Photoinduced Transformations. 73.[1] Transformations of Five- (and Six-) Membered Cyclic Alcohols into Five- (and Six-) Membered Cyclic Ethers—A New Method of a Two-Step Transformation of Hydroxy Steroids into Oxasteroids[2]

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We set out to describe a two-step transformation of saturated hydroxy steroids into oxasteroids with an oxygen-containing ring of the same size as that of the starting ring. The irradiation of the hypoiodites generated in situ by means of the reaction of the hydroxy steroids with an excess of mercury(II) oxide and iodine gives novel formates arising from the successive reactions triggered by a β-scission of the corresponding alkoxy radical. These formates can readily be transformed into oxasteroids by a treatment with a complex metal hydride or methyllithium. The method is exemplified by the transformations of 1-, 3-, and 17-hydroxy steroids into the corresponding oxasteroids. Experiments in which we have used ^{18}O labeled mercury(II) oxide as a source of $I_2{}^{18}O$ provide evidence that the oxygen atom in the oxasteroids is derived from the hydroxyl group of the starting alcohol and not from the oxygen of mercury(II) oxide. This suggests that the pathway of the formation of the formates involves (a) β-scission of the corresponding alkoxy radical to give a carbon centered radical intermediate with a carbonyl group, (b) its intramolecular combination with the carbonyl oxygen to form a tetrahydropyranyl radical or an oxepanyl radical, (c) its reaction with iodine oxide or ·OI to generate a new hypoiodite, and (d) a regiospecific β-scission of the second alkoxy radical generated from it.

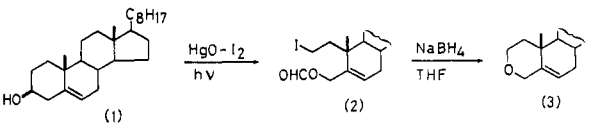
We have recently reported an unusual photoinduced radical rearrangement of cholesteryl hypoiodite (1), generated in situ by an excess of mercury(II) oxide and iodine,[3,4] to 2-iodo-A-nor-2,3-secocholest-5-en-3-yl formate (2) with accompanying formation of some other epoxy compounds.[5] Treatment of this formate with sodium borohydride in THF under reflux then readily gives 3-oxacholest-5-ene (3) in nearly quantitative yield (Scheme I).[5]

We reasoned that this novel photoinduced radical rearrangement, which can be carried out under nearly neutral conditions at room temperature, could be used to achieve an efficient synthesis of otherwise rather inaccessible oxasteroids from readily available saturated hydroxy steroids.

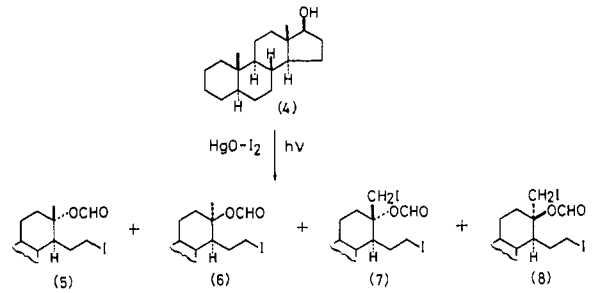
In this paper, we report full details of our new method[2] for a two-step transformation of saturated hydroxy steroids into oxasteroids with an oxygen-containing ring of the same size as that of the starting ring that carries the hydroxyl group.

Thus, 5α-androstan-17β-ol (4) in benzene containing mercury(II) oxide and iodine (each 3 mol equiv) in a Pyrex vessel was irradiated by a 100-W high-pressure mercury arc for 3 h under a nitrogen atmosphere to give a mixture of products. Separation of the products by preparative TLC gave one major fraction and two minor fractions. The PMR and IR spectra of the major fraction immediately indicated that it was a mixture of two expected formates, 16-iodo-D-nor-16,17-seco-5α-androstan-13α-yl formate (5) and its 13β-isomer (6) (Scheme II). The combined yield of the two formates was 48%. Spectral studies indicated that each of the two minor fractions was also a single formate with two iodine atoms each. High-resolution mass spectrometry of formates 7 and 8 indicated the molecular formula $C_{19}H_{30}I_2O_2$ for each. Their ^1H NMR spectra were consistent with the structure 16,18-diiodo-D-nor-16,17-seco-5α-androstan-13ξ-yl formate for 7 and 8. The configurations of their 13-substituents are not unambiguous but an inspection of the Dreiding models of 7 and 8 indicated that rotation of the C-13–CH_2I bond is likely to be more hindered in the formate containing 13α-iodo-

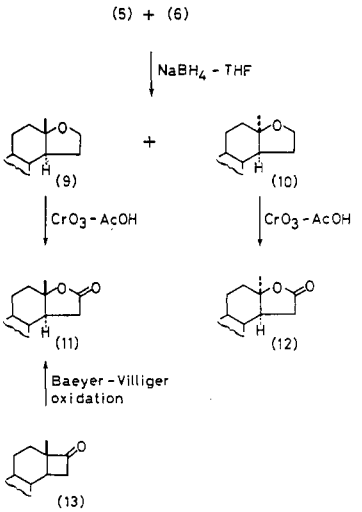
Scheme I



Scheme II



Scheme III



(1) Part 72: Suginome, H.; Yamada, S. *Tetrahedron Lett.*, in press.
(2) Preliminary communications: Suginome, H.; Yamada, S. *Chem. Lett.* **1982**, 1233. Suginome, H.; Yamada, S.; Miyaura, N. *Ibid.* **1983**, 55.
(3) Akhtar, M.; Barton, D. H. R. *J. Am. Chem. Soc.* **1964**, *86*, 1528.
(4) For a review of "the hypoiodite reaction" using this reagent, see: Kalvoda, J.; Heusler, K. *Synthesis* **1971**, 501.
(5) Suginome, H.; Furusaki, A.; Kato, K.; Maeda, N.; Yonebayashi, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 236.

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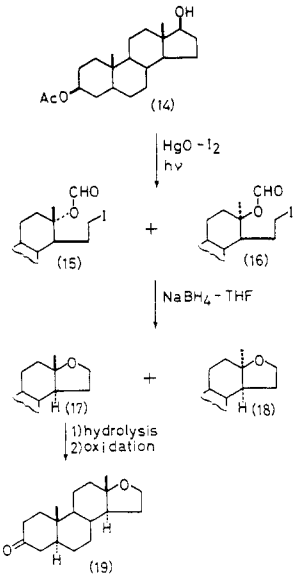
Scheme IV



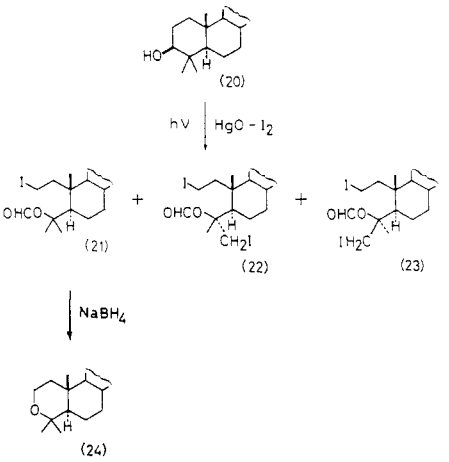
methyl. Signals due to the 13α-iodomethyl group should, therefore, be expected to appear as a clearer AB quartet. Since the signal due to the 13-iodomethyl group of **8** appeared as a sharper AB quartet, the 13-iodomethyl group of formate **8** is likely to be α-oriented. The mechanism of their formation is discussed later in this paper.

Treatment of the mixture of formates **5** and **6** with sodium borohydride in THF under reflux for 3.5 h gave a mixture of 17-oxa-5α-androstane (**9**) (72%) and 17-oxa-5α,13α-androstane (**10**) (9%) which were separable by preparative TLC. The configurations of their 13-methyl group were established by transforming them into the corresponding lactones (**11** and **12**) and by comparing the lactones with the authentic 17-oxa-5α-androstan-16-one (**11**). Thus, oxidation of **9** in acetic acid and water with chromium trioxide at 50–70 °C gave 17-oxa-5α-androstan-16-one (92% yield); this was identical with a specimen obtained by Baeyer–Villiger oxidation of D-nor-5α-androstan-16-one,[6] confirming the β configuration of the 13-methyl group. Similar oxidation of isomeric **10** gave an isomeric lactone, 17-oxa-5α,13α-androstan-16-one (**12**).

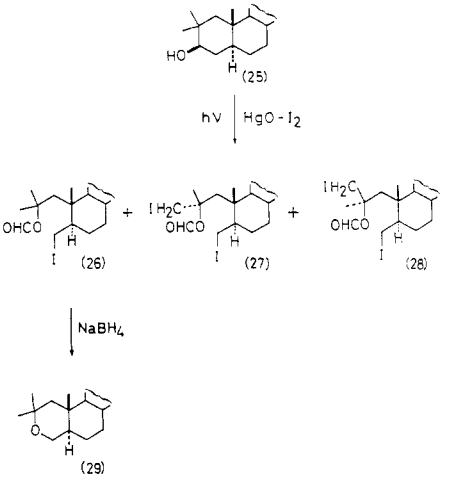
The above experiments confirmed that the procedure described above is useful for the preparation of oxasteroids. We have therefore used this procedure in order to synthesize 17-oxa-5α-androstan-3-one (**19**), which Rahkit and Gut prepared via eight steps from 3β-acetoxy-5α-androstan-17-one[7] and which is, to our knowledge, the only five-membered D ring oxasteroid ever reported (Scheme IV). The treatment of 5α-androstan-3α,17β-diol 3-acetate (**14**) by the above procedure gave a mixture of isomeric formates **15** and **16** in a combined yield of 60%. This mixture was then transformed into isomers of the oxasteroids **17** and **18** in THF with sodium borohydride. The mixture of oxasteroids was separated into its components by means of preparative TLC to give **17** in a 37% yield. Its hydrolysis with methanolic potassium hydroxide afforded 17-oxa-5α-androstan-3β-ol. Oxidation of the 3β-ol with Jones reagent gave 17-oxa-5α-androstan-3-one (**19**).[7] The overall yield of **19** from **14** was 20%.

The present procedure thus provides a convenient and useful method for synthesizing 17-oxasteroids with functional groups.

