this or other solvent. An acetic acid solution of a 3-g. batch from another run was treated with 3 g. of dichromate and refluxed, when it rapidly turned green. Another 3 g. of dichromate was added and the solution was refluxed for a total of 2.5 hr., when it was brownish-green. Dilution and extraction with ether gave 1.0 g. of acid, and this on Girard separation proved to be largely non-ketonic. A small ketonic fraction (0.08 g.), however, crystallized slowly from petroleum ether to give crystals melting at 142–143°, undepressed on admixture with duoannelic acid.

A solution of 5 g. of sodium dichromate in 15 ml. of acetic acid in a test-tube was cooled to 50°, 1.0 g. of pure Butenandt acid was added and washed down with 5 ml. of acetic acid. The tube was then inserted in a flask of refluxing toluene. Vigorous bubbling from evolution of carbon dioxide continued for about 2 hr. and the temperature rose 3.5° above that of the boiler (111°). The oxidation was stopped after 4 hr., when the green solution still showed a yellowish tinge. After extraction with ether the acidic material was extracted from the ether with sodium bicarbonate and obtained as a greenish resin (0.25 g.) which failed to crystallize from petroleum ether. However, Girard separation gave a ketonic fraction (0.14 g.) which crystallized readily from petroleum ether to give 38 mg. of duoannelic acid, m.p. and mixed m.p. 143–144°.

### Characterization (T. G.)

**Duoannelic Acid (7).**—The fully purified acid is a light powder of fine needles, m.p. 145—145.5°, $\alpha_D$ +17.8° Chf.

*Anal.* Calcd. for $C_{21}H_{36}O_3$ (336.50): C, 74.95; H, 10.77. Found: C, 74.90; H, 10.63.

**The methyl ester** (diazomethane) crystallized well from aqueous acetone (twice) in long needles, m.p. 77.5–78.5°. The infrared spectrum showed bands for both an ester and a ketone carbonyl group.

*Anal.* Calcd. for $C_{22}H_{38}O_3$ (350.52): C, 75.38; H, 10.93. Found: C, 75.24; H, 10.93.

**Dihydroduoannelic Acid (10).**—A solution of 500 mg. of duoannelic acid in 30 ml. of methanol was neutralized with 10% potassium hydroxide solution and treated with 150 mg. of sodium borohydride with ice cooling. After standing at room temperature overnight the solution was acidified, diluted, and extracted with ether. The crude product was crystalline, and crystallization from acetone afforded 285 mg. of needles, m.p. 156.5–157.5°. Recrystallized material had the constants m.p. 160–161.5°, $\alpha_D$ +19.5° Chf.

*Anal.* Calcd. for $C_{21}H_{38}O_3$ (338.51): C, 74.51; H, 11.32. Found: C, 74.59; H, 11.43.

**Dihydroduoannelic Acid Lactone (11).**—A solution of 150 mg. of the acid in a mixture of 7.5 ml. of methanol and 2.5 ml. of 10% hydrochloric acid was refluxed for 12 hr., diluted and extracted with ether. Evaporation of the solvent left an oil which soon solidified, and two crystallizations from methanol gave leaflets, m.p. 100.5°, $\alpha_D$ +16.4° Chf, $\lambda^{CS_2}$ 5.62 $\mu$.

*Anal.* Calcd. for $C_{21}H_{36}O_2$ (320.50): C, 78.69; H, 11.32. Found: C, 78.61; H, 11.37.

After shorter periods of refluxing the infrared spectrum indicated that the hydroxy acid had been merely esterified.

**Duoannelic Diacid.**—A suspension of 300 mg. of duoannelic acid in 5 ml. of water was brought into solution by neutralization with 10% potassium hydroxide. A solution prepared by addition of 0.18 ml. of bromine dropwise to an iced solution of 400 mg. of sodium hydroxide in 3 ml. of water and the hypobromite solution was added. After 2 hr. at 0° and 5 hr. at 26° the mixture was treated with 100 mg. of sodium bisulfite and acidified. The solid product that precipitated (m.p. 173–177°) on crystallization from aqueous acetone formed plates, m.p. 179–180.5°.

