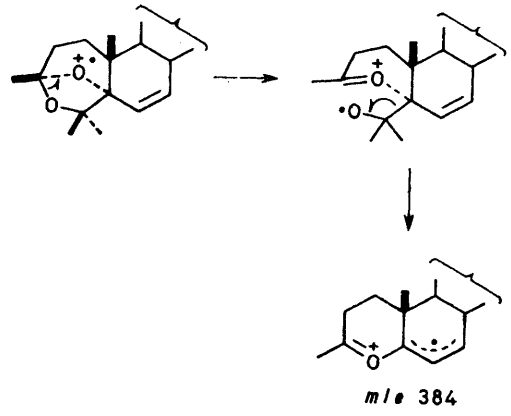
Irradiation of the 3α-ol (23) in benzene containing iodine and mercury(II) oxide,[4,5] (each 3.4 mol equiv.), with a 100-W high-pressure mercury arc for 8 h under an atmosphere of nitrogen, afforded a mixture of products from which four products, (24) (11%), (25) (12%), (26) (7%), and (27) (21%) (in order of their mobility) were isolated by careful preparative t.l.c. The structures of all these products were clarified on the basis of physical and chemical evidence. The iodide (24) showed a weak peak due to $M^+ - I$ at *m/e* 443 and the base peak at *m/e* 385, and the elemental analysis was in accord with the molecular formula $C_{30}H_{51}O_2I$. The full structure of (24) as 3α,5-epoxy-6β-iodo-3β,4a,4a-trimethyl-

A-homo-4-oxa-5α-cholestane was deduced by its $^1$H n.m.r. spectrum. It exhibited three 3H singlets at τ 8.63, 8.30, and 8.55 assignable to 3β-Me, 4aβ-Me, and 4aα-Me, two 3H singlets at τ 9.28 and 8.68 ascribable to 18-Me and 19-Me, and a 1H broad triplet at τ 5.74 ($J$ 1.5 Hz) assignable to 6α-H. The structure and the genesis of the base peak at *m/e* 385 is shown in Scheme 5. The molecular formula of




SCHEME 5

the crystalline product (25) was confirmed to be $C_{30}H_{50}O_2$ by the mass spectrum ($M^+$, 0.3%) and the elemental analysis, and the structure was ascertained to be 3β,5-epoxy-3β,4a,4a-trimethyl-A-homo-4-oxa-5α-cholest-6-ene (25) by spectral analysis. The mass spectrum exhibited a base peak at *m/e* 384, the structure and the genesis of which are shown in Scheme 6. The i.r. spectrum exhibited no carbonyl and hydroxy-bands and the n.m.r. spectrum showed three 3H singlets at τ 8.59, 8.53, and 8.66 assignable to 3β-Me and 4,4-$Me_2$, a double doublet at τ 4.02 ($J$ 10.2 and 1.5 Hz) assignable to 6-H, another double doublet at τ 4.41 ($J$ 2.4 and 10.2 Hz) assignable to 7-H, and two 3H singlets at τ 9.30 and 8.96 assignable to 18-Me and 19-Me. Another two crystalline products (26)




SCHEME 6

and (27) were shown to be stereoisomeric ketones by their i.r. spectra, which showed bands at 1 718 and 1 721 cm$^{-1}$ respectively, and by their qualitatively identical mass spectra. These ketones were epimeric at the carbon centre adjacent to the carbonyl group since treatment of ketone (27) in diethyl ether–methanol with potassium hydroxide for 5 h at room temperature transformed it into product (26). The structure, 2ξ-acetyl-4,4-dimethyl-3-oxacholest-5-ene accommodates the aforementioned results together with the mass and $^1$H n.m.r. spectra. The mass spectrum of (26) exhibited a molecular ion at *m/e* 442 ($M^+$, 2.3%), and prominent peaks at *m/e* 427 ($M^+$ − Me, 19.1%) and *m/e* 356 (100%). Its n.m.r. spectrum showed two 3H singlets at τ 8.80 and 8.69 (4,4-$Me_2$), a 3H singlet at τ 7.79 (2ξ-acetyl), a 1H triplet at τ 4.76 ($J$ 3.6 Hz, 6-H), two 3H singlets at τ 9.32 and 9.00 (18-Me and 19-Me), and a double doublet at τ 6.17 ($J$ 3.2 and 9.0 Hz, 2ξ-H). Its epimer (27) exhibited the molecular ion at *m/e* 442 (2.2%) and two prominent peaks at *m/e* 427 ($M^+$ − Me, 100%) and *m/e* 356 (38.7%) in the mass spectrum, and two 3H singlets at τ 8.68 and 8.65 (4,4-$Me_2$), a 3H singlet at τ 7.79 (2ξ-acetyl), a 1H triplet at τ 4.60 ($J$ 3.2 Hz, 6-H), two 3H singlets at τ 9.30 (18-Me) and τ 8.74 (19-Me), and a 1H double doublet at τ 5.68 ($J$ 4.2 and 10.5 Hz, 2z-H) in the $^1$H n.m.r. spectrum.

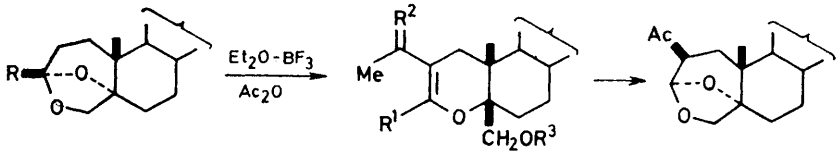
No unambiguous spectroscopic distinction of the configurations of the C-2 acetyl of products (26) and (27) was possible but an assessment of their relative stabilities by use of Dreiding models suggested that the acetyl group in the more stable epimer (26) is β and that in a less stable epimer it is α-oriented. Thus, the conformations of the flexible rings A of the 4,4-dimethyl-3-oxacholest-5-enes (26) and (27) may be analogous to those of Δ$^5$-3-oxo-4,4-dimethylsteroids.[16] Inspection of models of products (26) and (27) indicates that the most stable configuration for ring A having 2,4,4-trisubstituents would be a distorted boat for 2β-acetyl (axial) [compound (26)] and a chair or distorted boat for the 2α-acetyl (equatorial) [compound (27)]. The magnitude of the splitting of signals due to 2-H in the $^1$H n.m.r. of (26) and (27) (see above) are consistent with these assignments.

Attention was then turned to thermally-induced rearrangement. When the 3β-ol (23) in benzene containing mercury(II) oxide and iodine was heated at 55—60 °C for 10 h in the dark, a mixture of products resulted, from which oxepan (24), ketones (26) and (27), and a new product (28), were isolated in 7.5, 22 and 15, and 3% yields by careful preparative t.l.c. Olefin (25) was not detected in the t.l.c. of the product. The new product (28), m.p. 111—114 °C, proved to be 3,3,4-trimethylcholesta-4,6-diene, arising from a Wagner–Meerwein shift of a 4-methyl group of the hypoiodite of 3β-ol (23). Thus, its mass spectrum exhibited peaks at *m/e* 410 ($M^+$, 41.2%), and 395 (44.1%, $M^+$ − Me). In the u.v. spectrum, there was an intense absorption at 246 nm due to the steriod 4,6-diene group, and the n.m.r. spectrum showed two 3H singlets at τ 8.96 and 8.99 (3,3-$Me_2$), a 3H singlet at τ 8.32 (4-Me), a 1H double doublet at τ 4.42 ($J$ 1.5 and 9.8 Hz, 6-H), two 3H singlets at τ 9.26 and 9.10 (18-Me and 19-Me), and a 1H doublet doublet ($J$ 4.8 and 9.8 Hz, 7-H).

*Some Reactions of* 3α,5-*Epoxy*-A-*homo*-4-*oxa*-5α-*cholestane* (16) *and the Deuteriated Analogue* (17) (*Scheme* 7).—Treatment of the 3α,5-epoxide (16) in benzene with $BF_3$–ether–acetic anhydride at room temperature afforded a single product (29), m.p. 71—73 °C. However, compound (16) in THF was stable to hydrochloric acid at room temperature. The mass spectrum of the product (29) exhibited an intense molecular ion at *m/e* 486 (38%). The n.m.r. spectrum showed a singlet attributable to an olefinic proton at τ 2.48, an AB quartet [τ 5.82 and 5.91 ($J$ 12.0 Hz)] and two 3H singlets assignable to C=C–Ac and OAc at τ 7.80 and τ 7.94. The i.r. spectrum showed a band at 1 740 (OAc) and two

bands at 1 652 and 1 622 cm$^{-1}$ (αβ-unsaturated carbonyl group) in its carbonyl region. The presence of an αβ-unsaturated carbonyl group was confirmed by the u.v. spectrum, which exhibited an intense maximum at 255 nm.

Cleavage of one of the C–O bonds does not occur when epoxide (16) in THF was treated with boron trifluoride–ether only. The cleavage reaction is thus envisaged to proceed as depicted in Scheme 9.