Scheme V



Scheme VI

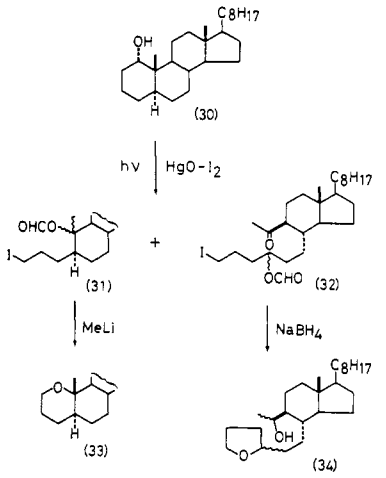


Attempts were then made to apply the present method to the synthesis of six-membered oxasteroids (Schemes V and VI). Irradiation of 4,4-dimethyl-5α-cholestan-3β-ol (**20**)[8] in benzene containing mercury(II) oxide and iodine gave 3,3-dimethyl-3-(formyloxy)-2-iodo-2,3-seco-A-nor-5α-cholestane (**21**) in a 38% yield. As in the case of 5α-androstan-17β-ol, two minor diiodo formates, **22** and **23**, were also formed during this reaction. Spectral properties of the two diiodo formates were in agreement with the structures 3-(formyloxy)-2-iodo-3-(iodomethyl)-3-methyl-2,3-seco-A-nor-5α-cholestane (**22**) and its 3-epimer (**23**). The formate **21** was again smoothly transformed into 4,4-dimethyl-3-oxa-5α-cholestane (**24**) by heating under reflux in THF containing sodium borohydride in a 60% yield.

2,2-Dimethyl-5α-cholestan-3β-ol (**25**)[9] can similarly be transformed into 2,2-dimethyl-3-oxa-5α-cholestane (**32**) (Scheme VI). Irradiation of 3β-ol (**25**), under the conditions described above, gave 2,2-dimethyl-2-(formyloxy)-3-iodo-2,3-seco-A-nor-5α-cholestane (**26**) as the major product (49% yield) together with isomeric 2-(formyloxy)-3-iodo-2-(iodomethyl)-2,3-seco-A-nor-5α-cholestanes (**27** and **28**) as the minor products. The results were entirely analogous to those obtained in the reaction of 4,4-dimethyl isomer (**20**). The formate (**26**) was again transformed into 2,2-dimethyl-3-oxa-5α-cholestane (**29**) with

(6) Suginome, H.; Uchida, T.; Kizuka, K.; Masamune, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2285.
(7) Rahkit, S.; Gut, M. *J. Org. Chem.* **1964**, 230.
(8) Mazur, Y.; Sondheimer, F. *J. Am. Chem. Soc.* **1958**, *80*, 5220. Chaudhry, G. R.; Halsall, T. G.; Jones, E. R. H. *J. Chem. Soc.* **1961**, 2725.
(9) (a) Mazur, Y.; Sondheimer, F. *J. Am. Chem. Soc.* **1958**, *80*, 5220. (b) Biellmann, J. F.; Witz, P. *Bull. Soc. Chim. Fr.* **1964**, 737.

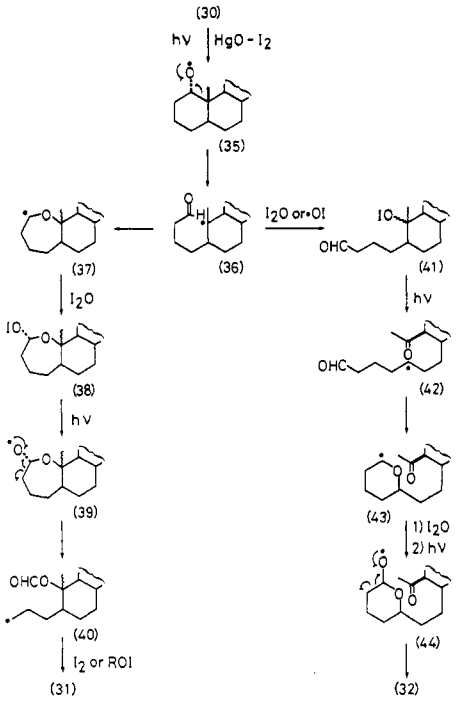
Scheme VII



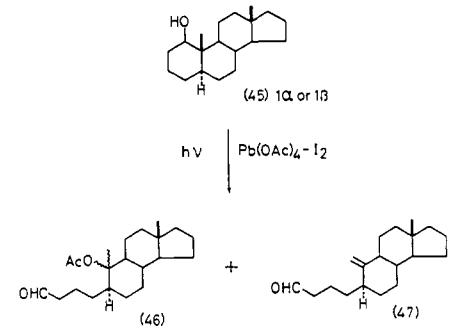
$NaBH_4$ in THF in a 64% yield.

1α-Hydroxy-5α-cholestane (**30**) can similarly be transformed by the present method into hitherto undescribed 1-oxa-5α-cholestane (**33**), *albeit* in a low yield (Scheme VII). Thus, the treatment of **30**[10] under the conditions described above gave a mixture of products from which two products **31** and **32** were isolated by preparative TLC and their structures were clarified. Spectral studies confirmed that the minor product **31** obtained in a 8% yield was the expected formate. High-resolution mass spectrometry revealed that the molecular formula was $C_{27}H_{47}IO_2$. The ^1H NMR spectrum was consistent with the structure, 10ξ-(formyloxy)-1-iodo-10,1-seco-A-nor-5α-cholestane. While attempts to cyclize formate **31** to 1-oxa-5α,10ξ-cholestane (**33**) by treatment with $NaBH_4$ under the conditions described above failed, we were nevertheless able to achieve the cyclization to 1-oxasteroid **33** by treatment with methyllithium instead of $NaBH_4$. We have not been able to establish the configuration of the 10-methyl group of **33** but a study of the Dreiding model of the isomers of **31** suggested that the intramolecular nucleophilic cyclization of 10β-(formyloxy)-1-iodo-1,10-seco-A-nor-5α-cholestane is likely to be difficult. It is therefore very probable that the obtained oxasteroid **33** is a more stable A/B trans 1-oxa-5α-cholestane having a 10β-methyl group as shown. Although the IR and ^1H NMR spectra of **35** proved that it is also an iodo formate, high-resolution mass spectrometry showed that it has a molecular formula $C_{27}H_{47}IO_3$. It is not therefore isomeric with the formate **34**. Besides the signals due to the formyloxy group, the ^1H NMR spectrum showed a singlet at δ 2.15 assignable to an acetyl group and a 2 H triplet at δ 3.17 assignable to a methylene group having an iodine and a 1 H multiplet at δ 4.95 assignable to a methine proton containing a formyloxy group. The ^1H NMR spectrum was devoid of a signal due to the presence of the 19-H of cholestane. Treatment of the formate **32** with $NaBH_4$ in THF under reflux gave a product **34**, whose molecular formula was determined by high-resolution mass spectrometry to be $C_{26}H_{48}O_2$. The ^1H NMR and the IR spectra indicated that the original formyloxy and $-CH_2I$ groups were lost by forming a cyclic ether in this transformation. Jones oxidation of **34** gave a ketone. A seco structure **32** and a tetrahydrofuran structure **33** accommodate all the above spectral data and the above chemical behavior. The formation of **31** and **32** can reasonably be understood by assuming the pathway shown in Scheme VIII involving a

Scheme VIII



Scheme IX



common intermediate **36** generated by a β-scission of an alkoxyl radical **35**. Both the pathway from **36** to the formates **31** and **32** involve the intramolecular combination between carbonyl oxygen and carbon-centered radical of the intermediary species. This process has been confirmed by an ^{18}O labeling study and will be discussed later in this paper. A minor formate **31** may thus be formed via **37**, **38**, **39**, and **40** while a major fraction of **36** reacts with I_2O to give an open chain hypoiodite **41** to give a secondary carbon-centered radical (**42**) by a β-scission. This radical gives the observed iodo formate **32** via **43** and **44** as depicted.

A lead tetraacetate oxidation of 5α-cholestan-1-ol[11] or a lead tetraacetate–iodine oxidation of 5α-androstan-1β- and -1α-ols (**45**) have already been reported.[12] Although both the oxidations involve an alkoxy radical as an intermediate, a lead tetraacetate–iodine oxidation of **45** is more relevant to the present investigation since lead tetraacetate–iodine is known to be another good reagent[13] for generating the hypoiodites. Thus, Mutzenbecher and Cross[12] have reported that both 5α-androstan-1α- and -1β-ols (**45**) gave a mixture of oily products when treated

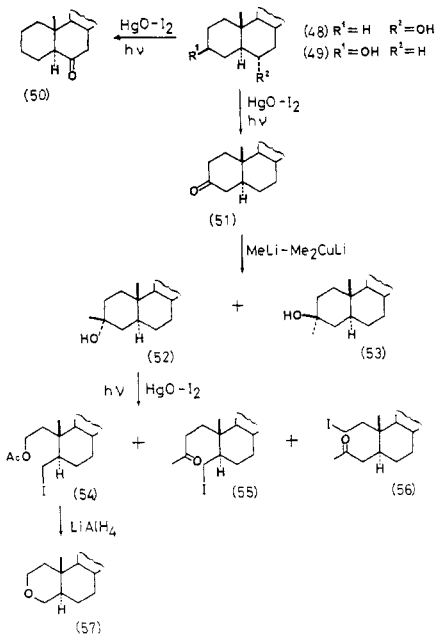
(10) Djerassi, C.; Williams, D. H.; Berkoz, B. *J. Org. Chem.* **1962**, *27*, 2205.

(11) Stefanović, M.; Casić, M.; Lorenc, L.; Mihailović, M. L. *Tetrahedron* **1964**, *20*, 2289.

(12) Von Mutzenbecher, G.; Cross, A. D. *Steroids* **1965**, 429.

(13) Meystre, C.; Heusler, K.; Kalvoda, J.; Wieland, P.; Anner, G.; Wettstein, A. *Helv. Chem. Acta* **1962**, *45*, 1317 and later papers. For a review, see: Heusler, K.; Kalvoda, J. *Angew. Chem.* **1964**, *76*, 518.

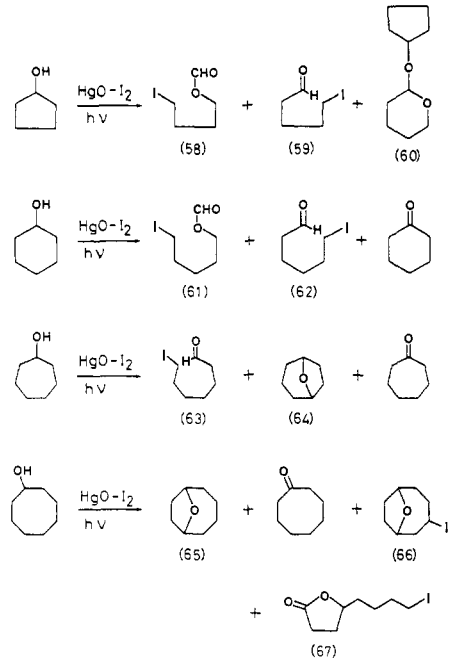
Scheme X



with 2 molar equiv of lead tetraacetate and iodine under exposure to a General Electric 150-W projector flood lamp. They isolated two oily compounds **46** and **47** from the products for which they assigned the seco structures as shown in Scheme IX.