*Anal.* Calcd. for $C_{20}H_{34}O_2$ (338.47): C, 70.97; H, 10.13. Found: C, 71.22; H, 9.99.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

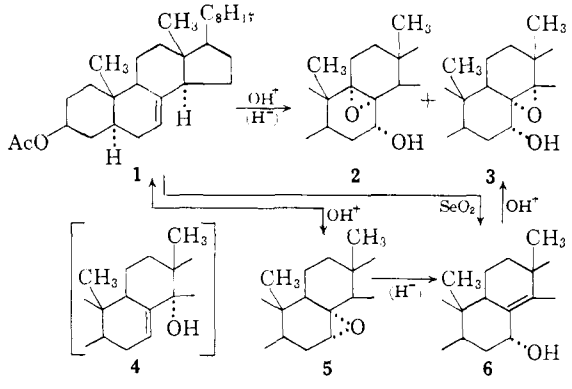
# Oxido Alcohols and Ketoxides

BY LOUIS F. FIESER AND TOSHIO GOTO[1]

RECEIVED AUGUST 17, 1959

The conversion of $\Delta^7$-cholestenyl acetate (**1**) into the 7$\alpha$-ol-8$\alpha$,14$\alpha$-oxide **3** on reaction with perbenzoic acid in chloroform is shown to involve formation of the 7$\alpha$,8$\alpha$-oxide and its cleavage by a trace of mineral acid to the $\Delta^{8(14)}$-ene-7$\alpha$-ol (**6**). Consideration of the possible mechanism of the formation of ketoxides on chromic acid oxidation of $\Delta^7$- and $\Delta^{8(14)}$-stenyl acetates (*e.g.*, **11** and **13**) suggested revision of the formula (**21a**) assigned by Ellis and Petrow to an alcohol resulting from selenium dioxide oxidation of Westphalen's diol. Evidence from ultraviolet and nuclear magnetic resonance spectra support the new formula **21b**.

An observation of Wintersteiner and Moore[2] that has not yet been clarified is that $\Delta^7$-cholestenyl acetate (**1**) reacts with two moles of perbenzoic acid in chloroform to give in good yield a mixture of the 8$\alpha$,9$\alpha$- and 8$\alpha$,14$\alpha$-oxido-7$\alpha$-ols **2** (minor product) and **3**,[3] of stereochemistry later deduced in our laboratory.[4] Fieser and Ourisson[4] found that the $\Delta^7$-compound **1** reacts with selenium dioxide in acetic acid or ethanol to give the $\Delta^{8(14)}$-ene-7$\alpha$-ol (**6**), isolated either as the acetate or the ethyl ether, and suggested that the oxido alcohol **3** may arise in the reaction with perbenzoic acid by allylic hydroxylation at $C_{14}$ (**4**), allylic rearrangement to **6**, and oxide formation. Indeed Saucy, *et al.*,[5] isolated the analogous $\Delta^7$-ene-9-ol along with




the $\Delta^{8(14)}$-ene-7$\alpha$-ol on oxidation of 5-dihydroergosteryl acetate with selenium dioxide. However, there is no evidence that a peracid can effect allylic hydroxylation, and indeed two $\Delta^7$-stenols

(1) Recipient of a Fulbright travel grant on leave from Nagoya University, Nagoya, Japan.

(2) O. Wintersteiner and M. Moore, THIS JOURNAL, **65**, 1507 (1943).

(3) Characterization of **3**: L. F. Fieser, K. Nakanishi and W.-Y. Huang, *ibid.*, **75**, 4719 (1953).

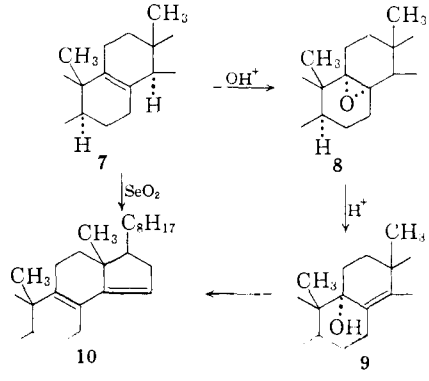
(4) L. F. Fieser and G. Ourisson, *ibid.*, **75**, 4404 (1953).

(5) G. Saucy, P. Geistlich, R. Hebling and H. Heusser, *Helv. Chim. Acta*, **37**, 250 (1954).

other than the one studied by Wintersteiner and Moore have been found to react with one mole of peracid to give 7,8-oxides, not allylic alcohols. 5-Dihydroergosteryl acetate on reaction with monoperphthalic acid in ether at 20° gave an oxide (no infrared hydroxyl band) which on acid-catalyzed dehydration gave a mixture of D- and $B_3$-type dienes and the 7-ketone,[6] and $\Delta^7$-ergostenol benzyl ether on treatment with perbenzoic acid in benzene at 5° gave an oxide.[7] However the compounds and conditions were different from those of Wintersteiner and Moore, and in neither case was the oxide treated with more peracid to see if it would yield an oxido alcohol.