(16) R = H
(17) R = D

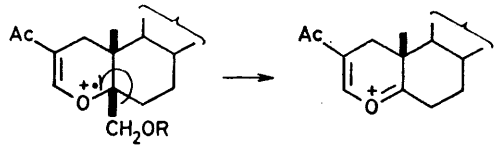
(29) $R^1$=H, $R^2$=O, $R^3$=Ac
(30) $R^1$=D, $R^2$=O, $R^3$=Ac
(31) $R^1$=H, $R^2$=NOH, $R^3$=Ac
(33) $R^1$=H, $R^2$=O, $R^3$=H

(32)

SCHEME 7

The position and intensity of the maximum corresponds to a partial structure RCO–CR=CHOR (calculated value; 255 nm). Product (17) containing a deuterium was also transformed into a product (30), corresponding to (29). The n.m.r. spectrum of (30) showed the absence of an olefinic proton at τ 2.48 found in the spectrum of (29). This confirmed that the olefinic proton is derived from a proton attached to C-3. The product (29) gave an oxime (31), m.p. 144.0—144.5 °C. The u.v., i.r., and n.m.r. spectral data are given in the Experimental section. Only the dihydropyran structure (29) accommodates all the spectral data, including those of oxime (31).

Dihydropyran (29) was treated with methanolic potassium hydroxide at room temperature to afford two amorphous products, (32) and (33), which were separated by column chromatography on silicic acid. The mass, u.v., i.r., and n.m.r. spectral data (Experimental section) of product (33) was in accord with an alcohol, formed by a normal hydrolysis. The i.r. spectrum of product (32) showed the absence of a hydroxy-band. The n.m.r. spectrum showed two doublets (each 1H) of an AB quartet at τ 5.96 and 6.88 with $J$ 7.5 Hz, and a broad 1H singlet at τ 4.31. In addition to these signals, which are similar to those in compound (16), the spectrum showed a 1H double doublet centred at τ 7.35 attributable to a proton attached to the acetyl-bearing carbon and a 3H singlet assignable to an acetyl group at τ 7.91. These spectral data can be accommodated by the structure depicted for compound (32), formed by an intramolecular Michael reaction of alcohol (33) catalysed either by base or by silicic acid. The




R=H or Ac  $m/e$ 413

SCHEME 8

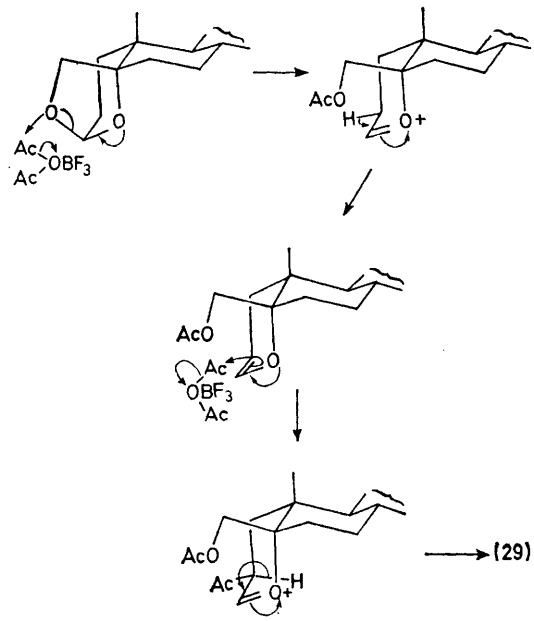
acetyl group at C-2 should be β-oriented on the basis of the magnitudes of the splitting of C-2α-H and the C-3-H.

In agreement with these assigned structures, the mass spectra of compounds (29) and (33) exhibited an intense fragment ion at $m/e$ 413 [46% for (29) and 100% for (33)]. On the basis of the assigned structures, the structure and the genesis of the ion of $m/e$ 413 are depicted in Scheme 8.

## DISCUSSION

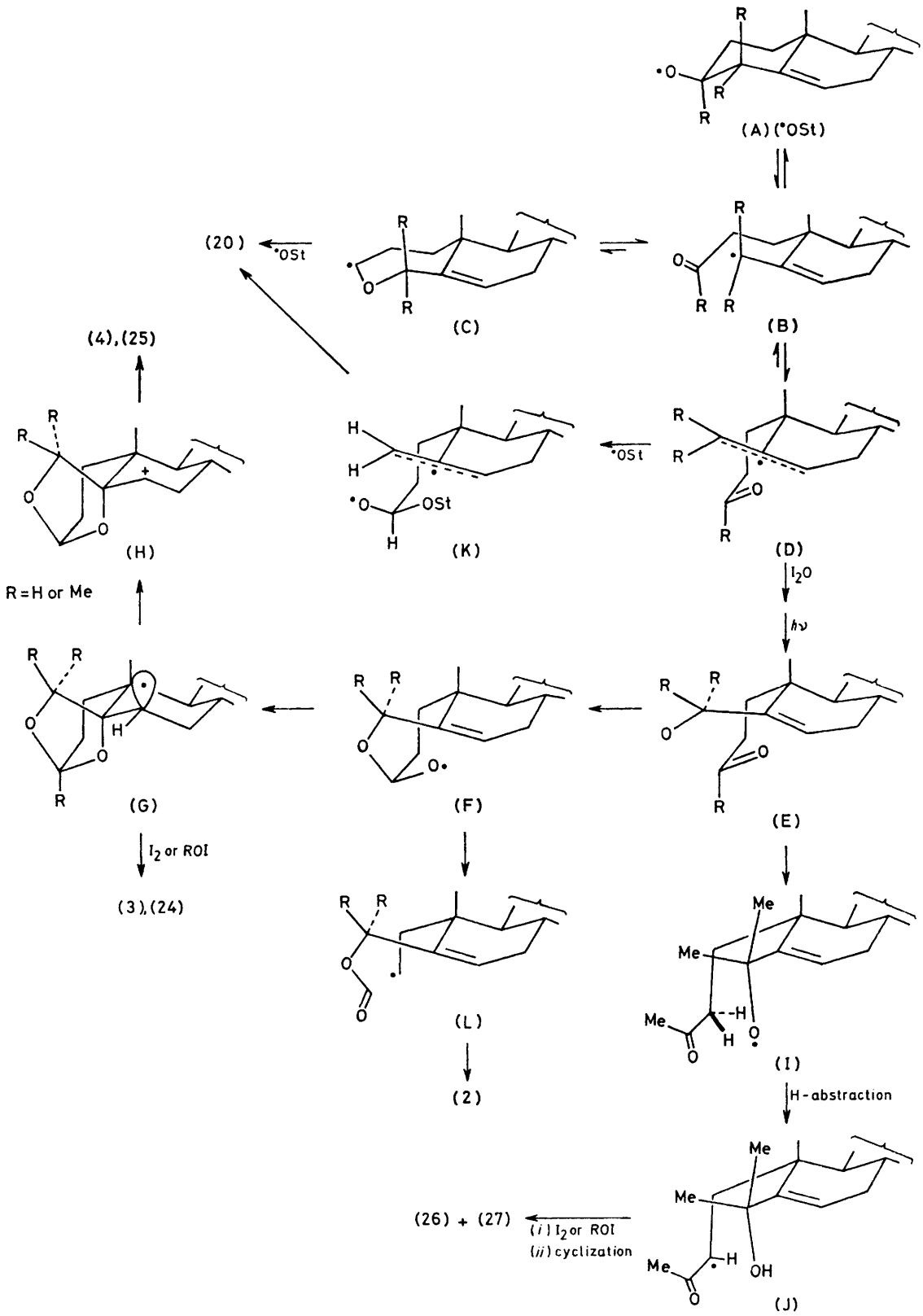
All the observed products with the exceptions of triol (5) and hydrocarbon (28) are derived from the reactions of an allyl radical intermediate (C) (Scheme 10) resulting from β-scission of a 3β-oxyl radical.

The results above indicate that the formation of




SCHEME 9

3α,5-epoxy-A-homo-4-oxasteroids is a general reaction of 3-hydroxy-Δ$^5$-steroids when they are irradiated or heated in the presence of mercury(II) oxide and iodine and that methyl groups at C-3 and/or C-4 significantly affect the type of products and their relative yields. Thus, the formation of 3-oxacholest-5-enes [*e.g.* (26) and (27)] was not seen in thermal and photo-induced reactions of cholesterol. Another result, which is attributable to alkyl substitution, is that no ether corresponding to cholest-5-en-3β-yl A-homo-4-oxacholest-5-




SCHEME 10

en-3α-yl ether is obtained in the thermal homolysis of 3α,4,4-trimethylcholest-5-ene hypoiodite. A probable path *via* an oxepan radical has been suggested for the formation of 3α,5-epoxides (3), (24), and (25).[2] The formation of 3-oxacholest-5-enes (26) and (27), and the stereoselective formation of 3α,5-epoxy-compounds (3), (4), (24), and (25) in the present experiments suggests the paths of formation which are summarized in Scheme 10. The formation of 3-oxacholest-5-enes (26) and (27) requires the intervention of a second oxyl radical (E) which is most probably formed from photo-induced or thermal homolysis of a second hypoiodite, generated from the reaction of an allyl radical (D) with iodine oxide.[17,18] The preferred conformation of the allyl radical, when it reacts with iodine oxide, would be such as in (D), in which intramolecular interactions between the C-10 substituent and the planar allyl radical portion are avoided. The oxyl radical can then either intramolecularly attack the formyl carbonyl from the β-side of the molecule to generate the 3α-oxyl radical (F), or abstract 2-H from structure (I) *via* a seven-membered transition state [19] to give species (J) and then products (26) and (27). Products from this intramolecular hydrogen abstraction can be observed only in the reaction of 3β,4,4-trimethylcholest-5-en-3α-ol (23), and not in the reaction of cholesterol. Presumably, one of the methyl groups at C-4 in (E), located in a *quasi*-1,3-diaxial relationship with the 10β-methyl group, destabilizes this conformation and facilitates the abstraction of the most weakly bound C-2-H in conformation (I). In conformation (I) collinearity [20] between the attacking radical centre and the C-2-H bond during hydrogen transfer may be achievable.