We then attempted to transform 5α-cholestan-6α-ol[14] **48** and -3β-ol[15] **49** into 6-oxa-5α-cholestane and 3-oxa-5α-cholestane by means of the present procedure (Scheme X). Prolonged irradiation of 5α-cholestan-6α-ol and -3β-ol in the presence of mercury(II) oxide and iodine, however, afforded only 5α-cholestan-6-one[16] (**50**) and 5α-cholestan-3-one[17] (**51**) that arise from disproportionations while none of the formates which stem from β-scission was obtained. We then converted the 3β-ol into 3β-methyl-5α-cholestan-3α-ol (**52**)[18] via its oxidation to 3-one **51** followed by a stereoselective methylation with a MeLi–Me_2CuLi reagent.[19] Irradiation of a benzene solution of 3α-ol **52** in the presence of mercury(II) oxide and iodine resulted in the expected β-scission and gave three products, **54**, **55**, and **56**. The IR, ^1H NMR, and mass spectra of a minor product **54**, obtained in a 7% yield, indicated that the structure was 3-iodo-A-nor-2,3-seco-5α-cholestan-2-ol acetate. Products **55** and **56** were obtained as an inseparable mixture but the studies of the IR, ^1H NMR, and mass spectra of the mixture indicated that it was a 63:37 mixture of 2-acetyl-3-iodo-2,3-seco-A-nor-5α-cholestane (**55**) and 3-acetyl-2-iodo-2,3-seco-A-nor-5α-cholestane (**56**). The assignments of the signals in the ^1H NMR spectrum of the mixture are described in the Experimental Section. It is interesting to note that iodides **55** and **56** which stem from the direct combination of a carbon-centered radical, generated by a β-scission with an iodine atom, are formed while the corresponding reaction of cholesterol did not give any iodides of this type.[5] The ^1H NMR spectra of acetate **54** and iodide **55** showed that the signals that are due to the 3-H appeared as the doublet of a doublet and thus

Scheme XI



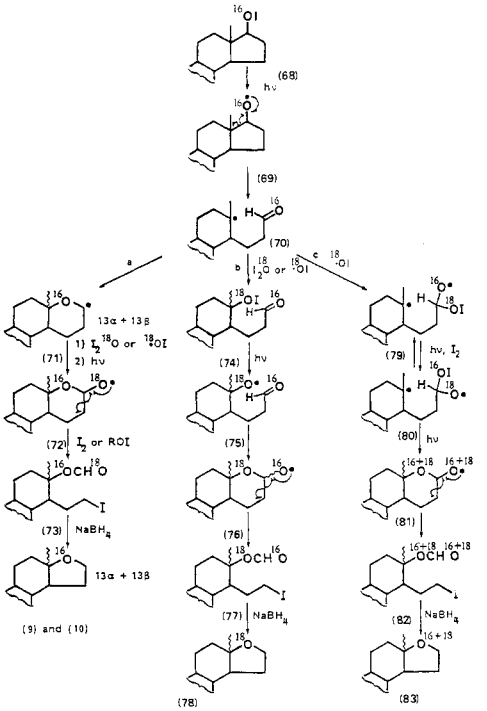
confirmed the substantial hindrance of the rotation around their C-3–C-5 bond. The ^1H NMR spectrum revealed that this rotation is also hindered in the C-1–C-2 bond of iodide **56**. A reflux of the acetate **54** in THF containing $NaBH_4$ did not afford the expected 3-oxa-5α-cholestane (**57**), although it was able to cyclize to give **57** in a good yield by the replacement of $NaBH_4$ by $LiAlH_4$. The scope of the synthesis of cyclic ethers by the present method can thus be extended to the cyclic alcohols, whose alkoxy radicals are reluctant to cleave, by converting them into the tertiary alcohols beforehand.

Finally, we studied the photolysis of the hypoiodites of conformationally mobile five- to eight-membered monocyclic alcohols (Scheme XI). Irradiation of cyclopentanol hypoiodite generated in situ by an excess of mercury(II) oxide and iodine gives rise to a 4-iodobutyl alcohol formate (**58**) as a major product (16%) with an accompanying formation of 5-iodopentanal (**59**)[20] (8%) and a cyclopentyl tetrahydropyranyl ether (**60**) (7%). The reaction of cyclohexanol similarly gave a 5-iodopentyl alcohol formate (**61**) (3%) together with 6-iodohexanal (**62**) (8%) and cyclohexanone (23%). The formates arising from β-scission are thus analogously formed by irradiation of the hypoiodites of the five- and six-membered monocyclic alcohols although their yield was low. Irradiation of cycloheptanol hypoiodite, however, gave not a formate but 7-iodohexanal (**63**) (2%), cycloheptanone (27%), and 1,4-epoxycycloheptane[21,22] (**64**) (11%). The results are analogous to those derived from the lead tetraacetate oxidation of cycloheptanol,[21,22] with the exception of the formation of 7-iodohexanal.

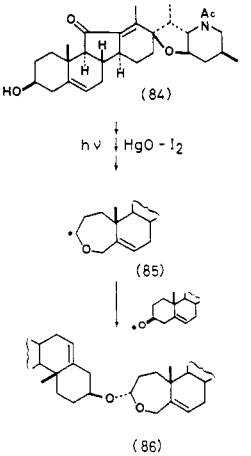
The reaction of cyclooctanol under the conditions described above was found to give four products. Two of them were 1,4-epoxycyclooctane (**65**) (13%) and cyclooctanone (19%). But the other two were new products. Spectral studies indicated that they were 6-iodo-1,4-epoxycyclooctane (**66**) (7%) and a γ-lactone (**67**) resulting

(14) Dauben, W. G.; Deviny, E. J. *J. Org. Chem.* **1966**, *31*, 3794.
(15) "Organic Syntheses"; Wiley: New York, 1943; Collect. Vol. 2, p 191.
(16) Tschesche, R. *Chem. Ber.* **1932**, *65*, 1932.
(17) Reference 15, p 139.
(18) (a) Barton, D. H. R.; Campos-news, A. S.; Cookson, R. C. *J. Chem. Soc.* **1956**, 3500. (b) Barnes, C. S.; Palmer, A. *Aust. J. Chem.* **1956**, *9*, 105. (c) Patel, M. S.; Peal, W. J. *Tetrahedron* **1964**, *20*, 2511.
(19) Macdonald, T. L.; Still, W. C. *J. Am. Chem. Soc.* **1975**, *97*, 5280.
(20) Akhtar, M.; Hunt, P.; Dewhurst, P. B. *J. Am. Chem. Soc.* **1965**, *87*, 1807.
(21) Cope, A. C.; Gordon, M.; Moon, S.; Park, C. H. *J. Am. Chem. Soc.* **1965**, *87*, 3119.
(22) Mihailović, M. L.; Ceković, Z.; Andrejević, V.; Jeremmic, D. *Tetrahedron* **1968**, *24*, 4947.

Scheme XII



Scheme XIII



from a β-scission (2%). None of the formates, however, was detected in the products. The pathway, by which the γ-lactone is formed, has not been defined, although several pathways can be envisaged for its formation. It has been reported that the lead tetraacetate oxidation of cyclooctanol gives 1,4-epoxycyclooctane (**64**)[21,22] and 1,5-epoxycyclooctane.[22]

Mechanism. An initial intermediate in the transformation of the hypoiodites [e.g., **68**] into the formates [e.g., **5**, **6**, **7**, and **8** in Scheme II] is a carbon-centered radical [e.g., **70**] formed by a β-scission[23] of the corresponding alkoxy radical [e.g., **69**] (Scheme XII).

Three radical pathways (a, b, and c) are possible for the formation of the formates from the carbon-centered radical intermediate **70**, as shown in Scheme XII. Thus, in the path a, the carbon-centered radical **70** combines intramolecularly with the carbonyl oxygen to form a tetrahydropyranyl radical **71** which reacts with iodine oxide or ·OI to generate a new hypoiodite. This hypoiodite may generate a second alkoxy radical **72** by irradiation and the β-scission gives the observed formate **73**. Alternatively, iodine oxide or ·OI may combine with the carbon-centered radical **70** directly to form a second hypoiodite **74**. This then generates the corresponding alkoxyl radical **75** by irradiation, which intramolecularly attacks the carbonyl carbon of the aldehyde to form a new alkoxyl radical **76**. The β-scission leads to the observed formates **77**. In a third pathway c, ·OI reacts with the carbonyl carbon of the carbon-centered radical intermediate **70** to form a hypothetical species such as **79**. This species may rearrange to another hypoiodite under the reaction conditions, as depicted, and the successive reactions via **81** involving this scrambling may give formate **82** (Scheme XII).

Which of these paths is operative can be distinguished by experiments which use ^{18}O labeled mercury(II) oxide as a reagent to generate $I_2{}^{18}O$. We confirmed that the formates **5** and **6** (Scheme II) derive from path a and not by path b or c by the following ^{18}O labeling study.

5α-Androstan-3β,17β-diol 3-acetate **14** was transformed into a mixture of formates **15** and **16** with mercury(II) oxide-^{18}O (48.9 atom% ^{18}O) and iodine under the above conditions. The mixture of the formates was converted into a mixture of oxasteroids which was separated to its components **17** and **18**. The extent of the incorporation of ^{18}O into **17** was then analyzed by mass spectrometry. The mass spectra showed that there is no incorporation of ^{18}O in **17**. The ^{18}O labeling study was performed also on 4,4-dimethyl-5α-cholestan-3β-ol (**20**) (Scheme V). The 3β-ol **20** was converted into formate **23** with mercury(II) oxide-^{18}O and iodine, and 4,4-dimethyl-3-oxa-5α-cholestane **24** obtained by its cyclization was analyzed by mass spectrometry. This again indicated no incorporation of ^{18}O into the oxasteroid.