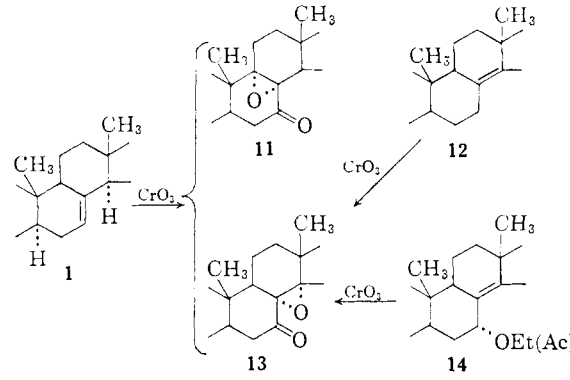
On reinvestigating the case of $\Delta^7$-cholestenyl acetate **1**, we found that this substance reacts with 1.1 moles of monoperphthalic acid in ether to give the 7$\alpha$,8$\alpha$-oxide **5** (no infrared band near 2.8 $\mu$, negative tetranitromethane test). The oxide was recovered unchanged after further treatment with monoperphthalic acid in ether, but in chloroform solution it consumed one mole of monoperphthalic acid and gave the oxido alcohol **3**. The oxide alone is stable in dry or wet chloroform containing benzoic acid and hence this reagent is not responsible for the cleavage and further reaction. In the usual procedure of preparing perbenzoic acid an aqueous solution of the sodium salt is acidified and extracted with chloroform and the extract is dried. We shook chloroform with 10% sulfuric acid, dried the solvent, and found that on brief standing in this solvent the oxide **5** is isomerized to the $\Delta^{8(14)}$-ene-7$\alpha$-ol **6**, isolated as the diacetate. Titration showed that the chloroform contained 0.2 mg. of sulfuric acid per 100 ml. The sequence of events in the experiment of Wintersteiner and Moore is thus formation of the 7$\alpha$,8$\alpha$-oxide, acid cleavage to the $\Delta^{8(14)}$-ene-7$\alpha$-ol **6** (with the $\Delta^8$-ene-7$\alpha$-ol as a minor product), and conversion to the oxido alcohol **3**. A trace of acid suffices for the cleavage, and the intermediate allylic alcohol **6** is sensitive to more strongly acidic conditions; thus **5** is converted by aqueous perchloric acid in tetrahydrofuran at 22° into a mixture of cholestadienols.

The same mechanism probably applies to the reaction of $\Delta^8$-cholestenyl acetate (**7**) with perbenzoic acid in chloroform, investigated by Windaus, Linsert and Eckhardt.[8] The product was




formulated by these authors as the allylic tertiary alcohol **9** because on reaction with acetic anhydride it was dehydrated to a substance corresponding closely in constants to the $B_1$-type diene **10**, later obtained by dehydrogenation of **7** with selenium dioxide.[9] Since Henbest and Wrigley[10] found $\Delta^8$-ergostenyl acetate to react with perbenzoic acid in benzene to give the $\alpha$-oxide in good yield, the production of the allylic alcohol **9** is attributable to formation of the oxide **8** and its cleavage by a trace of mineral acid present in the chloroform.

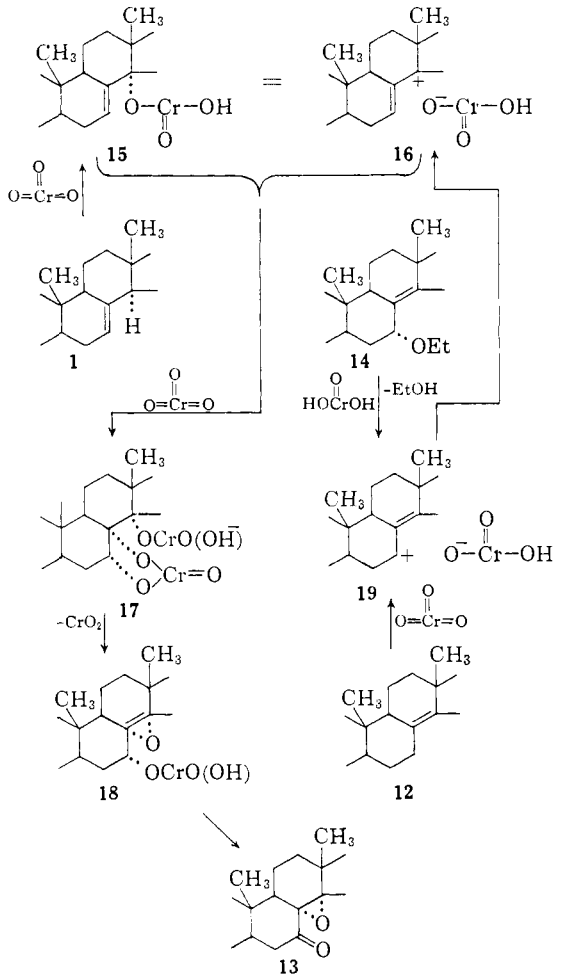
Following an initial discovery in the ergosterol series by Stavely and Bollenback,[11] it has been established[2,3,12] that oxidation of $\Delta^7$-cholestenyl acetate (**1**) with aqueous chromic acid in acetic acid at 25° gives an easily separable mixture of the 7-keto-8$\alpha$,9$\alpha$-oxide **11** and the less soluble 7-