It has been established that substituents approach cyclohexene from the axial direction in radical additions.[21] The oxyl radical portion of conformation (F), formed as described above, is ideally located with respect to the 5,6-double bond to add from an axial direction. Thus the 3α-oxyl portion of the radical (F) intramolecularly attacks the 5,6-double bond from the α-face of the molecule to generate a fused radical intermediate (G) which then preferentially abstracts an iodine atom from molecular iodine or hypoiodite to give the observed product (24) with β-axial iodine. Some of the 6β-iodide obtained in the photo-induced reaction is believed to be formed *via* isomerization of the 6α-iodide in the presence of mercury(II) oxide and iodine. Since this isomerization does not take place by irradiation in the presence of iodine only, it is conceivable that the metal oxide plays a role in this isomerization. Olefin (25) and 6α-iodide (obtainable from cholesterol) are believed to be formed by the reaction of carbocation (H), which is formed by oxidation of radical (G). It is of interest to note that the formation of these products can be seen only in the photo-induced reactions and that the 6-ene (25) instead of the 6α-iodide is formed in the reaction of 3β,4,4-trimethylcholest-5-en-3α-ol (24). Presumably, the dimethyl groups at C-4 of (24) hinder the reaction of the carbocation (H) with the iodine source, and thus lead to formation of the olefin. The proposed paths can explain the stereoselective formation of 3α,5-epoxy-A-homo-4-oxasteroids instead of the 3β,5-isomer.*

On the other hand, the reactions of the less-stable conformation (B), which are expected to be of minor importance, are either reversal to the starting oxyl radical (A) or reversible formation of an oxepan radical (C); the reactions of the latter also lead to epoxides (24) and (25).[2] However, this path does not easily explain the stereoselectivity in the formation of the epoxides. Species (C) appears to be unimportant in the present reaction, and in fact a recent work has shown the formation of cyclohexanol from an oxepan radical, and the equilibrium (A) ⇌ (B) ⇌ (C) seems to lie largely towards the oxygen-centred radical.[22]

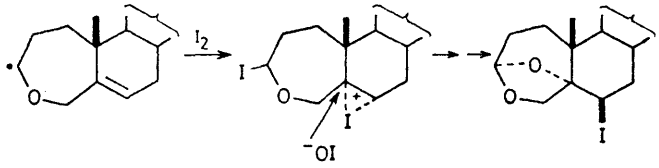
Thus, the stereochemical outcome of the present reactions can be understood as a consequence of the initial preferred arrangements of the formyl group and the planar allyl radical portion of the radical (D).

At least two possible paths are envisaged for the formation of ether (20) by thermal reaction, which are depicted in Scheme 10. In the first and most probable path, oxyl radical (A) attacks the formyl carbon of the allyl radical (D) to form a biradical (K), and its intramolecular combination gives the observed ether (20). In the second possibility, a radical combination of the oxepan radical (C) with the oxyl radical (A) may also give (20).

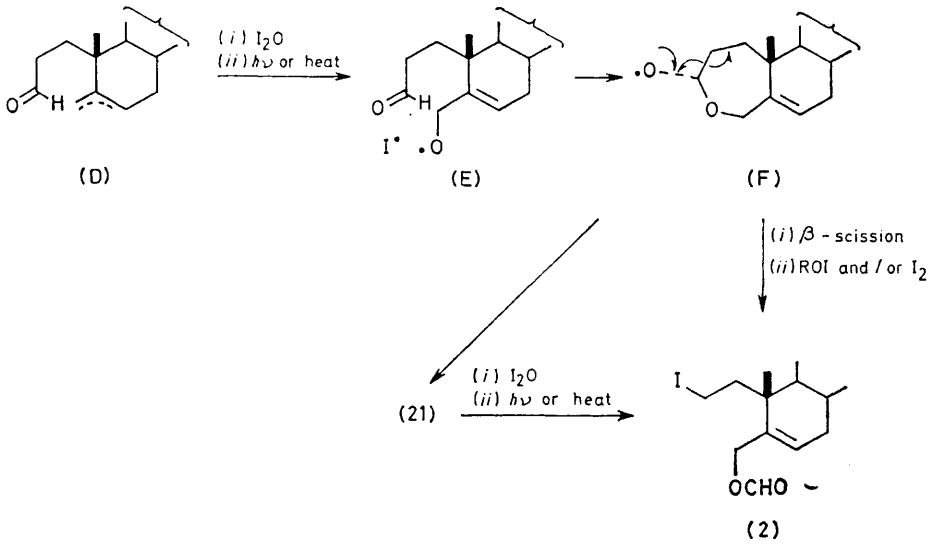
Bimolecular reactions of the allyl radical (D) or the oxepan radical (C) to form (20) would certainly be accelerated in the thermally induced reaction.

There are two probable pathways for the formation of compound (21); the first one is *via* hydrolysis of ether (20) during the course of the reaction or column chromatography, which we have demonstrated experimentally. The other path would be *via* intermediates (E) and (F), as shown in Scheme 11. The formation of formate (2) can then be readily explained as a result of β-cleavage of the oxyl radical (F) as depicted in Schemes (10) and (11).

* It has recently been shown [17] that the reaction of mercury(II) oxide–iodine with alkenes in aprotic solvents proceeds *via* iodine oxide which adds ionically to unsymmetrical alkenes in a Markownikov manner and the initial intermediate of the addition is an iodonium ion which is converted into a *trans*-iodo-hypoiodite. Thus, a path such as




may be another possibility. However, this possibility is excluded since it has recently been shown [18] that the reaction of 5α-androst-2-ene with iodine oxide in acetic anhydride gave 3β-iodo-5α-androstan-2β-ol *via* the formation of an α-iodonium ion at the less hindered α-face, and thus the above hypothetical path should lead to a 3β,5-epoxide *via* an α-iodonium ion at the less hindered α-face.




SCHEME 11

## EXPERIMENTAL

M.p.s were determined with a Yanagimoto micro m.p. apparatus. I.r. spectra were determined for Nujol mulls with a Jasco IR-E spectrophotometer unless stated otherwise. U.v. spectra were determined with a Hitachi 124 double-beam spectrophotometer. 100-MHz $^1$H N.m.r. spectra were determined with a JEOL PS 100 high-resolution spectrometer (solvent $CDCl_3$ : $SiMe_4$ as internal reference). $^{13}$C N.m.r. spectra were determined with a Brucker SXP pulsed Fourier-transform n.m.r. spectrometer (solvent $CDCl_3$ : $SiMe_4$ as internal reference). T.l.c. was carried out on Wako-gel B-5. Mass spectra were taken by the staff of the Faculty of Pharmaceutical Sciences of this University with a Hitachi RMU-6E spectrometer (direct inlet system: source temperature 200 °C and ionizing voltage 80 eV unless stated otherwise); mass spectra of compounds (16), (18), (24), (25), (26), (27), (29), and (32), and all the high-resolution mass spectra were recorded by Miss Yuko Chiba in the Faculty of Agriculture with a Hitachi JMS-D 300 spectrometer (70 eV). Elemental analyses were performed by the staff of the Faculty of Pharmaceutical Sciences. Rotations were measured with a JASCO DIP-SL automatic polarimeter.