These isotopic labeling experiments provide conclusive evidence that the oxygen atom in the oxasteroids is derived from the hydroxyl group of the starting alcohols and not from the oxygen of mercury(II) oxide and that the formates are formed by path a in Scheme XII, since ^{18}O should wholly or partly be incorporated in the 17-oxygen of oxasteroid **71** or **83** if they were formed via path b or c. It should be noted that since the epimeric formates **5** and **6** (Scheme II) are formed in the reaction of 5α-androstan-17β-ol (**4**) the rearrangement of alkoxyl radical **69** to tetrahydropyranyl radical **71** can not be a concerted process but must pass through a discrete carbon radical **70**. The formation of cyclopentyl tetrahydropyranyl ether (**60**) from cyclopentanol further supports the likelihood of the intervention of a discrete tetrahydropyranyl radical **71**. In this case, an intermediate **71** is trapped by the initially formed alkoxy radical. We previously found the formation of an analogous acetal in the photoreaction of a six-membered cyclic akcohol: the photolysis of the hypoiodite of *N*-acetyljervine **84** under the above experimental conditions therefore affords *N*-acetyl-11-oxojerva-5,12(13)-dien-3β-yl *N*-acetyl-A-homo-4-oxa-11-oxajerva-5,12(13)-dien-3α-yl ether (**86**) as the major product, proving the intervention of the oxepanyl radical **85** shown in Scheme XIII.[24]

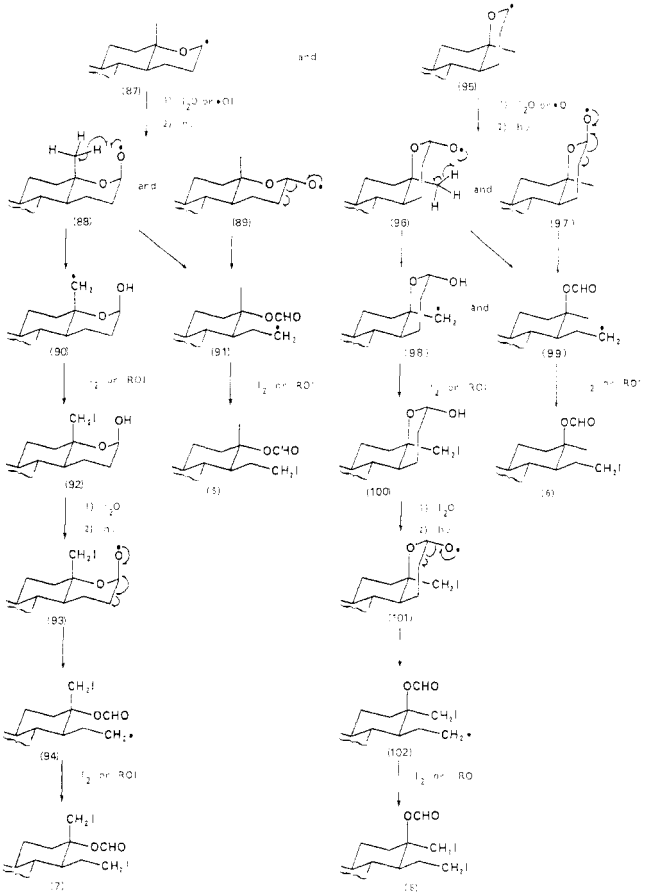
A carbon-centered radical intermediate equivalent to **70** is also generated in the photolysis of a nitrite corresponding to hypoiodite **68**.[25] In the nitrite photolysis, however, the

(23) For reviews, see: Walling, C. "Free Radicals in Solution"; Willey: New York, 1957; p 397. Kochi, J. K. In "Free Radicals"; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 2, p 665. Surzur, J. M. In "Reactive Intermadiates"; Abramovitch, R. A., Ed.; Plenum Press: New York, 1982; Vol. 2, p 121.

(24) Suginome, H.; Kato, K.; Masamune, T. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 3042.

(25) Robinson, C. H.; Gnoj, O.; Mitchell, A.; Oliveto, E. P.; Barton, D. H. R. *Tetrahedron* **1965**, *21*, 743. Suginome, H.; Yonekura, N.; Mizuguchi, T.; Masamune, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 3010.

Scheme XIV

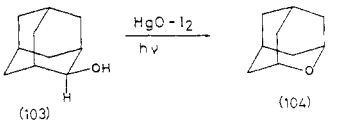


tertiary carbon-centered radical **70** combined with nitric oxide instead of with the carbonyl oxygen of the formyl group in the molecule. In the hypoiodite photolysis, the combination of bulky ·OI or I_2O with the tertiary carbon radical center of **70** may be sterically hindered so that the intramolecular combination with the carbonyl oxygen is the preferred course of the reaction of the intermediate **70**.

An epimeric pair of diiodo formates (**7** and **8** derived from **4**, **22** and **23** from **20**, and **27** and **28** from **5**) were always found to be accompanying minor products. The formation of these diiodo compounds can readily be accounted for within the framework of the pathway a shown in Scheme XII. The pathway of the formation of an epimeric pair of diiodo formates **7** and **8** from the hypoiodite of 5α-androstan-17β-ol (**4**) (Scheme II) is shown in Scheme XIV. As shown in Scheme XIV, a pair of axial (**88** and **96**) and equatorial (**89** and **97**) alkoxy radicals are generated from *trans*-**87** and *cis*-**95** fused tetrahydropyranyl radicals formed from the intermediate **71** with iodine oxide or ·OI radical. The axial alkoxy radical in cis and trans forms can collapse either by abstracting a hydrogen of the 13-methyl group to give a new carbon-centered radical **90** and **98** or by giving a new radical **91** and **99** by means of a β-scission. The iodo formates **5** and **6** are formed by the reactions of **91** and **99** with I_2O or ROI. On the other hand, the radicals **90** and **98** generate alcohols **92** and **100** and these alcohols finally generate a pair of observed diiodo formates **7** and **8** via the formation of the hypoiodites and its β-scission. Diiodo formates **22** and **23** from 3β-ol **20** and diiodo formates **27** and **28** from 3β-ol **25** should be formed via the pathways analogous to that shown in Scheme XIV.

The formation of the tetrahydropyranyl radical from the carbon-centered radical represents a novel intramolecular combination of a carbonyl oxygen with a carbon radical.

Scheme XV



An analogous intramolecular interaction between a carbonyl oxygen and a carbon radical has been postulated for the formation of 2-phenyltetrahydrofuran in the reduction of γ-chlorobutyrophenone with tributyltin hydride.[26]

Treatment of adamantan-2-ol (**103**) in benzene with mercury(II) oxide and iodine, followed by irradiation at 70 °C, has been reported to yield oxaadamantane (**104**) in ca. 50% yield[27] (Scheme XV). In view of the present results it seems very likely that this reaction involves the formation of a formate and follows a course analogous to the formation of the oxasteroids from steroidal alcohol.

Conclusions

A survey of the literature indicated that only a limited number of methods for the synthesis of oxasteroids has been available and that the number of oxasteroids synthesized are not as numerous as azasteroids.[28] The foregoing experiments have shown that a variety of oxasteroids can be obtained by only a two-step procedure from hydroxy steroids, provided that the corresponding alkoxyl radical is susceptible to β-scission. This procedure should be found to be applicable in the facile transformation of hydroxy steroids into oxasteroids under virtually neutral conditions. The process has been shown to involve a novel intramolecular combination of carbonyl oxygen with carbon-centered radical. Studies of the further extention of the scope of this method are in progress and will be reported at a later date.

Experimental Section

Melting points were recorded with a Yanagimoto micro melting point apparatus. Infrared spectra were determined for Nujol mulls by a Hitachi Model 285 infrared spectrophotometer unless otherwise indicated. Proton magnetic spectra were determined by a JEOL PS 200 high-resolution FT-NMR spectrometer (200 MHz) (solvent, $CDCl_3$, $SiMe_4$ as an internal standard) unless otherwise indicated (Faculty of Pharmaceutical Sciences of this university). TLC was carried out on a Merck Kiesel gel 60-PF_{254}. The high- and low-resolution mass spectra were determined by a JEOL JMS-D-300 spectrometer (70 eV) (Faculty of Agriculture of this university).

General Procedure of the Photolysis. A benzene solution of each steroidal alcohol containing mercury(II) oxide and iodine in a Pyrex vessel was flushed with oxygen-free nitrogen gas and irradiated with a 100-W high-pressure Hg arc (EIKOSHA, PIH-100) while being stirred until all the alcohol was decomposed. The progress of the photolysis was monitored by TLC at appropriate time intervals.

Irradiation of the Hypoiodite of 5α-Androstan-17β-ol (4) in the Presence of Mercury(II) Oxide and Iodine. 5α-Androstan-17β-ol (250 mg) in dry benzene (45 mL) containing mercury(II) oxide (590 mg) and iodine (690 mg) in a Pyrex vessel was irradiated by a 100-W high-pressure Hg arc in a nitrogen atmosphere. The irradiation was discontinued after 3 h since the starting alcohol had nearly disappeared. The solution was filtered

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(27) Black, R. M.; Gill, G. B.; Hands, D. *J. Chem. Soc., Chem. Commun.* **1972**, 311.
(28) For example, see: Morand, P.; Lyall, J. *Chem. Rev.* **1968**, *68*, 85. Pettit, G. R.; Kasturi, T. R. *J. Org. Chem.* **1961**, *26*, 4557. Pettit, G. R.; Dias, J. R. *Can. J. Chem.* **1969**, *47*, 1091. Huisman, H. O.; Speckamp, W. N. In "Steroids", International Review of Science, Organic Chemistry, Johns, W. F., Ed.; Butterworths: London, 1976; Series Two, Vol. 8, p 207.
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and the filtrate was worked up in the usual manner. The oily product was subjected to preparative TLC with a 1:1 mixture of hexane–benzene to give three fractions: A (26 mg), B (42 mg), C (181 mg). The ^{1}H NMR spectrum indicated that the most mobile fraction A was a formate **8**: oil; IR (neat) 1725 (OCHO) and 1169 cm^{-1} (OCHO); ^{1}H NMR δ 0.73 (3 H, s, 19-H), 3.28 (2 H, m, CH_2CH_2I), 3.44 and 4.18 (each 1 H, each d, J = 9.76, CH_2I), and 8.01 (1 H, s, OCHO); MS, m/e 544 (M^+, 0.03%), 498 (0.1, $M^+ - OCH_2O$), 417 (0.2, $M^+ - I$), 371 (15.6, $M^+ - I - CH_2O_2$), 217 (100), and 109 (88); high-resolution mass calcd for $C_{19}H_{30}I_2O_2$ m/e 544.0333, found 544.03245.

The next mobile fraction B was an isomeric formate **7**: oil, IR (neat) 1723 (OCHO) and 1177 cm^{-1} (OCHO); ^{1}H NMR δ 0.72 (3 H, s, 19-H), 2.98–3.24 (2 H, m, CH_2CH_2I), 3.43 and 3.53 (each 1 H, each d, J = 11.23, CH_2I), and 8.01 (1 H, s, OCHO); MS, m/e 544 (M^+, 0.1%), 498 (0.8, $M^+ - 46$), 417 (0.6, $M^+ - I$), 371 (78, $M^+ - I - CH_2O_2$), 217 (40.9), 109 (94.8), and 83 (100); high-resolution mass calcd for $C_{19}H_{30}I_2O_2$ m/e 544.0333, found 544.0378.

The least mobile crystalline fraction C was a mixture of two formates **5** and **6** which was immediately transformed into a mixture of oxasteroids.