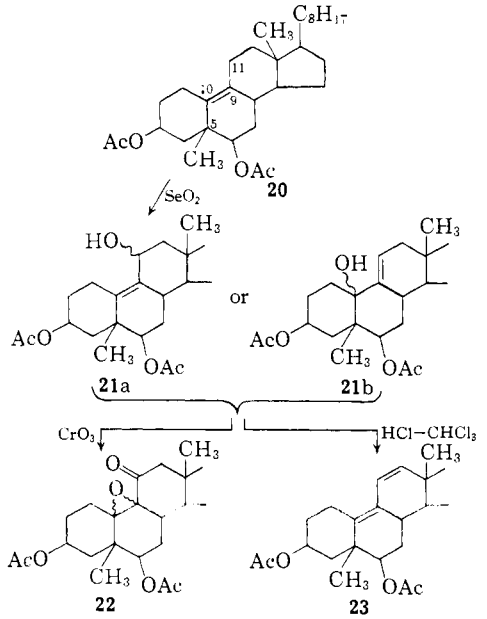

keto-8$\alpha$,14$\alpha$-oxide **13**. These products are obtainable also by oxidation of the oxido alcohols **2** and **3**, above, but these alcohols and the precursor oxide can hardly be intermediates in the chromic acid reaction. The 7-keto-8$\alpha$,14$\alpha$-oxide **13** is also formed on chromic acid oxidation of $\Delta^{8(14)}$-cholestenyl acetate[12] (**12**) and of both 7$\alpha$-ethoxy- and 7$\alpha$-acetoxy-$\Delta^{8(14)}$-cholestenyl acetate[4] (**14**). An approximate representation of a mechanism which seems applicable is as follows. The initial step in the reaction of the $\Delta^7$-compound is pictured as an allylic attack by chromic anhydride (or acid) to produce the Cr(IV) ester **15** or the equivalent ion pair **16**. Attack of the double bond in the manner of the reaction of an olefin with osmium tetroxide gives the ester **17**,[13] which collapses to the oxidic ester **18**, which is oxidized further to the ketoxide **13**. The $\Delta^{8(14)}$-stenyl acetate **12** also suffers initial allylic attack, and the secondary ion pair **19** rearranges to the more stable tertiary ion pair **16**. The ester or ion pair **19** is formulated as also an intermediate in the oxidation of the 7$\alpha$-ethoxy (or acetoxy) derivative **14**.

Although the mechanism suggested may require revision in some details, it led us to the view that allylic tertiary alcohols are capable of being oxidized to ketoxides. Ellis and Petrow[14] assigned

(6) G. H. Alt and D. H. R. Barton, *J. Chem. Soc.*, 1356 (1954).
(7) G. D. Meakins and J. S. Stephenson, *ibid.*, 526 (1958).
(8) A. Windaus, O. Linsert and H. J. Eckhardt, *Ann.*, **534**, 22 (1938).
(9) W. J. Adams, V. Petrow and R. Royer, *J. Chem. Soc.*, 678 (1951).
(10) H. B. Henbest and T. I. Wrigley, *ibid.*, 4596 (1957).
(11) H. E. Stavely and G. N. Bollenback, THIS JOURNAL, **65**, 1285, 1290 (1943).
(12) O. Wintersteiner and M. Moore, *ibid.*, **65**, 1513 (1943).
(13) Compare W. A. Waters, *Quart. Revs.*, **12**, 288 (1958).
(14) B. Ellis and V. Petrow, *J. Chem. Soc.*, 2246 (1952).



the structure **21a** to an alcohol obtained by oxidation of Westphalen's diol diacetate (**20**) with selenium dioxide on the ground that on chromic acid oxidation it yields a ketoxide (**22**). The hydroxyl group was placed at $C_{11}$ rather than at $C_1$ because



on reaction with hydrogen chloride in chloroform the alcohol is dehydrated to a product formulated as the diene **23** from the evidence of the ultraviolet absorption characteristics. Attempts to acetylate or benzoylate the free hydroxyl group were negative, as was attempted Oppenauer oxidation. This behavior seemed to us inconsistent with formula **21a**, for no particular hindrance of an 11-hydroxyl group ($\alpha$ or $\beta$) is apparent from a model. The alternative formulation of the substance as the tertiary alcohol **21b** accounts for the formation of the ketoxide **22** and the diene **23** and for the resistance to acylation and Oppenauer oxidation.

