3.65_w, 5.82_s (CHO); 8.75_s, 10.60_s, 10.90_s, 11.00_s μ (acetal in side chain); λ^{EtOH} 303 mμ (36).

3β,19-Oxido-5,14-dianhydrostrophanthidin Ethylal.—Jacobs and Collins[14] report m.p. 249–251° with sintering at 238°, α_D −142° Chf. Our sample formed needles, m.p. 229–235° dec., α_D −126° Chf; λ^{Chf} 5.61_s, 5.72_s, 6.13_m (lactone ring); 9.02_s, 9.72_s, 9.87_s, 10.03_s, 11.17_m, 11.60_m μ.

5,14-Dianhydrostrophanthidin is described[14] as m.p. 233–236°, α_D −222° Chf, λ^{EtOH} 303 mμ (126).[15] Our sample formed needles, m.p. 220–223°, α_D −212 Chf; λ^{Chf} 3.67_w, 5.82_s (CHO); 5.60_m, 5.72_s, 6.12_m (lactone ring); 9.57_m, 11.18_m, 11.58_m μ.

Trianhydrostrophanthidin (8), is described by Jacobs and Collins[14] as m.p. 135.5–137.5°, α_D +98° Chf; our sample: prisms, m.p. 133–135.5°, α_D +98.5° Chf; λ^{CS_2} 5.60_s, 5.70_s, 6.12_m (lactone ring); 9.39_s, 9.67_s, 9.81_s, 10.17_s, 11.31_s, 11.66_s, 12.27_s μ (1,2,3,4-tetrasubstituted benzene ring).

Methyl Trianhydrostrophanthidinethianate.—Finely powdered potassium permanganate (1 g.) was added portionwise to a solution of 1 g. of trianhydrostrophanthidin in 60 ml. of acetone with stirring at room temperature. After 30 min. another 0.5-g. portion of permanganate was added and the mixture was stirred for 1 hr. further and filtered. A suspension of the precipitated material in water was acidified with dil. sulfuric acid and extracted with chloroform, and the extract was washed, dried, and evaporated in vacuum. The residue (750 mg.) was treated with diazomethane in ether, and a solution of the crude ester in benzene was adsorbed onto 14 g. of alumina. Benzene eluates gave 240 mg. of crystalline solid which on crystallization from aqueous methanol formed long needles (200 mg.), m.p. 88–89°, α_D +122.3° Chf.

Anal. Calcd. for $C_{21}H_{26}O_3$ (326.42): C, 77.27; H, 8.03. Found: C, 77.17; H, 7.95.

Note.—We are indebted to a referee for the following comment: "Both trianhydrostrophanthidin and 3β,19-oxido-5-monoanhydrostrophanthidin ethylal exhibit *two* maxima in their carbonyl regions of the infrared while these compounds have only *one* carbonyl chromophore, the 5-membered α,β-unsaturated lactone. This fact is deserving of further explanation and is probably another example of Fermi resonance, an interpretation made more attractive by the intensification of the 5.60 μ band of **8** (CS_2) compared to that of **2b** ($CHCl_3$).[20] The presence of this band in several of the other compounds is also rationalized on this basis."

(20) R. N. Jones, T. Ito and C. L. Angell, *Angew. Chem.*, **69**, 645 (1957); P. Wieland, K. Heusler, H. Ueberwasser and A. Wettstein, *Helv. Chim. Acta*, **41**, 74 (1958); P. Yates, N. Yoda, W. Brown and B. Mann, THIS JOURNAL, **80**, 202 (1958); P. Yates and L. L. Williams, *ibid.*, **80**, 5896 (1958); R. Hirschmann, G. A. Bailey, R. Walker and J. M. Chemerda, *ibid.*, **81**, 2822 (1959).

CAMBRIDGE 38, MASS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Identification of Ketone 104 as 3,4-Secocholestane-6-one-(3α,5α)(3β,4)-dioxide

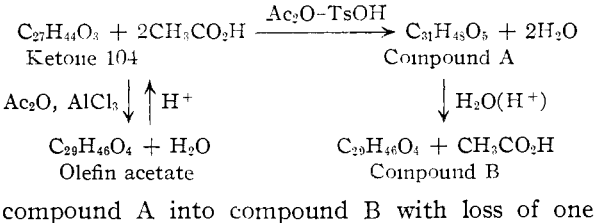
BY LOUIS F. FIESER.[1] TOSHIO GOTO[2] AND BIDYUT K. BHATTACHARYYA[3]

RECEIVED SEPTEMBER 3, 1959

Treatment of ketone 104 with acetic anhydride and aluminum chloride opens one of the two oxide bridges and gives the olefin acetate **4**, in which the double bond and acetate groups are isolated. Hydrogenation and acid hydrolysis gave a product (**6**) shown to be a primary alcohol by oxidation to an aldehyde and then to an acid. Under basic catalysis the hydroxymethyl group of **6** is eliminated as formaldehyde giving the ketone **7**. Wolff–Kishner reduction gave 4-oxacholestane 11, identical with material synthesized from the known **8**. The configuration of ketone 104 was established by synthesis of its desoxo derivative **22** starting with cholestane-3β,4β,5α-ol (**18**). Figure 1, reporting the n.m.r. spectrum, shows the conformation. The unusual reaction leading to ketone 104 is probably related to oxidative rearrangements of a type investigated by W. A. Mosher, and an analogous mechanism is suggested in formulas **29–32**.