Preparation of 17-Oxa-5α-androstane (9) and 17-Oxa-5α,13α-androstane (10) from a Mixture of 13α-Hydroxy-16-iodo-13,16-sec-*D*-nor-5α-androstan-13α-ol Formate (5) and 16-Iodo-13,16-seco-*D*-nor-5α,13α-androstan-13β-ol Formate (6). The mixture of formates **5** and **6** (364 mg) obtained by the above method was dissolved in THF (30 mL) containing $NaBH_4$ (300 mg). The solution was heated under reflux for 3.5 h. The usual workup of the solution afforded a product (233 mg) which was subjected to preparative TLC with benzene–diethyl ether (20:1) to give two fractions. The more mobile fraction (20 mg) was an oily 17-oxa-5α,13α-androstane (**10**): IR (neat) 1038 cm^{-1} (C–O); ^{1}H NMR δ 0.70 (3 H, s, 18-H), 1.07 (3 H, s, 19-H), and 3.83–3.91 (2 H, m, 16-H); MS, m/e 262 (M^+, 0.2%), 248 (6), and 247 (M^+ – Me, 100); high-resolution mass calcd for $C_{18}H_{30}O$ m/e 262.2294, found 262.2284.

The less mobile fraction (165 mg) was recrystallized from acetone–methanol to yield 17-oxa-5α-androstane (**9**) (147 mg): mp 90.5–91.5 °C; IR (Nujol) 999, 1126 and 1167 cm^{-1}; ^{1}H NMR δ 0.78 (3 H, s, 18-H), 0.95 (3 H, s, 19-H), 3.77–3.97 (2 H, m, 16-H); MS, m/e 262 (M^+, 1.5) and 247 (M^+ – Me, 100%). Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.10; H, 11.44.

17-Oxa-5α-androstan-16-one (11).[6] To the solution of 17-oxa-5α-androstane (**9**) (60 mg) in acetic acid (6 mL) were added dropwise chromium trioxide (230 mg) in acetic acid (4 mL) and water (0.5 mL) at 50–70 °C (bath temperature). The solution was stirred for another 1 h at that temperature. After the solution has cooled to room temperature, water was added and the solution was twice extracted with chloroform. The chloroform layer was worked up in the usual way to give lactone **11** (58 mg). The lactone was recrystallized from acetone to yield an analytical specimen, mp 183.5–185.5 °C (lit.[6] mp 185–187 °C). This lactone was identical with an authentic specimen.

17-Oxa-5α,13α-androstan-16-one (12). To the solution of 17-oxa-5α,13α-androstane (**10**) (15 mg) in acetic acid (3 mL) were added chromium trioxide (70 mg) in acetic acid (2 mL) and water (0.5 mL) at 50–70 °C. The oxidation was carried out in the same manner as in the case of 17-oxa-5α-androstane (**9**) to yield an oily lactone (**12**). Purification of this lactone with preparative TLC with benzene–diethyl ether (10:1) gave a pure specimen (8 mg): mp 94–96 °C; IR (Nujol) 1776 cm^{-1} (lactonic CO); ^{1}H NMR δ 0.69 (3 H, s, 18-H), 1.32 (3 H, s, 19-H), 2.30 (1 H, d, J = 17.6, 15α-H), and 2.88 (1 H, dd, J = 17.6 and 6.8, 15β-H); MS, m/e 276 (M^+, 5.3%) and 261 (M^+ – Me, 100%); high-resolution mass calcd for $C_{18}H_{28}O_2$ m/e 276.2087, found 276.2077.

Irradiation of the Hypoiodite of 5α-Androstane-3β,17β-diol 3-Acetate (14) in the Presence of Mercury(II) Oxide and Iodine. 5α-Androstane-3β,17β-diol 3-acetate (**14**) (200 mg) in dry benzene (30 mL) containing mercury(II) oxide (392 mg) and iodine (456 mg) in a Pyrex vessel was irradiated by a 100-W high-pressure mercury arc in a nitrogen atmosphere for 2 h. The solution was worked up in the usual manner. The oily product (328 mg) was subjected to preparative TLC with benzene to give two fractions A and B. The more mobile fraction A (32 mg) was a mixture of two diiodo formates. The crystalline fraction B (171 mg) was recrystallized from acetone to yield iodo formate **15**: mp 178–184 °C; IR (Nujol) 1728 (CHO), and 1170 cm^{-1} (OCHO); ^{1}H NMR δ 0.77 (3 H, s, 19-H) 1.43 (3 H, s, 18-H), 2.02 (3 H, s, OAc), 3.19 (2 H, t, J = 8.3, CH_2I), 4.69 (1 H, m, 3α-H) and 8.02 (1 H, s, OCHO); MS, m/e 430 ($M^+ - OCH_2O$, 10.2%), 303 ($M^+ - OCH_2O - I$, 3.3), 289 (58.3), 243 (100), 215 (37.7), 107 (74.5), 93 (55.0), 81 (72.7), and 43 (62.7). Anal. Calcd for $C_{12}H_{33}IO_4$: C, 52.95; H, 6.98; I, 26.64. Found: C, 52.78; H, 7.03; I, 27.83.

Preparation of 17-Oxa-5α-androstan-3β-ol Acetate (17). The formate (152 mg) in THF (15 mL) containing $NaBH_4$ (120 mg) was heated under reflux for 9 h. The solution was worked up as usual. The product was subjected to preparative TLC with benzene to give two fractions A (4 mg) and B (36 mg). The less mobile fraction B was an oily oxasteroid **17**: IR (neat) 1736 (OAC), 1245 (O), and 1036 cm^{-1}; ^{1}H NMR δ (90 MHz), 0.67 (3 H, s, 19-H), 0.89 (3 H, s, 18-H), 1.92 (3 H, s, OAc), 3.71–3.88 (2 H, m, 16-H), and 4.62 (1 H, m, 3α-H); MS, m/e 320 (M^+, 0.5) and 305 (M^+ – Me, 100).

17-Oxa-5α-androstan-3β-ol. The above acetate **17** (30 mg) in methanol (2 mL) containing potassium hydroxide (15 mg) was heated under reflux for 1 h. The reaction mixture was worked up in the usual way to give a product which was recrystallized from methanol to give 17-oxa-5α-androstan-3β-ol (24 mg): mp 112–114 °C and 135–139 °C; IR (Nujol) 3350 (br, OH), and 1040 cm^{-1} (O); ^{1}H NMR δ 0.81 (3 H, s, 19-H), 0.95 (3 H, s, 18-H), 3.60 (1 H, m, 3-H), and 3.81–3.97 (2 H, m, 16-H); MS, m/e 278 (M^+, 0.8%) and 263 (M^+ – Me, 100); high-resolution mass calcd for $C_{18}H_{30}O_2$ m/e 278.2241, found 278.2241.

17-Oxa-5α-androstan-3-one (19). The above alcohol was oxidized with Jones reagent to give 3-ketone **19** in the usual way. The alcohol melted at 108–110 °C (lit.[7] mp 109–110 °C); IR (Nujol) 1175 cm^{-1} (C=O); ^{1}H NMR δ 0.98 (3 H, s, 18-H), 1.01 (3 H, s, 19-H), 3.83–3.99 (2 H, m, 16-H); MS, m/e 276 (M^+, 0.7%) and 261 (M^+ – Me, 100).

Irradiation of Hypoiodite of 4,4-Dimethyl-5α-cholestan-3β-ol (20)[8] in the Presence of Mercury(II) Oxide and Iodine. The 3β-ol (**20**) (250 mg) in benzene (30 mL) containing mercury(II) oxide (389 mg) and iodine (458 mg) in a Pyrex vessel was irradiated as in the case of 5α-androstan-17β-ol for 4 h. The solution was filtered and the filtrate was worked up in the usual manner. The oily product (332 mg) was subjected to preparative TLC with benzene–hexane (1:3) to give three fractions A–C in an order of decreasing mobility. The fraction A (28 mg) and fraction B (30 mg) were isomeric diiodo formates (**22** or **23**). The fraction C (138 mg) was the formate **21**.

22: oil; IR (neat) 1722 (CHO) and 1183 cm^{-1} (OCHO); ^{1}H NMR δ 0.64 (3 H, s, 18-H), 0.96 (3 H, s, 19-H), 1.67 (3 H, s, 3-CH_3), 3.07–3.16 (2 H, m, 2-CH_2I), 3.56 and 4.11 (each 1 H, each d, J = 10.26 CCH_2I) and 8.12 (1 H, s, OCHO); MS, m/e 638 (0.2%, $M^+ - OCH_2O$), 556 (M^+ – HI 0.3), 511 ($M^+ - OCH_2I$ 1.7), 95 (80.9), 81 (76.2), 55 (88.9) and 43 (100); high-resolution mass calcd for $C_{28}H_{48}I_2$ m/e ($M^+ - OCH_2O$) 638.1843, found 638.1821. **23**: oil; IR (neat) 1630 (OCHO), and 1170 cm^{-1} (OCHO) ^{1}H NMR δ 0.64 (3 H, s, 18-H), 0.98 (3 H, s, 19-H), 1.76 (3 H, s, 3-Me), 3.10 and 3.52 (each 1 H, each m, 3-CH_2I), 3.42 and 4.40 (each 1 H, each d, J = 11.72 Hz); MS, m/e 638 ($M^+ - OCH_2O$ 0.2%), 511 ($M^+ - OCH_2O - I$ 2.9), 95 (100), 81 (70.3), 55 (70.3) and 43 (71.3); high-resolution mass calcd for $C_{28}H_{48}I_2$ m/e ($M^+ - OCH_2O$) 638.1846, found 638.1903. **21**: IR (neat) 1725 (OCHO), 1168 and 1188 cm^{-1} (OCHO); ^{1}H NMR δ 0.64 (3 H, s, 18-H), 0.96 (3 H, s, 19-H), 1.55 and 1.60 (each 3 H, each s, 3-*gem*-Me_2), 3.10 (1 H, ddd, J = 5.7, 8.8, and 12.8 2-H), 3.45 (1 H, ddd, J = 3.8, 9.3, and 12.8, 2-H), and 8.14 (1 H, s, OCHO); MS, m/e 512 ($M^+ - OCH_2O$ 0.2%), 384 ($M^+ - OCH_2O$ – HI 100), 364 ($M^+ - OCH_2O$ – HI – Me 88.8), 271 (34.1), 95 (57.2), 81 (38.6), and 55 (31.2); high-resolution mass calcd for $C_{28}H_{49}I$ m/e ($M^+ - OCH_2O$) 512.2879, found 512.2881.