*The Hypoiodite Reaction of Cholesterol in the Presence of Mercury*(II) *Oxide and Iodine.*—(*a*) Cholesterol (386 mg, 1 mmol) in benzene (70 ml) in the presence of mercury(II) oxide (651 mg, 3 mmol) and iodine (762 mg, 3 mmol) was irradiated under an atmosphere of a nitrogen for 9 h. After removal of the precipitate by filtration, the solution was washed twice, with 5% sodium thiosulphate solution and saturated brine, and then dried ($Na_2SO_4$). After the usual work-up the residue (505 mg) was subjected to preparative t.l.c., with a benzene–hexane (3 : 1). The most mobile fraction (137 mg, 27%) was the formate (2) $\lambda_{max.}$ (pentane) 237 nm (ε 2 700); τ 9.33 (3 H, s, 18-Me), 9.01 (3 H, s, 19-Me), 4.12 (1 H, d, *J* 6.0 Hz, 6-H), 1.90 (1 H, s, OCHO), and 5.36 and 5.51 (each 1 H, d, *J* 12.0 Hz, 3-H); $\nu_{max.}$ (neat) 1 731 (C=O), 1 468, 1 383, 1 166 (formate C–O), 849, and 764 cm$^{-1}$; *m/e* 527 ($M^+$): the next fraction (40 mg, 8%) was the cyclic ether (3) which was recrystallized from acetone, m.p. 80—81 °C; $[\alpha]_D^{29}$ −35.4° (*c* 1.0 in $CHCl_3$) (Found: C, 61.6, H, 8.65, I, 23.2; $C_{27}H_{45}IO_2$ requires C, 61.35, H, 8.58, I, 24.01%); $\nu_{max.}$ 1 105, 1 013, and 902 cm$^{-1}$; τ 9.28 (3 H, s, 18-Me), 8.67 (3 H, s, 19-Me), 4.40 (1 H, s, $W_{\frac{1}{2}}$ 3.7 Hz, 3-H), 5.77 and 6.68 (each 1 H, d, *J* 8.1 Hz, 4-H), and 5.78 (1 H, t, superimposed on one of signals due to C-4-methylene, 6-H); *m/e* 528 ($M^+$ +1, 0.9), 401 (71), 383 (40), 371 (49), 327 (40), 301 (31), 95 (96), 55 (83), and 57 (100): the third fraction (56 mg, 11%) was an isomeric ether (4) which was recrystallized from diethyl ether–acetone, m.p. 145.0—147.0 °C; $[\alpha]_D^{28}$ −10.0: (*c* 1.0 in $CHCl_3$) (Found: C, 61.15; H, 8.55; I, 23.9. $C_{27}H_{45}IO_2$ requires C, 61.35; H, 8.58; I, 24.01%); $\nu_{max.}$ 1 115, 1 018, 999, and 907 cm$^{-1}$; τ 9.35 (3 H, s, 18-Me), 9.10 (3 H, s, 19-Me), 4.48 (1 H, s, $W_{\frac{1}{2}}$ 4.1 Hz, 3-H), 5.82 and 6.28 (each 1 H, d, *J* 7.5 Hz, 4-H), and 5.45 (1 H, q, $J_{6\beta,7\beta}$ 6.0 Hz and $J_{6\beta,7\alpha}$ 12.0 Hz); *m/e* 401 ($M^+$ — I, 100), 383 (25), 247 (11), 207 (16), 95 (63), 57 (53), and 55 (53). Fractions more polar than these compounds were an intractable mixture of several minor unidentified products, including 3β,5α,6β-trihydroxy-5α-cholestane which was isolated by column chromatography as described in procedure (*b*) below.

(*b*) Cholesterol (3 g) in dry benzene (150 ml) containing mercury(II) oxide (5.1 g) and iodine (6.0 g) were irradiated for 6 h as described in (*a*). The product was subjected to column chromatography (Mallincrodt silicic acid) eluting with hexane–benzene (with increasing amounts of benzene), then with benzene to remove products (2), (3), (4), and several minor products less polar than product (5). The column was finally eluted with diethyl ether to afford almost pure 3β,5α,6β-trihydroxycholestane (5). This was recrystallized from acetone to yield the pure compound (50 mg), m.p. 239—241 °C (lit.,[6c] m.p. 237—239 °C); τ ([$^2H_6$]-acetone 9.28 (3 H, s, 18-Me), 8.80 (3 H, s, 19-Me), 6.00 (1 H, br s, 3-H), and 6.47 (1 H, t, *J* 3 Hz, 6-H); ([$^2H_5$]pyridine) 9.30 (3 H, s, 18-Me), 8.45 (3 H, s, 19-Me), 5.35 (1 H, br s, 3-H), and 5.95 (1 H, br s, 6-H); *m/e* 420 ($M^+$, 2%), 402 ($M^+ - H_2O$, 81), 384 ($M^+ - 2H_2O$, 81), 369 ($M^+ - 2H_2O$ — Me, 36), 351 (12), 348 (12), 331 (15), 303 (18), 271 (19), 262 (41), 247 (63), 229 (63), 95 (87), 81 (88), 69 (67), 57 (69), 55 (97), and 43 (100). The diacetate (6) was prepared as follows. The triol (70 mg) and acetic anhydride–pyridine (2 ml) were stirred for 5.5 h at room temperature. Usual work-up of the reaction mixture afforded a residue (57 mg)

which showed two spots on t.l.c. This was subjected to column chromatography (Merck silica gel, 70—230 mesh, 2.5 g). Elution with a hexane–diethyl ether (4 : 1) afforded the diacetate (6) (32 mg) which was recrystallized from methanol, m.p. 166—168 °C (lit.,[6a] 165 °C; lit.,[6b] 166 °C); τ 9.32 (3 H, s, 18-Me), 8.83 (3 H, s, 19-Me), 4.84 (1 H, br s, 3-H), 5.29 (1 H, t, $J$ 2 Hz), and 7.91 and 7.97 (each 3 H, s, 2 × OAc). Further elutions with hexane–diethyl ether (2 : 1) afforded another acetate (17 mg), probably 3β,5α,6β-trihydroxycholestane 3-acetate.

*The Hypoiodite Reaction of Epicholesterol* (11).[8]—The epicholesterol (11) [8] (300 mg) in dry benzene (25 ml) in the presence of mercury(II) oxide (500 mg) and iodine (590 mg) was irradiated in a Pyrex vessel under an argon atmosphere for 5 h (slow bubbling of argon). After work-up as for cholesterol hypoiodite, the residue (420 mg) was subjected to preparative t.l.c. to afford products in essentially the same ratio with those for cholesterol hypoiodite.

*The Hypoiodite Reaction of Androst-5-en-3β-ol* (12) *in the Presence of Mercury*(II) *Oxide and Iodine.*—Androst-5-en-3β-ol (300 mg) in dry benzene (60 ml) containing mercury(II) oxide (710 mg) and iodine (840 mg) was irradiated in an atmosphere of an argon. After the usual work-up, the product (440 mg) was subjected to preparative t.l.c. with hexane–benzene (1 : 2). The most mobile fraction (134 mg) was the gummy formyl ester (13); $\nu_{max.}$ (neat) 1 726 (C=O), 1 448, 1 378, and 1 157 cm$^{-1}$ (formyl C–O); τ 9.31 (3 H, s, 18-Me), 9.02 (3 H, s, 19-Me), 5.30 and 5.48 (each 1 H, d, $J$ 12.0 3-H), 4.07 (1 H, d, $J$ 4.5 Hz, 6-H), and 1.86 (1 H, s, OCHO).

The next most mobile fraction (20 mg) was the cyclic ether (14); $\nu_{max.}$ (neat) 1 452, 1 106, 1 011, and 902 cm$^{-1}$; τ 9.26 (3 H, s, 18-Me), 8.67 (3 H, s, 19-Me), 4.38 (1 H, s, $W_{\frac{1}{2}}$ 4.2 Hz, 3-H), 5.74 and 6.67 (each 1 H, d, $J$ 7.5 Hz, 4-H), and 5.75 (1 H, t, superimposed on one of C-4 methylene signals, 6α-H). The third most mobile fraction (48 mg) was the isomeric cyclic ether (15); τ 9.33 (3 H, s, 18-Me), 9.11 (3 H, s, 19-Me), 4.45 (1 H, s, $W_{\frac{1}{2}}$ 3.8 Hz, 3-H), 5.65 and 6.27 (each 1 H, $J$ 7.5 Hz, 4-H), and 5.22 (1 H, q, $J_{6\beta,7\beta}$ 5.3 and $J_{6\beta,7\alpha}$ 12.0 Hz, 6β-H). Products less mobile than the third fraction were not identified.

3-*Deuteriocholesterol.*[14]—This compound was prepared by sodium borodeuteride reduction of cholest-5-en-3-one prepared by reduction [23] of 5α,6β-dichromocholestan-3β-ol [24] with zinc.

*The Hypoiodite Reaction of 3-Deuteriocholesterol.*[14]—3-Deuteriocholesterol [14] (600 mg) in dry benzene (60 ml) in the presence of mercury(II) oxide (1 g) and iodine (1.18 g) was irradiated under a nitrogen atmosphere for 4 h. Work-up of the solution as for cholesterol hypoiodite afforded a residue (838 mg). Examination of the product by t.l.c. indicated essentially an identical pattern of spots as for cholesterol hypoiodite. The product was subjected to preparative t.l.c. with benzene–hexane (2 : 1) to afford three products (8), (9), and (10). The n.m.r. spectra of these deuteriated products (Table 2) were identical with those of the products (2), (3), and (4) from cholesterol hypoiodite with the exceptions of the absence of signals due to 3-H. However, signals corresponding to a singlet at τ 1.90 in (2), a singlet at τ 4.48 in (3), and a singlet at τ 4.40 in (4) were absent in the spectra of (8), (9), and (10).

*The Cyclization of Formyl Ester* (2) *to 3-Oxacholest-5-ene* (18) *with Alumina.*—The formyl ester (2) (260 mg) dissolved in hexane was adsorbed on Merck neutral alumina (6 g, Merck neutral alumina, activity grade II–III). The column was eluted with hexane (200 ml), hexane–benzene (10 : 1) (200 ml), (6 : 1) (200 ml), and (4 : 1) to give 3-oxacholest-5-ene (18) (173 mg) as virtually a single product. The cyclization with Woelm neutral alumina (activity grade II–III) gave similar results. After recrystallization from diethyl ether it had m.p. 75—77 °C (Found: $M^+$ 372.337 4; C, 83.6; H, 11.6%. $C_{26}H_{44}O$ requires $M^+$, 372.3390; C, 83.8; H, 11.90%); $\nu_{max.}$ 1 225, 1 110, 970, 921, and 874 cm$^{-1}$; for n.m.r. spectrum see Table 2; *m/e* 372 ($M^+$, 78.9), 357 ($M^+$ — Me, 12.4), 123 (53.9), and 110 (100).