Bladon, Henbest and Wood[15] have demonstrated that di- and trisubstituted olefins are distinguishable from the position and slope of the ultraviolet absorption curves in the region of short wave length. The curves of Fig. 1 clearly fall into two groups. Curves 1, 2 and 3 are for steroids known

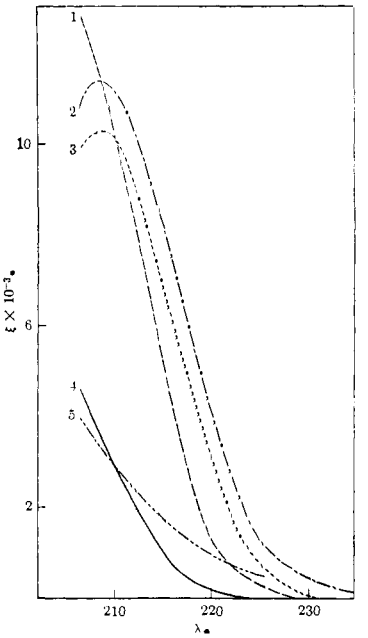
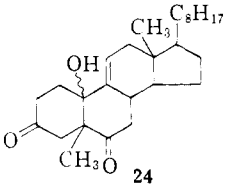



Fig. 1.—Ultraviolet spectra: 1, Westphalen's diol diacetate; 2, $\Delta^{8(14)}$-cholestene-3$\beta$,7$\alpha$-diol diacetate; 3, $\Delta^{8(14)}$-cholestene-3$\beta$,7$\alpha$-diol; 4, selenium dioxide oxidation product **21b**; 5, compound **24**.

to have a tetrasubstituted double bond. Curve 5 is for the unsaturated oldione **24** described by Ellis and Petrow,[14] and the curve is in the location char-



acteristic of a trisubstituted olefin. Curve 4 for the product of selenium dioxide oxidation of Westphalen's diol diacetate indicates that this substance is likewise trisubstituted, as in formula **21b**.

(15) P. Bladon, H. B. Henbest and G. W. Wood, *J. Chem. Soc.*, 2737 (1952).

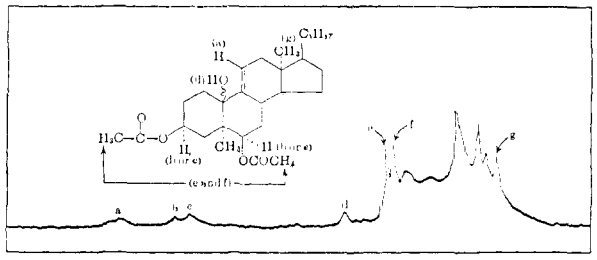


Fig. 2.—N.m.r. spectrum of the alcoholic oxidation product of Westphalen's diol diacetate in cycles per sec.: a, 27 (olefinic 11-H); b, 57, and c, 65 (3$\alpha$-H and 6$\alpha$-H on carbons carrying axial acetoxyl groups); d, 147 (ionizable proton of the 10-OH group; e, 171, and f, 175 (acetate protons); g, 228 (13-$CH_3$).