Preparation of 4,4-Dimethyl-3-oxa-5α-cholestane (24) from 3,3-Dimethyl-3-(formyloxy)-2-iodo-2,3-seco-5α-cholestane (21). The formate (**21**) (60 mg) was dissolved in THF (10 ml) containing $NaBH_4$ (70 mg). The solution was heated under reflux for 2 h. A usual workup of the solution gave a product (36 mg). This product was subjected to preparative TLC with hexane–diethyl ether (1:1) to give two fractions. The more mobile fraction (30 mg) was crystalline 4,4-dimethyl-3-oxa-5α-cholestane (**24**). It was recrystallized from acetone to give a specimen for analysis: mp 98–100 °C; IR 1095 cm^{-1} (COC); ^{1}H NMR δ 0.64 (3 H, s, 18-H), 0.98 (3 H, s, 19-H), 1.13 and 1.15 (each 3 H, each s, 4,4-Me_2) 3.65

(1 H, ddd, J = 2.4, 4.9, and 12.2, 2α-H) and 3.80 (1 H, ddd, J = 11.7, 12.2, and 2.9); MS, m/e 402 (M^+, 0.2%), 387 (64.5, M^+ – Me), 344 (17.4) and 316 (100, $M^+ - CH_2CH_2O^+{=}CMe_2$). Anal. Calcd for $C_{28}H_{50}O$: C, 83.51; H, 12.51. Found: C, 83.46; H, 12.66.

2,2-Dimethyl-5α-cholestan-3β-ol (25). This 3β-ol was prepared from the corresponding 3-one as described by Biellman:[9b] mp 145–147 °C (acetone–methanol) (lit.[9a] mp 116–118 °C; lit.[9b] mp 146–147 °C); ^{1}H NMR δ 0.64 (3 H, s, 18-H), 0.87 (3 H, s, 19-H), 0.95 (3 H, s, 2-Me), 0.97 (3 H, s, 2-Me), and 3.34 (1 H, dd, J = 4.4 and 10.7 3α-H); MS, m/e 416 (M^+, 54.0%), 401 (M^+ – Me, 8.7), 398 ($M^+ - H_2O$, 55.3), 383 ($M^+ - H_2O$ – Me, 39.6), 135 (94.1), 95 (100), 81 (78.9), 55 (75.2), and 43 (77.0).

The parent 2,2-dimethyl-5α-cholestan-3-one[9b] was prepared by a method different from the published procedure. To lithium metal (0.19 g) dissolved in liquid ammonia was added dry dioxan–dry diethyl ether (1:1) (20 mL) containing 2,2-dimethylcholest-4-en-3-one (1.5 g) dropwise for a period of 10 min. The solution was stirred for 1 h at −50 to 60 °C (dry ice–methanol). Ammonium chloride was added to the solution and the ammonia was removed. The residue was extracted with dichloromethane. The solution was worked up as usual. The residue was recrystallized from methanol to yield the 3-one, mp 102–103 °C (lit.[9a] mp 111–113 °C; lit.[9b] mp 99.5–101 °C).

Irradiation of Hypoiodite of 2,2-Dimethyl-5α-cholestan-3β-ol (25) in the Presence of Mercury(II) Oxide and Iodine. The 3β-ol (200 mg) in benzene (25 mL) containing mercury(II) oxide (311 mg) and iodine (366 mg) in a Pyrex vessel was irradiated by a 100-W high-pressure mercury arc in a nitrogen atmosphere for 4 h. The solution was filtered and the filtrate was worked up in the usual manner. The oily product was subjected to preparative TLC with a 1:3 mixture of benzene–hexane to give three fractions A (36 mg), B (26 mg), and C (130 mg). The most mobile fraction A was formate **27** or **28**: IR (neat) 1724 (CHO), and 1165 (OCHO); ^{1}H NMR δ 0.66 (3 H, s, 18-H), 0.76 (3 H, s, 19-H), 1.86 (3 H, s, 2-Me), 2.84 (1 H, dd, J = 8.8 and 9.3, 3-H), 3.83 (1 H, d, J = 10.3, 2-CH_2I), and 8.22 (1H, s, OCHO); MS, m/e 557 (M^+ – I, 0.2%), 511 (1.1), 457 (4.8), 254 (2.6), 81 (53.2), 57 (68.5), 55 (80.8), and 43 (100); high-resolution mass calcd for $C_{29}H_{50}I_2O_2$ m/e (M^+ – I) 557.2853, found 557.2825. The second mobile fraction B was a formate **27** or **28**: IR (neat) 1722 (CHO), and 1074 cm^{-1} (OCHO); ^{1}H NMR 0.67 (3 H, s, 18-H), 0.77 (3 H, s, 19-H), 1.85 (3 H, s, 2-Me), 2.87 (1 H, t, J = 8.30, 3-H), 3.53 (1 H, d, J = 8.30, 3 H), 3.73 (1 H, d, J = 10.3, 2-CH_2I), 3.86 (1 H, d, J = 10.3, 3-CH_2I), and 8.04 (1 H, s, OCHO); MS, m/e 557 (M^+ – I, 0.1%), 457 (3.9), 384 (5.4), 316 (2.2), 254 (62.2), 127 (71.7), 57 (60.9), and 43 (100); high-resolution mass calcd for $C_{29}H_{50}I_2O_2$ m/e (M^+ – I) 557.2855, found 557.2826. The least mobile fraction C was formate **26**: IR (neat) 1725 (CHO), 1148, 1170 cm^{-1} (OCHO); ^{1}H NMR δ 0.65 (3 H, s, 18-H), 0.73 (3 H, s, 19-H), 1.60 (3 H, s, 2-Me), 1.70 (3 H, s, 2-Me), 2.86 (1 H, dd, J = 9 and 10.7, 3-H), 3.77 (1 H, dd, J = 1.5 and 9, 3-H), and 8.15 (1 H, s, OCHO); MS, m/e 559 (M^+ + 1, 58.6%), 513 (M^+ – OCHO, 100), and 457 (21.9); high-resolution field-desorption mass calcd for $C_{29}H_{52}IO_2$ m/e $(M + 1)^+$ 559.3010, found 559.2979.

Preparation of 2,2-Dimethyl-3-oxa-5α-cholestane (29). The formate **26** (90 mg) in THF containing $NaBH_4$ (50 mg) was heated under reflux for 6 h. The usual workup of the solution gave a product which was subjected to preparative TLC with hexane–diethyl ether (4:1) to give two fractions. The more mobile fraction (42 mg) was recrystallized from acetone to yield oxasteroid: mp 110–111.5 °C; IR (Nujol) 1073 cm^{-1} (O); ^{1}H NMR δ 0.65 (3 H, s, 18-H), 0.98 (3 H, s, 19-H), 1.18 (3 H, s, 2-Me), 1.25 (3 H, s, 2-Me), 3.32 (1 H, dd, J = 11.7 and 3.9, 4α-H), and 3.52 (1 H, dd, J = 11.7 and 11.7, 4β-H); MS, m/e 402 (M^+, 0.1%), and 387 (M^+ – Me, 100); high-resolution mass calcd for $C_{28}H_{50}O$ m/e 402.3862, found 402.3897.

Irradiation of Hypoiodite of 5α-Cholestan-1α-ol (30) in the Presence of Mercury(II) Oxide and Iodine. 5α-Cholestan-1α-ol[10] (**30**) (500 mg) in dry benzene (65 mL) containing mercury(II) oxide (839 mg) and iodine (982 mg) in a Pyrex vessel was irradiated by a 100-W high-pressure Hg arc in a nitrogen atmosphere. The irradiation was discontinued after 5 h. The solution was worked up by the usual method. The oily product (652 mg) was subjected to preparative TLC with a 3:2 mixture of benzene–hexane to give six fractions: A (6 mg), B (49 mg), C (12 mg), D (17 mg), E (26 mg), and F (353 mg) in an order of mobility on TLC. The most mobile fraction A and fractions C and D were unidentified oils. The fraction B was on oily formate **31** containing an iodine: IR (neat) 1724 (OCHO) and 1191 cm^{-1} (OCHO); ^{1}H NMR δ 0.67 (3 H, s, 18-H), 1.22 (3 H, s, 19-H), 3.20 (2 H, m, CH_2CH_2I), and 8.09 (1 H, s, OCHO); MS, m/e 530 (M^+, 0.5%), 500 ($M^+ - CH_2O$, 2.9), 484 ($M^+ - OCH_2O$, 100), 371 (20), 357 (19), 329 (29), and 315 (37); high-resolution mass calcd for $C_{26}H_{45}I$ m/e ($M^+ - OCH_2O$) 484.2486, found 484.2496.

Fraction E was identical with the starting alcohol **30**. Fraction F was not pure material and was twice subjected to preparative TLC (the first with a 1:1 mixture of benzene and diethyl ether and then with a 3:1 mixture of hexane and diethyl ether) to give an oily formate **32** (132 mg, 19%): IR (neat) 1725 (OCHO and Ac) and 1178 cm^{-1} (OCHO); ^{1}H NMR δ 0.65 (3 H, s, 18-H), 2.15 (3 H, s, Ac), 3.17 (2 H, t, J = 6.4 Hz), 4.95 (1 H, m, CH_2CH-(OCHO)CH_2), and 8.06 (1 H, s, OCHO); MS, m/e 546 (M^+, 8.7%), 500 ($M^+ - CH_2O_2$, 44), 461 (45), 415 (100), 387 (26), 277 (65), 107 (53), 95 (55), 81 (62), and 43 (99); high-resolution mass calcd for $C_{27}H_{47}IO_3$ m/e 546.2567, found 546.2542.

1-Oxa-5α-cholestane (33). To the iodo formate **31** (15 mg) in THF (6 ml) at −78 °C was added dropwise methyllithium (0.06 mL, 1 M solution). The solution was stirred at −78 °C for 2 h after which the temperature of the solution was raised to room temperature. The usual workup gave an oily product which was subjected to preparative TLC with benzene to give **33** (4 mg). This was recrystallized from methanol: mp 79–80 °C; IR (Nujol) 1099 (CO); ^{1}H NMR δ 0.67 (3 H, s, 18-H), 1.11 (3 H, s, 19-H), 3.68 (2 H, m, 2-H); MS, m/e 374 (M^+, 17.9%), 359 (M^+ – Me, 5.8), and 111 (100); high-resolution mass calcd for $C_{26}H_{46}O$ m/e 374.3546, found 374.3546.

Cyclization of Iodo Formate 32 with $NaBH_4$. Iodo formate **32** (92 mg) in THF (10 mL) containing $NaBH_4$ (100 mg) was heated under reflux for 1 h. The solution was worked up in the usual manner to give a mixture of the products. The mixture was subjected to preparative TLC with a 5:1 mixture of benzene–diethyl ether to give a product **34** (31 mg): oil; IR (neat) 3370 (OH) and 1061 cm^{-1} (O); ^{1}H NMR δ 0.68 (18-H), 1.25 (3 H, d, J = 1.95 Hz, MeCH(OH)), 3.65–3.87 (3 H, m, CH_2OCH), and 4.34 (1 H, m, MeCHOH); MS, m/e 392 (M^+, 2.4%), 374 ($M^+ - H_2O$, 2.7), 348 (18), 97 (100), 84 (89), and 71 (95, $\overline{O^+(CH_2)_3CH}$); high-resolution mass calcd for $C_{26}H_{48}O_2$ m/e 392.3651, found 392.3626.