*Reductive Hydrolysis of Formyl Ester* (2) *with Sodium Borohydride.*—(*a*) To formyl ester (2) (300 mg) in diethyl ether (15 ml) and methanol (5 ml), was added portionwise sodium borohydride (100 mg) with cooling in ice–water and the solution was stirred for 30 min. After addition of water, the solution was extracted with diethyl ether. Work-up in the usual manner gave amorphous 3-hydroxy-2-iodo-A-nor-2,3-secocholest-5-ene (19). The compound was unstable and coloured on standing. This was dissolved in benzene and evaporation of the solvent left crystals. After washing with methanol it had m.p. 45—48 °C and was positive for the Beilstein test; $\nu_{max.}$ 3 300 cm$^{-1}$ (OH), no band due to carbonyl group; *m/e* 372 ($M^+$ — HI, 58), 357 ($M^+$ — HI — Me, 32), 123 (56), and 110 (100). The compound was immediately used for the next reaction.

(*b*) To formyl ester (2) (700 mg) in THF (30 ml), was added sodium borohydride (700 mg) with cooling in ice–water. The solution was refluxed for 5 h. After addition of ethanol, ethyl acetate, and water, the solution was filtered and the filtrate was extracted with chloroform. The chloroform solution was worked up as usual. The product was subjected to preparative t.l.c. with hexane–diethyl ether (1 : 1) to give 3-oxacholest-5-ene (364 mg).

*Preparation of 3-Oxacholest-5-ene* (18) *from 3-Hydroxy-2-iodo-A-nor-2,3-secocholest-5-ene* (19).—(a) *With potassium t-butoxide in t-butyl alcohol.* 3-Hydroxy-2-iodo-A-nor-2,3-secocholest-5-ene (19) (40 mg) in t-butyl alcohol (5 ml) containing potassium t-butoxide (50 mg) was stirred for 30 min under an argon atmosphere. After the addition of water, the solution was extracted with diethyl ether, and the organic layer washed with water and dried. Evaporation of the solvent gave crystalline 3-oxacholest-5-ene (18) (28 mg), identical with the specimen obtained by an alumina-induced cyclization of formate (2).

(b) *With alumina.* 3-Hydroxy-2-iodo-A-nor-2,3-secocholest-5-ene (19) (100 mg) dissolved in a small volume of hexane was adsorbed on neutral alumina (6 g, Alumina Woelm, neutral, activity grade II–III for chromatography). The column was then eluted with benzene to give 3-oxacholest-5-ene (18) in over 90% yield.

*Hydrogenolysis of the Product* (3) *with Palladium–Charcoal Catalyst.*—The product (3) (150 mg) in a mixed solvent of diethyl ether (5 ml) and ethanol (8 ml) in the presence of 10% palladium–charcoal catalyst [25] (80 mg) and potassium acetate (30 mg) was hydrogenated. After 48 h a further amount (40 mg) of palladium–charcoal was added and hydrogenation was continued for another 24 h. Removal of the catalyst and solvent afforded compound (16) as a colourless gum (150 mg) (Found: $M^+$ 402.351 0. $C_{27}H_{46}O_2$ requires $M$, 402.349 8); $\nu_{max.}$ (neat) 1 463, 1 380, 1 123, 1 022, 1 005, 911, and 830 cm$^{-1}$; τ 9.36 (3 H, s, 18-Me), 9.13 (3 H, s, 19-Me), 4.53 (1 H, br s, $W_{\frac{1}{2}}$ 5.0 Hz, 3-H), and 5.89 and 6.85 (each 1 H, d, $J$ 7.5 Hz, 4-H); *m/e* 402 ($M^+$, 100), 401 (25.3), 372 (51.6), 328 (39.8), 288 (23.6), 247 (49.4), 215

(18.9), 147 (36.3), 95 (69.5), 81 (69.2), 55 (78.0), and 43 (74.7).

*Removal of Iodine from Product* (4) *with Sodium–n-Butyl Alcohol.*—Product (4) (80 mg) in n-butyl alcohol (20 ml) was refluxed and to this solution there was added sodium metal (1.5 g). After the sodium had dissolved, the solution was brought to room temperature and the sodium was decomposed with water. The mixture was extracted with water, dried over $Na_2SO_4$, and solvent removed to give a residue which showed several spots in t.l.c. The product was subjected to preparative t.l.c. with benzene–chloroform (2 : 1) to afford an amorphous compound (7 mg) as the most mobile fraction. The i.r. and the n.m.r. spectra were identical with those of compound (16).

*Hydrogenolysis of Product* (4) *with Palladium–Charcoal Catalyst.*—The product (4) (100 mg) in a mixture of diethyl ether (5 ml) and ethanol (5 ml) in the presence of 10% palladium–charcoal catalyst (50 mg) and potassium acetate (20 mg) was hydrogenated for 24 h at room temperature with constant stirring. Work-up as described for the product (3) afforded a colourless gum (83 mg) which was identical with compound (16) obtained from the product (3).

X-*Ray Structure Determination of* 3α,5-*Epoxy*-6β-*iodo*-A-*homo*-4-*oxa*-5α-*cholestane.*—Crystal data are as follows: $C_{27}H_{45}IO_2$, $M$ = 528.56. Monoclinic, $a$ = 17.698 (5), $b$ = 7.018 (3), $c$ = 10.265 (4) Å, β = 92.11 (3)°, $U$ = 1 274.1 Å$^3$, $D_c$ = 1.378 g cm$^{-3}$, $Z$ = 2, F(000) = 552, (Cu-$K_\alpha$) = 101.0 cm$^{-1}$. Systematic absences: $0k0$ for $k$ odd, space group $P2_1$.

A single crystal with dimensions 0.3 × 0.3 × 0.1 mm$^3$ was used for the $X$-ray measurement. Cell dimensions and reflection intensities were measured on a Rigaku four-circle diffractometer using LiF-monochromated Cu-$K_\alpha$ radiation (λ = 1.541 8 Å). The intensity measurement was made by the θ—2θ continuous-scan technique at a 2θ scan rate of 2° min$^{-1}$; the background was measured for 30 s at each end of the scan range. Three standard reflections, measured at intervals of every 62 reflections, showed no significant decrease in intensity during the course of data collection. The intensities were corrected for the Lorentz and polarization factors, but not for absorption. In the range of 2θ values up to 140°, 2 210 unique structure factor magnitudes above $3\sigma(F_o)$ were selected for the subsequent structure analysis and refinement.

The structure was solved by the heavy-atom method. Approximate co-ordinates of the non-hydrogen atoms were refined by the block-diagonal-matrix least-squares method, at first with isotropic and then with anisotropic temperature factors. Since the absolute configuration of the molecule was known, the least-squares refinement was further repeated including anomalous dispersion effects of iodine atoms for Cu-$K_\alpha$ radiation. The function minimized was $\Sigma w(|F_o| - |F_c|)^2$ with $w = 1/[\sigma(F_o)^2 \exp(AX)^2 + BY^2 CXY + DX + EY)]$, where $X = |F_o|$ and $Y = \sin\theta/\lambda$. The intensity data were grouped with constant intervals along two co-ordinates, $X$ and $Y$. The coefficients, $A$, $B$, $C$, $D$, and $E$, were determined by the least-squares fit so as to give as equal values of $\langle w|\Delta F\rangle^2$ for all the groups as possible. The final $R$ was 9.8%. The results are given in Tables 3—5 and the Figure.*

All calculations were performed on a FACOM 230-75 computer at Hokkaido University Computing Centre using our own programs. The atomic scattering factors were taken from International Tables.[26]

*Irradiation of* 6α-*Iodide* (4) *in Benzene containing Iodine and Mercury*(II) *Oxide* (By Chi-Ming Shea).—6α-Iodide (4) (30 mg) in benzene (2.5 ml, Special grade, Wako Japan) containing mercury(II) oxide (18 mg) and iodine (21 mg) was irradiated in Pyrex vessel with a Hanovia 450-W high-pressure mercury arc under an atmosphere of argon for 14 h. Usual work-up gave a brownish yellow product, t.l.c. of which indicated that it was a mixture of the 6α- and 6β-iodides. The n.m.r. spectrum showed that it consisted of 81% of the 6α-iodide and 19% of the 6β-iodide.