Further evidence is provided by the nuclear magnetic resonance spectrum (Fig. 2), determined at 40 megacycles/sec. in $CDCl_3$ (external benzene as zero of reference). Of the peaks that can be identified (those lettered; see legend), four (a-d) are in the region characteristic of a lone hydrogen on an olefinic carbon or on a carbon carrying a hydroxyl or acetoxyl group. Peaks b and c, of nearly the same position and intensity, can be identified by analogy to known examples[16] as the hydrogens at $C_3$ and $C_6$ carrying axial acetoxyl groups. Peaks a and d seemed most probably due, respectively, to the olefinic 11-hydrogen and the ionizable hydrogen of the 10-hydroxyl group. To make sure that this assignment should not be reversed, the spectrum was determined for a solution in carbon tetrachloride, for this should cause a shift in the peak due to the ionizable hydrogen. All the peaks remained the same except that peak d, originally at 147 c.p.s., was shifted to 158 c.p.s., and hence this peak is associated with the hydroxyl group. However, before concluding that peak a at 27 c.p.s. is due to olefinic hydrogen, it seemed necessary to consider the possibility that it is due to the allylic hydrogen on the hydroxylated 11-carbon in formula **21a** of Ellis and Petrow. As a model allylic secondary alcohol for comparison, we selected $\Delta^{(8(14))}$-cholestene-3$\beta$,7$\alpha$-diol, which gave the spectrum reproduced in Fig. 3. Evidence that the model is a satisfactory one is as follows. A cholestane-3$\beta$-ol shows a 3$\alpha$-H peak between 113 and 116 c.p.s., and a cholestane-11$\beta$-ol has an 11$\alpha$-H peak between 77 and 82 c.p.s., and the difference is about 35 c.p.s. The model chosen shows a 3$\alpha$-H band at 112 c.p.s. and a 7$\beta$-H peak at 76 c.p.s., and the difference of 36 c.p.s. is practically the same. $\Delta^{(8(14))}$-Cholestene-3$\beta$,7$\alpha$-diol diacetate shows corresponding bands at 69 and 34 c.p.s. and the difference is 35 c.p.s. From the close agreement with the $\Delta$-value for saturated sterols, it would appear that the 8(14)-double bond has no effect on the hydrogen at $C_7$; usually an allylic double bond shifts a proton peak to a lower field by about 30 c.p.s. Since the allylic 7$\beta$-hydrogen of the model compound shows a peak at 76 c.p.s., the 11$\alpha$-hydrogen of formula **21a** can be expected to show an 11$\alpha$-hydrogen peak at a comparable value, and surely not in the region of 27 c.p.s. If the compound were an 11$\alpha$-ol, the 11$\beta$-hydrogen being axial should give rise to a peak at a field still higher by about 20 c.p.s. The only reasonable assignment of the peak observed at 27 c.p.s. is thus to the olefinic 11-hydrogen of formula **21b**.

(16) J. N. Shoolery, THIS JOURNAL, **80**, 5121 (1958).

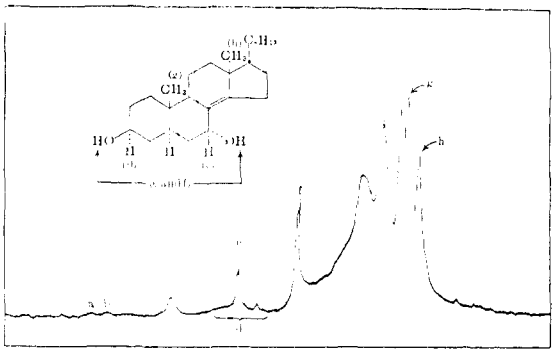


Fig. 3.—N.m.r. spectrum of $\Delta^{8(14)}$-cholestene-3$\beta$,7$\alpha$-diol in cycles per sec.: a, 25 and b, 35 (olefinic hydrogens of a trace of diene present); c, 76 (7$\beta$-H); d, broad band centering at 112 (3$\alpha$-H); e, 119 and f, 155 (ionizable protons of the 3- and 7-OH groups); g, 222 (10-$CH_3$); h, 229 (13-$CH_3$).

An incidental observation is that $\Delta^{8(14)}$-cholestene-3$\beta$,7$\alpha$-diol decomposes slowly on standing in $CDCl_3$ solution at room temperature. The spectrum when taken after 2 hr. was entirely changed: peak c at 76 c.p.s. had disappeared and two new peaks appeared at 25 and 35 c.p s. attributable to the olefinic 7- and 15-hydrogens of the $\Delta^{7,14}$-diene.

**Acknowledgment.**—This work was supported by grants from the National Cancer Institute of the National Institutes of Health (CY1696), Research Corporation, and the Higgins Fund of Harvard University.

## Experimental

**7$\alpha$,8$\alpha$-Oxidocholestane-3$\beta$-ol Acetate (5).**—A solution of 2.15 g. of $\Delta^7$-cholestenyl acetate in 10 ml. of ether was treated with 12 ml. of an ethereal solution of monoperphthalic acid (1.1 equiv.) and let stand at 22° for 44 hr. The solution was decanted from precipitated phthalic acid (680 mg.) and washed with water, bicarbonate solution, water, and saturated sodium chloride solution, and dried over sodium sulfate and evaporated at reduced pressure. The semi-solid residue was dissolved in a small amount of petroleum ether and dropwise addition of methanol caused the product to separate as needles (1.44 g., m.p. 86–93°). Recrystallization from methanol gave two polymorphic forms which were interconvertible by crystallization from methanol and which are identical in rotation, tetranitromethane test (negative), and infrared spectrum (no hydroxyl band around 2.8 $\mu$): (a) cotton-like slender needles, m.p. 84.5–85°, $\alpha_D$ +7.3° Chf; (b) needles, m.p. 96–97°, $\alpha_D$ +8.5° Chf.