Irradiation of the Hypoiodite of 5α-Cholestan-3β-ol (49). The 3β-ol (500 mg) in benzene (64 mL) containing mercury(II) oxide (839 mg) and iodine (982 mg) was irradiated for 6 h by the standard procedure. The solution was worked up in the usual way. The crystalline product was subjected to preparative TLC with benzene to give three fractions A, B, and C. The fraction A (23 mg) was an intractable mixture. The fraction B (154 mg) was identical with 5α-cholestan-3-one (**51**). The fraction C (227 mg) was the starting 3β-ol.

Irradiation of the Hypoiodite of 5α-Cholestan-6α-ol (48). The 6α-ol (500 mg) in benzene (64 mL) containing mercury(II) oxide (837 mg) and iodine (981 mg) was irradiated for 8 h. The solution was worked up in the usual manner. The crystalline product was subjected to preparative TLC with benzene to give four fractions A–D. The fractions A (35 mg) and C (30 mg) were intractable mixtures. The fraction B (67 mg) was identical with 5α-cholestan-6-one. The fraction D (210 mg) was the starting 6α-ol.

Synthesis of 3β-Methyl-5α-cholestan-3α-ol (52). The previous Grignard procedure[18c] was found to be replaced by the following stereoselective procedure which gave a 88:12 mixture of 3α- and 3β-ol. Cuprous iodide (3.7 g) was suspended in 63 mL of anhydrous diethyl ether at 0 °C in a nitrogen atmosphere. Ethereal methyllithium (1 M) (43 mL) was added and was stirred before cooling to −70 °C.[19] 5α-Cholestan-3-one (**51**) (2.5 g) in 5 mL of anhydrous diethyl ether was then added, stirring all the time. The solution was kept at −70 °C for 30 min and then warmed to room temperature. The solution was stirred for 2 h. The solution was poured into saturated ammonium chloride solution. The aqueous layer was separated and extracted with diethyl ether. The organic layers were combined and then dried over anhydrous sodium sulfate. The usual workup of the ethereal solution gave a mixture of 3β-methyl-5α-cholestan-3α-ol (**52**) and its epimer (**53**) (2.57 g). This mixture was subjected to column

chromatography with silica gel (Merck, silica gel 60, 70–230 mesh, 100 g). Elution with a 15:1 mixture of benzene–diethyl ether gave two fractions. The first fraction (1.933 g) was 3α-ol **52** which had been recrystallized from a mixture of ethanol and methanol: mp 128–129 °C (lit.[18c] mp 127–129 °C); ^{1}H NMR δ 0.65 (3 H, s, 18-H), 0.74 (3 H, s, 19-H), and 1.19 (3 H, s, 3β-Me).

The second fraction was recrystallized from methanol to give 3β-ol **53** (270 mg): mp 150–151 °C (lit.[18c] mp 150–152 °C); ^{1}H NMR δ 0.65 (3 H, s, 18-H), 0.81 (3 H, s, 19-H), and 1.25 (3 H, s, 3α-Me).

Irradiation of the Hypoiodite of 3β-Methyl-5α-cholestan-3α-ol (52) in the Presence of Mercury(II) Oxide and Iodine. Steroidal alcohol (**52**) (500 mg) in dry benzene (62 mL) containing mercury(II) oxide (810 mg) and iodine (948 mg) in a Pyrex vessel was irradiated by a 100-W high-pressure mercury arc in a nitrogen atmosphere for 5 h. The solution was worked up in the usual manner. The oily product (675 mg) was subjected to preparative TLC with benzene to give three fractions A, B, and C. The most mobile fraction A (40 mg) was the acetate **54**: IR 1730 (OAc) and 1228 cm^{-1} (O-Ac); ^{1}H NMR δ 0.64 (3 H, s, 18-H), 0.76 (3 H, s, 19-H), 2.10 (3 H, s, OAc), 2.83 (1 H, dd, J = 9.5 and 11.4 Hz, 3-H), 3.64 (1 H, dd, J = 2.2 and 9.5 Hz, 3-H), and 4.07 (2 H, t, J = 7.0 Hz, 2-H); MS, m/e 544 (M^+, 4%), 457 (24, $M^+ - CH_2CH_2OAc$), 417 (13, $M^+ - I$), 357 (89), 329 (32), 95 (100), 81 (91), and 43 (70); high-resolution mass calcd for $C_{28}H_{49}IO_2$ m/e 544.2774, found 544.2759. Fraction B (307 mg) was a mixture of two iodo ketones **55** and **56**: IR 1719 cm^{-1} (Ac); ^{1}H NMR δ 0.64 (s, 18-H of **55** and **56**), 0.73 (s, 19-H of **56**), 0.77 (s, 19-H of **55**), 2.16 (s, Ac of **56**) 2.18 (s, Ac of **55**), 2.78 (dd, J = 10.2 and 9.8, 3-H of **55**), 3.10 (m, 2-H of **56**), 3.48 (dd, J = 2.2 and 10.2 Hz, 3-H of **55**); MS, m/e 528 (M^+, 2%), 457 ($M^+ - AcOCH_2CH_2$, 11), and 401 ($M^+ - I$, 100). The most polar fraction (58 mg) was the starting 3α-ol.

The Synthesis of 3-Oxa-5α-cholestane (57). Acetate **54** (33 mg) in THF (6 mL) containing lithium aluminum hydride (40 mg) was heated under reflux for 2 h. The solution was worked up in the usual manner to give crude 3-oxacholestane (**57**) (22 mg) which was then subjected to preparative TLC to remove any byproducts. The 3-oxa-5α-cholestane (**57**) was recrystallized from acetone–methanol to give pure material **57**: mp 86–87 °C; IR (Nujol) 1118 (O), and 871 cm^{-1}; ^{1}H NMR δ 0.66 (3 H, s, 18-H), 0.92 (3 H, s, 19-H), 3.34 (1 H, t, J = 11.2 and 11, 4β-H), 3.43 (1 H, dd, J = 11.2 and 4.9, 4α-H), 3.65 (1 H, dt, J = 2.9, 11.7, and 11.7, 2β-H), and 3.80 (1 H, ddd, 2.0, 4.9 and 11.7, 2α-H); MS, m/e 374 (M^+, 79%), 359 (M^+ – Me, 19), and 219 (100). Anal. Calcd for $C_{28}H_{46}O$: C, 83.35; H, 12.38. Found: C, 83.09; H, 12.38.

Irradiation of the Hypoiodite of Cyclopentanol in the Presence of Mercury(II) Oxide and Iodine. Cyclopentanol (500 mg) in benzene (50 mL) containing mercury(II) oxide (3.78 g) and iodine (4.43 g) in a Pyrex vessel was irradiated as in the case of steroidal alcohol for 7 h. The solution was filtered and the filtrate was worked up in the usual manner. The oily product (562 mg) was subjected to preparative TLC with benzene to afford four fractions A–D in an order of decreasing mobility. The fraction A (180 mg) was an oily formate **58**: IR (neat) 1728 (CHO) and 1172 cm^{-1} (OCHO); ^{1}H NMR (100 MHz) δ 1.62–2.01 (4 H, m, 2- and 3-CH_2), 3.22 (2 H, t, J = 6.5 Hz, CH_2I), 4.20 (2 H, t, J = 5.2 Hz, CH_2OCHO), and 8.06 (1 H, s, OCHO); MS, m/e 228 (M^+, 0.5%), 101 ($M^+ - I$, 22.9) and 55 (100); high-resolution mass calcd for $C_5H_9IO_2$ m/e 227.9648, found 227.9666.

The next mobile fraction B (82 mg) was 5-iodopentanal (**59**): IR (neat) 1723 cm^{-1} (CHO); ^{1}H NMR (100 MHz) δ 0.64–0.83 (4 H, m, 3- and 4-CH_2), 2.58 (2 H, t, J = 6 Hz, CH_2CHO), 3.16 (2 H, t, J = 6 Hz, CH_2I), and 9.75 (1 H, t, J = 2 Hz, CHO); MS, m/e 212 (M^+ 5.0%), 85 ($M^+ - I$, 100), and 41 (76.9%); high-resolution mass calcd for $C_5H_{19}IO$ m/e 212.9774, found 212.9772.

The fraction C was cyclopentyl tetrahydropyranyl ether (**60**): IR (neat) 1020 and 1133 cm^{-1}; ^{1}H NMR (100 MHz) δ 1.53–1.71 (14 H, m, 7-CH_2), 3.50 and 3.91 (each 1 H, each m, OCH_2), 4.25 (1 H, m, $(CH_2)_4CHO$); MS, m/e 170 (M^+ 2.0%) and 85 (100); high-resolution mass calcd for $C_{10}H_{18}O_2$ m/e 170.1305, found 170.1300.

Irradiation of the Hypoiodite of Cyclohexanol in the Presence of Mercury(II) Oxide and Iodine. Cyclohexanol (500 mg) in benzene (60 mL) containing mercury(II) oxide (3.26 g) and iodine (3.81 g) in a Pyrex vessel was irradiated for 8 h. The solution was worked up in the usual manner. The oily products (560 mg) were subjected to preparative TLC with benzene to afford four fractions A–D in an order of decreasing mobility. The fraction A (32 mg) was again subjected to preparative TLC with a 6:1 hexane–diethyl ether to give an oily formate **61** (25 mg): IR (neat) 1724 (OCHO), 1186 cm^{-1} (OCHO); ^{1}H NMR δ 1.41–1.94 (6 H, m, 2-, 3-, and 4-CH_2), 3.20 (2 H, t, J = 6.8, CH_2I), 4.18 (2 H, t, J = 6.4, CH_2OCHO), and 8.06 (1 H, s, OCHO); MS, m/e 243 ($M^+ + 1$, 9%), 242 (M^+, 7.5), and 115 ($M^+ - I$, 100); high-resolution mass calcd for $C_6H_{12}IO_2$ m/e 241.9802, found 241.9802.

The fraction B (51 mg) was 6-iodohexanal (**62**): IR (neat) 2715 (CHO) and 1724 (CHO); ^{1}H NMR δ 1.40–1.89 (6 H, m, 3-, 4-, and 5-CH_2), 2.47 (2 H, t, J = 7.1, CH_2CHO), 3.20 (2 H, t, J = 6.8, CH_2I), and 9.78 (1 H, br s, CHO); MS, m/e 227 ($M^+ + 1$, 0.2%), 226 (M^+, 0.2), 225 ($M^+ - I$, 0.7), 99 ($M^+ - I$, 15.6), 81 (81.3), and 55 (100); high-resolution mass calcd for $C_6H_{11}IO$ m/e 225.9847, found 225.9824. Fraction C (67 mg) was cyclohexanone and fraction D (193 mg) was the starting cyclohexanol.