*Thermal Decomposition of Cholesterol Hypoiodite in the Presence of Mercury*(II) *Oxide and Iodine.*—Cholesterol (3 g), mercury(II) oxide (5.10 g), and iodine (5.95 g) in dry benzene (200 ml) were placed in a three-necked flask. This solution was heated at 55—60 °C in the dark for 5 h while argon gas was slowly bubbled through. After removal of the precipitate, the filtrate was washed twice with 5% sodium thiosulphate, then water, and dried over sodium sulphate. Removal of the solvent afforded an amorphous residue (3.22 g). This was subjected to column chromatography (Merck, Silica gel 60, 70—230 mesh, 105 g). Elutions with hexane–benzene (7 : 1) then hexane–benzene with increasing amounts of benzene, and finally with benzene, afforded 5 fractions (A—E). Fraction A (200 mg) was the crystalline ether (20), which was recrystallized from acetone to yield an analytical specimen (46 mg), m.p. 218—220 °C (Found: C, 84.0; H, 11.8. $C_{54}H_{90}O_2$ requires C, 84.09; H, 11.76%); $\nu_{max.}$ 1 128 and 1 040 cm$^{-1}$; for n.m.r. spectral data see text; *m/e* 402 (0.2), 400 (0.3), 398 (0.3), 396 (0.2), 394 (0.2), 386 (35.8), 384 (32.2), 368 (62.2), 366 (32.2), 247 (52.2), 159 (34.3), 145 (61.2), 135 (58.3), 121 (52.2), 119 (63.5), 107 (72.4), 105 (68.6), 95 (95.0), 93 (59.7), 91 (56.3), 81 (100), 57 (64.8), 55 (77.0), 43 (95.6), and 41 (53.0).

Fraction B (119 mg) was a mixture of ether (20) and the 6β-iodo-compound (3). Fraction C (346 mg) was the 6β-iodo-compound (3) and this was recrystallized from acetone to afford pure (3) (96 mg), m.p. 80—81 °C, identical with the specimen obtained from the photo-reaction. Fraction D (150 mg) was a mixture of the 6β-iodo-compound and ether (20). Fraction E (180 mg) showed two spots on t.l.c. and it was the crude alcohol (21). It was recrystallized from acetone to yield compound (21) (76 mg), m.p. 210—212 °C (Found: $M^+$ 402.346 9. $C_{27}H_{46}O_2$ requires $M$, 402.349 5). Fractions B, D, and the residue from the filtrate of recrystallization of fraction E were combined and subjected to preparative t.l.c. with benzene as eluant and further amounts of ether (20) (15 mg), 6β-iodo-compound (3) (103 mg), and compound (21) (32 mg) were obtained. Thus, the total yields of the three compounds (20), (3), and (21) were 7, 11, and 4%. No well-defined compounds were obtained from fractions more polar than those containing the above compounds.

*Transformation of Ether* (20) *into Alcohol* (21) *with Silica Gel.*—The ether (20) (10 mg) dissolved in diethyl ether was adsorbed on a silica gel column (Merck, silica gel 60, 70—230 mesh ASTM for column chromatography, 2.5 g). After 22 h, the column was eluted with diethyl ether. A mixture of ether (20) and alcohol (21) was obtained. This was subjected to column chromatography (silica gel 1.5 g). Elution with hexane–benzene (2 : 1) afforded the ether (20) (3.5 mg). Further elution of the column with benzene afforded alcohol (21) (2 mg).

* The anisotropic temperature factors, and a list of observed and calculated structure factors are available in Supplementary Publication No. SUP 22875 (11 pp.). For details see Notice to Authors No. 7. in *J.C.S. Perkin II*, 1979, Index issue.

*Hydrolysis of Ether* (20) *with Hydrochloric Acid*.—To a solution of ether (20) (30 mg) in THF (4 ml) was added concentrated hydrochloric acid (0.7 ml) and the solution was stirred for 2 h at room temperature. After evaporation of solvent the residue was neutralized with 10% sodium carbonate and extracted with chloroform. The chloroform solution was worked up in the usual way. The residue was subjected to column chromatography (silica gel, 70—270 mesh, 4.5 g). Elution of the residue with hexane–benzene (1 : 1) afforded the alcohol (21) (10 mg) and then cholesterol (7 mg).

*Preparation of* 3β-*Hydroxy*-3α,4,4-*trimethylcholest*-5-*ene* (23).—4,4-Dimethyl-3-oxacholest-5-ene (22) (1.8 g) in dry diethyl ether (120 ml) was added dropwise to a stirred solution of methylmagnesium iodide, prepared from methyl iodide (2 ml) and magnesium turnings (500 mg) in dry diethyl ether (30 ml), under an atmosphere of nitrogen. The solution was set aside overnight at room temperature and was poured into ice–water containing ammonium chloride. The mixture was then extracted with diethyl ether, and the ethereal solution was washed with 2N-hydrochloric acid and water, and dried ($Na_2SO_4$). The residue was subjected to column chromatography on alumina (Merck, activity II–III, 70—230 mesh, 60 g). Elution with hexane–benzene (7 : 1) gave the starting ketone (22) (280 mg). Recrystallization from diethyl ether–methanol afforded the pure ketone (182 mg, 10%). The column was eluted further with hexane–benzene containing increasing amounts of benzene. Elution with hexane–benzene (2 : 1) afforded crude 3β-hydroxy-3α,4,4-trimethylcholest-5-ene (23) (1.493 g). Recrystallization from methanol afforded a pure specimen (1.286 g, 64%), m.p. 122.0—124.0 °C (Found: C, 84.0; H, 12.1. $C_{30}H_{52}O$ requires C, 84.04; H, 12.23%); $[\alpha]_D^{21}$ −62.0 (*c* 1.0 $CHCl_3$); $\nu_{max.}$ 3 300 br (OH), 1 133, 1 099, 1 038, and 1 022 $cm^{-1}$; *m/e* (79 eV) 428 ($M^+$, 9.6%), 410 ($M^+ - H_2O$, 10.6%), 395 ($M^+ - H_2O$ – Me, 12.8%), and 357 (100%); τ 8.93, 8.89, or 8.83 (3 H, s, 3α-Me), two of 8.93, 8.89, and 8.83 (3 H, s, 4a-*gem*-$Me_2$), 4.54 (1 H, dd, *J* 2.2 and 4.5 Hz, 6-H), 9.32 (3 H, s, 18-Me), and 8.93, 8.89, or 8.83 (3 H, s, 19-Me). Further elutions with hexane–benzene (4 : 3), hexane–benzene (1 : 1), benzene, and finally diethyl ether gave a fraction which was recrystallized from methanol to give 3β-hydroxy-3α,4,4-trimethylcholest-5-ene (209 mg), m.p. 216—218 °C; $\nu_{max.}$ 3 280 br (OH), 1 133, 1 062, and 924 $cm^{-1}$.

*The Irradiation of* 3β-*Hydroxy*-3α,4,4-*trimethylcholest*-5-*ene Hypoiodite in the Presence of Mercury*(II) *Oxide and Iodine*.—3β-Hydroxy-3α,4,4-trimethylcholest-5-ene (22) (500 mg, 1.17 mmol), mercury(II) oxide (740 mg, 3.42 mmol), and iodine (860 mg, 3.38 mmol) in benzene (60 ml) were irradiated under a nitrogen atmosphere for 8 h. The solution was filtered and the filtrate was extracted with diethyl ether. The organic layer was twice washed with 5% aqueous sodium hydrogensulphite solution, then with water, and dried ($Na_2SO_4$). Evaporation of the solvent at 27 °C left a residue (768 mg) which was subjected to preparative t.l.c. with benzene to afford 6 fractions; A (70 mg), B (23 mg), C (17 mg), D (62 mg), E (42 mg), and F (280 mg), in order of decreasing mobility. The most mobile fraction A (70 mg) was recrystallized from methanol to give epoxide (24), m.p. 146.0—150.0 °C; a specimen for analysis was obtained by recrystallization from acetone, m.p. 147.5—149.5 °C (Found: C, 63.05; H, 9.0; I, 24.15: $C_{30}H_{51}IO_2$ requires C, 63.14; H, 9.01; I, 22.24%); $[\alpha]_D^{21}$ −44.4 (*c* 0.9, $CHCl_3$); $\nu_{max.}$ 1 290, 1 230, 1 220, and 990 $cm^{-1}$; *m/e* 443 ($M^+$ – I, 0.1%), 386 (24.6), 385 (100), and 43 (19.3); τ 8.63 (3 H, s, 3β-Me), 8.30 (3 H, s, 4aβ-Me), 8.55 (3 H, s, 4aα-Me), 5.74 (1 H, br t, *J* 1.5 Hz, 6α-H), 9.28 (3 H, s, 18-Me), 8.68 (3 H, s, 19-Me). The fourth fraction (62 mg, 12%) was an epoxide (25) which was recrystallized from methanol to give crystals (38 mg), m.p. 111.0—114.0 °C; a specimen for analysis was obtained by recrystallization from acetone–methanol, m.p. 118.0—119.0 °C (Found: C, 81.4; H, 11.25; $C_{30}H_{50}O_2$ requires C, 81.39; H, 11.38%); $[\alpha]_D^{20}$ −39.0° (*c* 1.0, $CHCl_3$); $\nu_{max.}$ 1 219, 1 125, 1 081, and 982 $cm^{-1}$; *m/e* 442 ($M^+$, 0.1%), 384 (100), 354 (17.4), 339 (63.1), and 43 (26.3); τ 8.59 (3 H, s, 3β-Me), 8.53 and 8.66 (each 3 H, s, 4a-$Me_2$), 4.02 (1 H, dd, *J* 10.2 and 1.5 Hz, 6-H), 9.30 (3 H, s, 18-Me), 8.96 (3 H, s, 19-Me), and 4.41 (1 H, dd, 2.4 and 10.2 Hz, 7-H). The least mobile fraction F (280 mg) was a mixture of two products which were separated by preparative t.l.c. with hexane–diethyl ether (4 : 1). Two developments with the mixed solvent afforded fractions G (35 mg, 7%) and H (107 mg, 21%). The more mobile fraction G was recrystallized from methanol to afford the tetrahydropyran (26), m.p. 105.0—107.5 °C. The specimen for the analysis was obtained by recrystallization from methanol, m.p. 107.0—108.0 °C (Found: C, 81.25; H, 11.45. $C_{30}H_{50}O_2$ requires C, 81.39; H, 11.38%); $[\alpha]_D^{22}$ −47.3° (*c* 1.0, $CHCl_3$); $\nu_{max.}$ 1 718 (C=O), 1 258, 1 234, and 1 081 $cm^{-1}$; *m/e* 442 ($M^+$, 2.3%), 427 ($M^+$ – Me, 19.1), 356 (100), 247 (11.3), 243 (32.7), 149 (18.6), 148 (21.1), 95 (21.5), 57 (34.7), and 43 (35.0); τ 8.80 and 8.69 (each 3 H, s, 4,4-$Me_2$), 7.79 (3 H, s, 2β-OAc), 4.76 (1 H, t, *J* 3.6 Hz, 6-H), 9.32 (3 H, s, 18-Me), 9.00 (3 H, s, 19-Me), and 6.17 (1 H, dd, *J* 3.2 and 9.0 Hz, 2α-H).