*Anal.* Calcd. for $C_{29}H_{48}O_3$ (444.67): C, 78.32; H, 10.88. Found: (a) C, 78.04; H, 10.94; (b) C, 78.25; H, 10.95.

**Acid Cleavage of the Oxide.**—A solution of 200 mg. of **5** in 5 ml. of tetrahydrofuran was treated with 0.6 ml. of 25% aqueous perchloric acid and let stand at 22° for 5 hr. The solution was diluted with water and extracted with ether. The washed and dried extract on evaporation left an oily residue which crystallized from ether–methanol in needles, m.p. 105–110°, $\alpha_D$ −4.5° Chf; $\lambda^{EtOH}$ 235 m$\mu$ (12,700), 242 (14,200), 250 (shoulder, 9,650); $\lambda^{CS_2}$ 5.76, 8.08 $\mu$. The spectral characteristics and analysis indicate that the substance is a mixture of $\Delta^{7,9(11)}$- and $\Delta^{7,14}$-cholestadiene-3$\beta$-ol.

*Anal.* Calcd. for $C_{29}H_{46}O_2$ (426.66): C, 81.63; H, 10.87. Found: C, 81.66; H, 10.85.

**Action of Monoperphthalic Acid on the Oxide 5.**—(a) A solution of 200 mg. of **5** in 2.5 ml. of ether was treated with 2.5 ml. of an ethereal solution of monoperphthalic acid

(2.2 equiv.). After 48 hr. at 22° no phthalic acid had separated and the oxide **5** was recovered unchanged.

(b) A solution of 200 mg. of **5** in 2.5 ml. of chloroform (ordinary) was treated with 2.5 ml. of an ethereal solution of monoperphthalic acid (2.2 equiv.) at 22° for 48 hr., when 1 equivalent of reagent had been consumed. The recovered product solidified readily and crystallization from acetone gave 48 mg. of needles, m.p. 110–115.5°, $\alpha_D$ +12° Chf. Further crystallization from methanol gave needles, m.p. 117–118°, and a mixture with authentic 8α,14α-oxidocholestane-3β,7α-diol 3-acetate (m.p. 122–123°) melted at 117–119°.

**Action of Chloroform on the Oxide 5.**—(a) A solution of 200 mg. of **5** and 100 mg. of benzoic acid in 5 ml. of pure, dry chloroform was let stand at 22° for 48 hr. Unchanged starting material was recovered.

(b) The experiment was repeated but a drop of water was added. The result was the same.

(c) Chloroform (5 ml.) was shaken with 10% sulfuric acid (3 ml.) and the organic solvent was separated and dried for 10 min. over sodium sulfate. A solution of 200 mg. of the oxide **5** in this sample of chloroform was let stand at 22° for 48 hr. Evaporation of a washed and dried chloroform–ether extract left an oily residue which gave a positive tetranitromethane test and an infrared spectrum showing a band at 2.77 μ. The oil was let stand overnight in a mixture of 2 ml. each of acetic anhydride and pyridine. After recovery of product in the usual way it was adsorbed from petroleum ether onto 5 g. of alumina. Elution with petroleum ether–benzene (9:1) afforded 60 mg. of crystals which on crystallization from ether–methanol gave needles (15 mg.), m.p. 98–100°, identified as a mixture of $\Delta^{7,9(11)}$- and $\Delta^{7,14}$-cholestadiene-3β-ol acetate from spectrographic data: $\lambda^{EtOH}$ 242 mμ (9,700), shoulders at 235 mμ (8,650) and 250 mμ (6,770); $\lambda^{CS_2}$ 5.77, 8.08, 9.75 μ. Further elution with petroleum ether–benzene (4:1 and 2:1) gave about 60 mg. of oily product which crystallized from acetone to give 20 mg. of prisms, m.p. 128–131°. A further crystallization from acetone gave material (13 mg.) of m.p. 130–134.5°, $\alpha_D$ −3.8° Chf, tetranitromethane test positive, $\lambda^{EtOH}$ 207 mμ (11,200). A mixture with authentic $\Delta^{8(14)}$-cholestene-3β,7α-diol diacetate, m.p. 138–140°, melted at 130–137°.