Irradiation of the Hypoiodite of Cycloheptanol in the Presence of Mercury(II) Oxide and Iodine. Cycloheptanol (500 mg) in benzene (60 mL) containing mercury(II) oxide (2.84 g) and iodine (3.34 g) in a Pyrex vessel was irradiated by a 450-W Hanovia Hg arc lamp for 3 h. The solution was worked up in a usual manner. The oily product (512 mg) was subjected to preparative TLC with benzene to afford four fractions A–D in an order of decreasing mobility. The fraction A (13 mg) was an aldehyde **63**: IR (neat) 2700 (CHO) and 1722 (CHO); ^{1}H NMR δ 2.48 (2 H, dt, J = 1.5 and 7.1 CH_2CHO)), 3.19 (2 H, t, J = 6.8, CH_2I), and 9.77 (1 H, t, J = 1.5); MS, m/e 239 ($M^+ - I$, 0.5%), 103 ($M^+ - I$, 5.1), 69 ($CH_2{=}CHCH_2CH_2CH_2^+$, 43), and 41 (100); high-resolution mass calcd for $C_7H_{12}IO$ m/e 238.9932, found 238.9917.

The fraction B (69 mg) was cycloheptanone and the fraction C (29 mg) was 1,4-epoxycycloheptane. The fraction D (237 mg) was the starting cycloheptanol.

Irradiation of Hypoiodite of Cyclooctanol in the Presence of Mercury(II) Oxide and Iodine. Cyclooctanol (500 mg) in benzene (60 mL) containing mercury(II) oxide (2.53 g) and iodine (2.97 g) in a Pyrex vessel was irradiated for 7 h. The solution was worked up in the usual manner. The oily product was subjected to preparative TLC with benzene to afford three fractions A, B, and C in an order of decreasing mobility. The fraction A was 1,4-epoxy-6-iodocyclooctane (**66**) (67 mg): IR (neat) 1166, 1080, and 975 cm^{-1}; ^{1}H NMR δ 1.46–2.10 (9 H, $4CH_2$ and a hydrogen adjacent to CHI), 2.46–2.77 (1 H, ddd, a proton adjacent to CHI), and 4.00–4.59 (3 H, superimposed m, CHOCH and CHI); MS, m/e 252 (M^+, 2.8%), 125 ($M^+ - I$, 100), 107 (68), 81 (81), 55 (87) and 41 (77); high-resolution mass calcd for $C_8H_{13}IO$ m/e 252.0012, found 252.0014.

The fraction B was a mixture and therefore subjected to preparative GLC [Silicone OV-17 (10% on Uniport B), 2 m] to give two fractions. The first fraction (63 mg) was 1,4-epoxycyclooctane (**65**) which was identical with an authentic specimen. The second fraction 95 mg was cyclooctanone. The fraction C (132 mg) was twice subjected to preparative TLC with a 15:1 benzene–diethyl ether to give γ-lactone **67** (20 mg): IR 1773 (γ-lactone), and 1177 cm^{-1} (OCOR); ^{1}H NMR δ 3.20 (2 H, t, J = 6.8 Hz, CH_2I) and 4.50 (1 H, m, OCH); MS, m/e 141 ($M^+ - I$ 14%) and 85 ($COO^+{=}C$, 100); high-resolution mass calcd for $C_8H_{13}O_2$ m/e 141.0915, found 141.0920.

Preparation of Mercury(II) Oxide-^{18}O. HgO-^{18}O (48.9 atom % ^{18}O) was prepared by the reaction of mercury(II) chloride in H_2O–$H_2{}^{18}O$ [prepared by diluting water-^{18}O, (Merck Sharp and Dohme Canada Ltd., 97 atom % ^{18}O)] with sodium hydroxide–water-^{18}O.

The ^{18}O Labeling Experiments. (a) Preparation of a Formate Corresponding to Formate 15 by Irradiation of the Hypoiodite of 5α-Androstane-3β,17β-diol 3-Acetate (14) in the Presence of Mercury(II) Oxide-^{18}O (48.9 atom % ^{18}O) and Iodine and Its Transformation into Oxasteroid 17. Steroidal alcohol **14** (100 mg) in dry benzene (15 mL) containing mercury(II) oxide-^{18}O (196 mg) and iodine (228 mg) in a Pyrex vessel was irradiated for 2 h as for the case of the reaction with ordinary mercury(II) oxide. A mixture of formates corresponding to formates **15** and **16** was dissolved in THF (5 mL) containing $NaBH_4$ (50 mg) and heated under reflux for 9 h. After the usual workup, the product was subjected to preparative TLC with

benzene to give 17-oxa-5α-androstan-3β-ol 3-acetate (13 mg). The mass spectral fragmentation pattern and the intensity of each fragment of this oxasteroid was entirely identical with those obtained from oxasteroid **17** prepared with ordinary mercury(II) oxide.

(b) Preparation of a Formate Corresponding to Formate 18 by Irradiation of the Hypoiodite of 4,4-Dimethyl-5α-cholestan-3β-ol in the Presence of Mercury(II) Oxide-^{18}O and Iodine and Its Transformation into Oxasteroid 24. Steroidal alcohol **20** (89 mg) in benzene (11 mL) containing mercury(II) oxide-^{18}O (140 mg) and iodine (163 mg) in a Pyrex vessel was treated as in the case of the reaction with ordinary mercury oxide. The resulting formate **21** (28 mg) was transformed into oxasteroid **24** (14 mg). The mass spectrum of **24** showed that the fragmentation pattern and the intensity of each fragment was identical with those obtained from oxasteroid **24** prepared with ordinary mercury(II) oxide.

Registry No. **4**, 1225-43-0; **5**, 83625-92-7; **6**, 83625-93-8; **7**, 91712-60-6; **8**, 91712-61-7; **9**, 83679-49-6; **10**, 83679-50-9; **11**, 54482-41-6; **12**, 83679-51-0; **14**, 3090-70-8; **15**, 83625-94-9; **16**, 83625-95-0; **17**, 83625-96-1; **17**-ol, 83632-45-5; **18**, 83679-52-1; **19**, 83625-97-2; **20**, 2550-84-7; **21**, 85382-31-6; **22**, 91712-62-8; **23**, 91712-63-9; **24**, 83626-02-2; **25**, 2542-65-6; **26**, 91712-64-0; **27**, 91712-65-1; **28**, 91712-66-2; **29**, 83626-01-1; **30**, 15064-05-8; **31**, 91712-67-3; **32**, 91712-68-4; **33**, 91712-69-5; **34**, 91712-70-8; **48**, 19043-45-9; **49**, 80-97-7; **51**, 566-88-1; **52**, 1251-59-8; **53**, 1251-58-7; **54**, 91712-71-9; **55**, 91712-72-0; **56**, 91712-73-1; **57**, 91796-74-6; **58**, 85382-32-7; **59**, 49540-03-6; **60**, 85382-33-8; **61**, 91712-74-2; **62**, 91712-75-3; **63**, 72489-61-3; **64**, 280-11-5; **65**, 284-20-8; **66**, 91712-76-4; **67**, 91712-77-5; $Hg^{18}O$, 91712-78-6; 2,2-dimethyl-cholest-4-en-3-one, 17305-84-9; 2,2-dimethyl-5α-cholestan-3-one, 2542-57-6; cyclopentanal, 96-41-3; cyclohexanol, 108-93-0; cyclohexanone, 108-94-1; cycloheptanol, 502-41-0; cycloheptanone, 502-42-1; cyclooctanol, 696-71-9; cyclooctanone, 502-49-8.

Structural Studies of the Mycotoxin Verrucosidin

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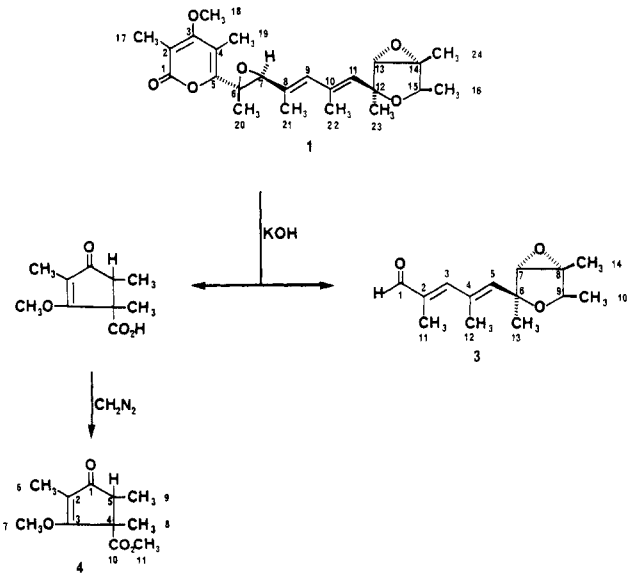
Structure 1 has been established for verrucosidin, a neurotoxin isolated from *Penicillium verrucosum* var. *cyclopium*. A novel fragmentation in base yields aldehyde **3** and a rearranged cyclopentenone carboxylic acid. The structure of the methyl ester **4** of this acid has been established by independent synthesis. A mechanism is proposed for the formation of the cyclopentenone ring of **4** from the epoxy α-pyrone of **1**.

In a recent report we reported the structure of the tremorgenic mycotoxin, verrucosidin (**1**), which was isolated from *Penicillium verrucosum* var. *cyclopium*.[1] The isolation and identification of verrucosidin were prompted by local reports of neurotoxicoses in cattle caused by hay; investigations of this hay revealed the presence of two tremorgen-producing fungi, one of which is *P. verrucosum* var. *cyclopium*, the other has not yet been identified.[2]

Verrucosidin, a potent neurotoxin (LD_{50} in mice, 4 mg/kg, i.p.) which causes sustained tremoring in experimental animals, was isolated from the hay samples. Larger quantities have been obtained by growing the fungus on a potato–milk–sucrose medium and extracting the air-dried fungal pad with ether. Silica gel chromatography followed by recrystallization from ether gave **1** as colorless plates, mp 90–91 °C, $[a]^{26}_D$ +92.4° (*c* 0.25, methanol). The empirical formula $C_{24}H_{32}O_6$ was determined by mass spectrometry (*m/z* 416) and by elemental analysis.

The ^1H NMR spectrum was rather simple in appearance, consisting of nine methyl resonances, only one of which showed substantial coupling, and five signals integrating for one hydrogen each, two of which were vinyl hydrogens and the other three methines. Only one of the methines showed substantial coupling (to the methyl group); the other one-proton signals were somewhat broadened but no useful coupling information could be obtained at 90 MHz. Twenty-four resonances were observed in the ^{13}C NMR spectrum. The chemical shifts of the five downfield signals suggested an α-pyrone unit. This

Scheme I



hypothesis was corroborated by the IR (ν_{max} 1700 cm^{-1}) and UV (λ_{max} 294 nm, ε 13 000 and 241 nm, ε 21 000) spectra.

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