Fraction H was recrystallized from methanol to yield the epimeric (27) (65 mg), m.p. 87.0—89.5 °C (Found: C, 81.1; H, 11.35. $C_{30}H_{50}O_2$ requires C, 81.39; H, 11.38%); $[\alpha]_D^{22}$ +21.7 (*c* 1.0 $CHCl_3$); $\nu_{max.}$ 1 721 (C=O), 1 239, 1 064, and 971 $cm^{-1}$; *m/e* 442 ($M^+$, 2.2%), 427 ($M^+$ – Me, 100%), 356 (38.7), 247 (4.6), 243 (9.6), 149 (4.2), 148 (4.3), 95 (8.0), 57 (5.1), and 43 (25.6); τ 8.68 and 8.65 (each 3 H, s, 4,4-$Me_2$), 7.79 (3 H, s, 2α-OAc), 4.60 (1 H, t, *J* 3.2 Hz, 6-H), 9.30 (3 H, s, 18-Me), 8.74 (3 H, s, 19-Me), and 5.68 (1 H, dd, *J* 4.2 and 10.5 Hz, 2β-H).

*The Thermal Decomposition of* 3β-*Hydroxy*-3α,4,4-*trimethylcholest*-5-*ene Hypoiodite in the Presence of Mercury*(II) *Oxide and Iodine*.—Trimethylcholest-5-ene (23) (500 mg, 1.31 mmol), mercury(II) oxide (860 mg, 3.79 mmol), and iodine (975 mg, 3.84 mmol) in benzene (75 ml) were heated at 55—60 °C under a nitrogen atmosphere for 10 h in the dark. The reaction mixture was worked up as usual and the crude product (920 mg) was subjected to preparative t.l.c. with benzene. Eight fractions A (60 mg), B (32 mg), C (50 mg), D (53 mg), E (25 mg), F (15 mg), G (20 mg), and H (234 mg) in order of decreasing mobility were obtained. Fraction A was again subjected to preparative t.l.c. with hexane to give 3,3,4 trimethylcholesta-4,6-diene (28) (15 mg, 3%). After recrystallization from diethyl ether–methanol, the analytical specimen had m.p. 111.0—115.0 °C; $[\alpha]_D^{19}$ +48.3° (*c* 0.66, $CHCl_3$); $\lambda_{max.}$ (ethanol) 246 nm (ε 16 200); $\nu_{max.}$ 1 258, 1 169, 1 158, and 1 058 $cm^{-1}$; *m/e* (79 eV) 410 ($M^+$, 41.2%), 395 ($M^+$ – Me, 44.1), and 163 (100); τ 8.96 and 8.99 (each 3 H, s, 3-$Me_2$), 8.32 (3 H, s, 4-Me), 4.42 (1 H, dd, 1.5 and 9.8 Hz, 6-H), 9.26 (3 H, s, 18-Me), 9.10 (3 H, s, 19-Me), and 3.70 (1 H, dd, 4.8 and 9.8 Hz, 7-H).

Fraction C was the oxepan (24) which was recrystallized from diethyl ether–methanol to yield an analytical specimen

(22 mg), identical with the sample obtained from photolysis. Fraction H was subjected to preparative t.l.c. with hexane–diethyl ether (4 : 1) to give two fractions $H_1$ and $H_2$. The more mobile fraction (113 mg, 22%) was the tetrahydropyran (26) which was recrystallized from methanol to give an analytical specimen (81 mg). Fraction $H_2$ (76 mg, 15%) was recrystallized from methanol to give the tetrahydropyran (27) identical with the specimen obtained from the photolysis.

*The Isomerization of* (27) *to* (26) *with Base.*—Oxa-steroid (27) (62 mg) in diethyl ether (2 ml) and methanol (3 ml) containing potassium hydroxide (100 mg) was stirred for 5 h at room temperature. The reaction mixture was neutralized with aqueous 2N hydrochloric acid, extracted with diethyl ether, and the organic layer worked up in the usual way. The crude product (61 mg) was almost pure and was recrystallized from methanol to give the isomeric (26) (52 mg).

*Reaction of Compound* (16) *with Boron Trifluoride–Diethyl Ether in the Presence of Acetic Anhydride.*—Compound (16) (150 mg) in dry benzene (2 ml) containing $BF_3$–ether (0.1 ml) and acetic anhydride (1 ml) was stirred for 10 min at room temperature. The reddish brown solution was neutralized with 5% potassium hydroxide extracted with diethyl ether, and the ether solution washed with water and dried over $Na_2SO_4$. Evaporation of the ether gave a residue (180 mg) which exhibited two spots with similar $R_F$ values on t.l.c. with chloroform. The more mobile spot was the starting material and the less mobile one was product (29). The residue was then subjected to preparative t.l.c., developing twice with chloroform–benzene (4 : 1), twice with chloroform, and finally with chloroform–diethyl ether (5 : 1) afforded product (29) (100 mg), as a gum. It crystallized on setting aside, m.p. 71—73 °C (Found: $M^+$, 486.371 9. $C_{31}H_{50}O_4$ requires $M$, 486.370 9); $\nu_{max.}$ (neat) 1 740 (OAc), 1 652 and 1 622 (–CH–C=CH–), 1 216, 1 157, 1 037, and 753 $cm^{-1}$; $\lambda_{max.}$ ethanol 255 nm (ε 11 000); τ 2.48 (1 H, s, 3-H), 5.79 and 5.94 (each 1 H, d, $J$ 12.0 Hz, 5-$CH_2O$), 7.80 (3 H, s, 2-Ac), 7.94 (3 H, s, OAc), 8.96 (3 H, s, 19-Me), and 9.35 (3 H, s, 18-Me); *m/e* 486 ($M^+$, 14.2), 413 (14.1), 327 (13.0), 215 (3.5), 95 (14.6), 57 (21.2), 55 (19.6), and 44 (100).

*Preparation of the Oxime* (31) *of Ketone* (29).—Compound (29) (50 mg) in methanol (10 ml) and diethyl ether (2 ml) containing hydroxylamine hydrochloride (230 mg) and sodium acetate trihydrate (350 mg) was refluxed for 1 h. The solution was extracted with diethyl ether and the organic layer was worked up as usual. The crude oxime (30) (47 mg) was recrystallized from acetone, m.p. 144—145.5 °C (Found: C, 73.8; H, 10.25; N, 2.75. $C_{31}H_{51}NO_4$ requires C, 74.21; H, 10.25; N, 2.79%); $\nu_{max.}$ 1 745 (OAc), and 1 632 $cm^{-1}$ (–CH=C–C=NOH); $\lambda_{max.}$ ethanol 246 nm (ε 14 200); τ 3.23 (1 H, s, 3-H, $W_{\frac{1}{2}}$ 3.6 Hz), 5.82 and 5.94 (each 1 H, d, $J$ 12.8 Hz, 5-$CH_2O$), 7.96 [3 H, s, C(*Me*)=NOH], 8.06 (3 H, s, OAc), 8.99 (3 H, s, 19-Me), and 9.37 (3 H, s, 18-Me); *m/e* 501 ($M^+$, 3), 485 (23), 442 (9), 426 (16), 412 (27), 327 (19), 328 (19), 98 (100), 57 (26), 55 (30), and 43 (48).