*Anal.* Calcd. for $C_{31}H_{50}O_4$ (486.71): C, 76.50; H, 10.36. Found: C, 77.12; H, 10.33.

**Titration of Acid-treated Chloroform.**—A 100-ml. portion of chloroform was shaken with 10% sulfuric acid (30 ml.), dried over sodium sulfate for 10 min., and evaporated. A solution of the residue in 3 ml. of water was treated with potassium iodide–iodate–starch solution and the iodine liberated was titrated with 0.01 *N* thiosulfate solution; 0.4 ml. was consumed, which is equivalent to 0.2 mg. of sulfuric acid.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

# Anhydro Derivatives of Strophanthidin

BY LOUIS F. FIESER AND TOSHIO GOTO[1]

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A substance prepared by W. A. Jacobs and co-workers by the reaction of strophanthidin with ethanol containing hydrogen chloride and regarded as the ethylal of 14-anhydrostrophanthidin (**2a**) is in fact the 5-anhydro derivative **2b**. The substance now identified as 5-anhydrostrophanthidin (**3b**) permits evaluation of the effect on cardiotonic activity of a 5,6-double bond. Assays show that this structural feature decreases but does not abolish activity. The seven-ring structure **8** proposed for trianhydrostrophanthidin in 1936 is supported by the nuclear magnetic resonance spectrum of the compound.

In the course of W. A. Jacob's classical investigations of strophanthidin (**1**) Jacobs and Hoffmann[2] found that when dihydrostrophanthidin[3] is refluxed with hydrochloric acid in approximately 50% aqueous methanol one of the two tertiary hydroxyl groups is eliminated with formation of monoanhydrodihydrostrophanthidin. The observation proved important because hydroxylation of the anhydro linkage and oxidation established that the double bond is in a five-membered ring.[4] The degradation also showed that the hydroxyl group at $C_{14}$ is eliminated more readily than that at $C_5$. Jacobs and Collins[5] found that a solution of strophanthidin in absolute ethanol containing 10% of dry hydrogen chloride on standing at 25° deposits crystals of a monoanhydrostrophanthidin ethylal and, in view of the evidence cited, Jacobs and Elderfield[6] assumed this also to be a 14-anhydro derivative and formulated it as **2a**. The monoanhydrostrophanthidin obtained on hydrolysis of the ethylal was thus formulated as in **3a**.

We noticed that whereas conversion of dihydrostrophanthidin ($\alpha_D$ +35° MeOH) to the 14-anhydro derivative ($\alpha_D$ +48.5° Py) is attended with little change in rotation, conversion of strophanthidin ($\alpha_D$ +43° Al) to the monoanhydride ($\alpha_D$ −145° Al) is marked by a very large levorotatory shift. The strong levorotation of both the monoanhydride and its ethylal ($\alpha_D$ −50° Chf) suggested that they are the $\Delta^5$-derivatives **2b** and **3b**. If the 14β-hydroxyl group is retained, formation of the iso compound **4** should be possible, and indeed Jacobs and Elderfield found that the monoanhydrostrophanthidin is isomerized by base. Convinced that the double bond is at the 14,15-position, they interpreted the isomerization as involving either migration of the double bond in the lactone ring into conjugation with the anhydro linkage or migration of both double bonds to produce a $\Delta^{15,17}$-diene. Actually their isomonoanhydrostrophanthidin is not a conjugated diene, and the ultraviolet and infrared spectra are fully consistent with its formulation as the iso compound **4**. The preferential elimination of the 5-hydroxyl group in the reaction of strophanthidin in anhydrous ethanol indicates that the elimination is coupled with the closing of the 3β,19-oxide bridge. A model of the hypothetical ethylal of strophanthidin shows that rings A and B are both forced to assume the boat conformation and hence that the molecule is under considerable strain. However, the 5β-hydroxyl and the 6α-hydrogen are in the *trans* antiparallel orientation favorable for elimination, and formation of a 5,6-double bond ma-

(1) Recipient of a Fulbright travel grant on leave from Nagoya University, Nagoya, Japan.

(2) W. A. Jacobs and A. Hoffmann, *J. Biol. Chem.*, **74**, 791 (1927).

(3) W. A. Jacobs and M. Heidelberger, *ibid.*, **54**, 253 (1922).

(4) W. A. Jacobs and R. C. Elderfield, *ibid.*, **108**, 693 (1935).

(5) W. A. Jacobs and A. M. Collins, *ibid.*, **59**, 713 (1924).

(6) W. A. Jacobs and R. C. Elderfield, *ibid.*, **108**, 693 (1935).