*Hydrolysis of the* $BF_3$*-cleaved Product* (29).—Oxepan (16) (60 mg) in methanol (4 ml) and diethyl ether (1.5 ml) containing potassium hydroxide (170 mg) was stirred for 30 min at room temperature. The solution was neutralized with 2N-hydrochloric acid and worked up as usual. The crude product (54 mg) was subjected to column chromatography (Mallincrodt silicic acid, 2 g). Elution with benzene afforded compound (32) (*ca.* 10 mg); τ 9.36 (3 H, s, 18-Me), 9.12 (3 H, s, 19-Me), 7.91 (3 H, s, OAc), 6.88 and 5.96 (each 1 H, d, $J$ 7.5 $H_2$, 5-$H_2$), 7.35 (1 H, dd, $J$ 4.5 and 12.0 Hz, 2α-H), 4.31 (1 H, br s, $W_{\frac{1}{2}}$ 3.6 Hz, 3β-H). Elution with benzene–diethyl ether (4 : 1) afforded the alcohol (33) (*ca.* 20 mg) (Found: $M^+$, 444.362 1. $C_{29}H_{48}O_3$ requires $M$, 444.360 4): τ 2.31 (1 H, s, 3-H), 6.57 and 6.29 (each 1 H, d, $J$ 12.0 Hz, 5-$H_2$), 7.82 (3 H, s, 2-Ac), 9.03 (3 H, s, 19-Me), and 9.37 (3 H, s, 18-Me); $\nu_{max.}$ 3 400 (OH), 1 647 and 1 608 (COC=C), and 1 221 $cm^{-1}$; $\lambda_{max.}$ ethanol 257 nm (ε 13 300); *m/e* 444 ($M^+$, 29.3), 413 (98.0), 395 (6.3), 328 (28.0), 95 (51.7), 81 (38.6), 71 (25.8), 57 (50.6), 55 (52.8), and 43 (100).

We thank Professors T. Masamune and T. Matsumoto in this Department for their interest in this work. We also thank Mr. Chi-Ming Shea for the experiments with regard to inter-conversions of the 6β- and 6α-iodides (3) and (4), Mrs. T. Okayama and Miss H. Maki for the n.m.r. spectra and spin decoupling experiments, and Mr. K. Matsushita of the Application laboratory, JEOL Ltd., for the measurement of the $^{13}C$ n.m.r. spectrum of compound (18).

[9/1596 *Received*, 9*th October*, 1979]

REFERENCES

[1] Part 50, H. Suginome and Chi-Ming Shea, *J.C.S. Perkin I*, 1980, 2268.

[2] (*a*) Preliminary communications; H. Suginome and K. Kato, *Tetrahedron Letters*, 1973, 4139; (*b*) H. Suginome, A. Furusaki, K. Kato, and T. Matsumoto, *ibid.*, 1975, 2757.

[3] (*a*) H. Suginome, N. Sato, and T. Masamune, *Tetrahedron Letters*, 1969, 3353; *Tetrahedron*, 1971, **27**, 4863; H. Suginome, T. Mizuguchi, and T. Masamune, *J.C.S. Chem. Comm.*, 1972, 376; *Tetrahedron Letters*, 1971, 4723; *J.C.S. Perkin I*, 1976, 2365; H. Suginome, T. Mizuguchi, S. Honda, and T. Masamune, *J.C.S. Perkin I*, 1977, 927; (*b*) H. Suginome, T. Tsuneno, N. Sato, and T. Masamune, *Tetrahedron Letters*, 1972, 661; H. Suginome, T. Tsuneno, N. Sato, N. Maeda, and T. Masamune, H. Shimanouchi, Y. Tsuchida, and Y. Sasada, *J.C.S. Perkin I*, 1976, 1297; (*c*) H. Takahashi, M. Ito, and H. Suginome, *Chem. Letters*, 1977, 241; H. Takahashi, M. Ito, H. Suginome, and T. Masamune, *ibid.*, 1979, 901.

[4] For a review of the 'hypoiodite reaction' see K. Heusler and J. Kalvoda, *Angew. Chem.*, 1964, **76**, 518; J. Kalvoda and K. Heusler, *Synthesis*, 1971, 501.

[5] M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, 1964, **86**, 1528.

[6] (*a*) R. H. Pickard and J. Yates, *J. Chem. Soc.*, 1908, **93**, 1678; (*b*) T. Westphalen, *Ber.*, 1915, **48**, 1064; (*c*) L. F. Fieser and S. Rajagopalan, *J. Amer. Chem. Soc.*, 1949, **71**, 3938.

[7] V. A. Petrow, *J. Chem. Soc.*, 1937, 1077.

[8] R. B. Clayton, H. B. Henbest, and M. Smith, *J. Chem. Soc.*, 1957, 1982.

[9] This product (2) was erroneously formulated as 4-iodo-3,4-secocholest-5-en-3-al in our preliminary communication.[2a] We gratefully acknowledge the kindness of Professor J. Wolinsky, Department of Chemistry, Purdue University, for informing us of the inadequacy of the assigned formula of compound (2) and for suggesting a possibility of the formate structure; he based his view on his spectral comparisons with 6-chloro-3,4-secocholest-4-en-3-als (J. Wolinsky, personal communication).

[10] O. E. Edwards and M. Lesage, *Canad. J. Chem.*, 1963, **41**, 1592; D. G. Kowalewski and V. J. Kowalewski, *Mol. Phys.*, 1964, **8**, 93.

[11] N. F. Chamberlain 'The Practice of NMR Spectroscopy' Plenum Press, New York, 1974, pp. 131 and 141.

[12] H. Suginome and K. Kato, *Tetrahedron Letters*, 1973, 4143.

[13] G. C. Levy and G. L. Nelson, 'Carbon-13 Nuclear Magnetic Resonance for Organic Chemists,' Wiley Interscience, New York, 1972; H. J. Reich, M. Jautelat, M. Y. T. Messe, F. J. Weigert, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1969, **91**, 7445; '$^{13}C$ FT NMR Spectra,' vol. 1, JEOL Ltd., Tokyo, 1974.

[14] R. S. Rosenfeld, D. K. Fukushima, L. Hellman, and T. F. Gallagher, *J. Biol. Chem.*, 1954, **211**, 301.

[15] R. B. Woodward, A. A. Patchett, D. H. R. Barton, D. A. J. Ives, and R. B. Kelly, *J. Chem. Soc.*, 1957, 1131.

[16] (*a*) G. Ferguson, E. W. Macaulay, J. M. Midgley, J. M. Robertson, and W. B. Whalley, *Chem. Comm.*, 1970, 954; (*b*) U. Burkert and N. L. Allinger, *Tetrahedron*, 1978, **34**, 807; (*c*) D. A. Dougherty, K. Mislow, J. W. Huffman, and J. Jacobs, *J. Org. Chem.*, 1979, **44**, 1585.

[17] M. Akhtar and S. Marsh, *J. Chem. Soc.* (*C*), 1966, 937; C. P. Forbes, A. Goosen, and H. A. H. Laue, *J. S. African Chem. Inst.*, 1972, **25**, 144; C. P. Forbes, A. Goosen, and H. A. H. Laue, *J.C.S. Perkin I*, 1974, 2346.

[18] R. C. Cambie, R. C. Hayward, B. G. Lindsay, A. I. T. Phan, P. S. Rutledge, and P. D. Woodgate, *J.C.S. Perkin I*, 1976, 1961.

[19] A. C. Cope, R. S. Bly, M. M. Martin, and R. C. Petterson, *J. Amer. Chem. Soc.*, 1965, **87**, 3111; A. C. Cope, M. Gordon, S. Moon, and C. H. Park, *J. Amer. Chem. Soc.*, 1965, **87**, 3119; J. R. Hanson, *Tetrahedron*, 1966, **22**, 1701.

[20] R. K. Freidlina, in 'Advances in Free Radical Chemistry,' vol. 1, ed. G. H. Williams, Logos Press, London, 1965, p. 271.

[21] C. W. Shoppee, M. I. Akhtar, and R. E. Lack, *J. Chem. Soc.*, 1964, 877; E. S. Huyser and J. R. Jeffrey, *Tetrahedron*, 1965, **21**, 3083; P. D. Readio and P. S. Skell, *J. Org. Chem.*, 1966, **31**, 759; F. G. Bordwell, P. S. Landis, and G. S. Whitney, *J. Org. Chem.*, 1965, **30**, 3764; R. M. Dodson, P. B. Sollman, and J. R. Deason, *J. Org. Chem.*, 1965, **30**, 2009; S. J. Cristol and J. A. Reeder, *J. Org. Chem.*, 1961, **26**, 2182; N. A. LeBel and A. DeBoer, *J. Amer. Chem. Soc.*, 1967, **89**, 2784; J. G. Traynham, A. G. Lane, and N. S. Bhacca, *J. Org. Chem.*, 1969, **34**, 1302.

[22] M. F. Flies, R. Lalande, and B. Maillard, *Tetrahedron Letters*, 1976, 439.

[23] A. Butenandt and J. Schmid-Thome, *Ber.*, 1936, **69**, 882.

[24] L. Ruzicka and J. Meyer, *Helv. Chim. Acta.*, 1934, **17**, 1407.

[25] F. W. Newman, N. B. Sommer, C. C. Kaslow, and R. L. Shriner, *Org. Synth.*, Coll. Vol. III, 1955, 519.

[26] 'International Tables for *X*-Ray Crystallography,' Kynoch Press, Birmingham, 1962, vol. 3.