Ketone 104,[4] a dioxidic product of the formula $C_{27}H_{44}O_3$ easily obtainable in 4% yield by high-temperature oxidation of cholesterol,[5] is unreactive to the Girard reagent[4] and has previously been characterized by the preparation of the following derivatives[6]: the corresponding alcohol and its acetate, the 2,4-dinitrophenylhydrazone, oxime, lactone, ethylenethioketal, desoxo derivative, and a substance regarded as an "enol acetate." In the first phase of the work now reported, one of us (B.K.B.) effected the transformation of the ketone into a succession of degradation products and derivatives designated by the letters A-J. The results were consistent with the presence of two oxidic bridges, but no known product was encountered and no fully satisfactory interpretation was arrived at. T. Goto later resumed work on the problem and by further characterizations of some of the products with the aid of new and improved instrumental facilities was able to work out the structures and interpretations presented in this paper and in a second one to follow.

Compound A, obtained in good yield by reaction of ketone 104 with acetic anhydride and *p*-toluenesulfonic acid at 25° and decomposition of the reaction mixture with ice and water, bears the relationship to the starting material indicated in the chart. The reaction involves condensation with two molecules of acetic acid, and acid hydrolysis transforms



compound A into compound B with loss of one molecule of acetic acid. Since the strong infrared bands in the fingerprint region[5] disappear on conversion to compound A but reappear on hydrolysis to B, the acetolysis to A involves opening of one oxide bridge and the hydrolysis to B is attended with reformation of this linkage. A fuller study of the infrared spectrum of the supposed "enol acetate," obtained[6] by reaction of ketone 104 with acetic

(1) Paper No. 300.

(2) Recipient of a Fulbright travel grant on leave (1957–1959) from Nagoya University, Nagoya, Japan.

(3) Work done as postdoctoral fellow in 1952–1953.

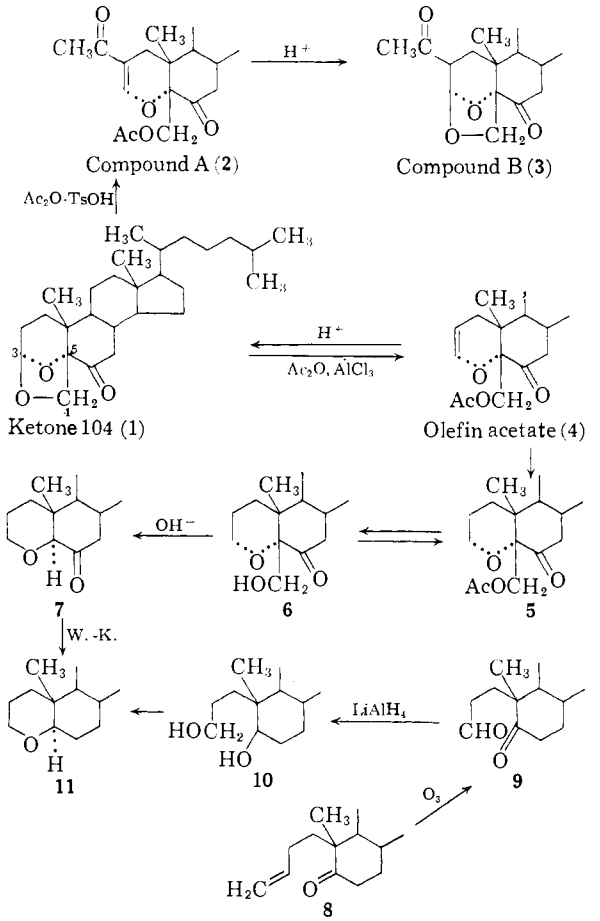
(4) L. F. Fieser, THIS JOURNAL, **75**, 4395 (1953).

(5) L. F. Fieser, W.-Y. Huang and T. Goto, *ibid.*, **82**, 1688 (1960).

(6) L. F. Fieser and B. K. Bhattacharyya, *ibid.*, **75**, 4418 (1953).

anhydride in the presence of aluminum chloride, revealed the presence of a keto carbonyl band in the original position in addition to the acetate carbonyl band and hence showed that the double bond is isolated from the ester function. The substance is thus more properly described as an olefin acetate. The conditions of formation are similar to those for production of compound A, but the reaction is less extensive and involves incorporation of just one molecule of acetic acid; under the best conditions found for production of compound A, a substantial amount of the olefinic acetate was also isolated. Like A, the olefin acetate lacks the stronger fingerprint bands but on acid hydrolysis reverts to ketone 104, with reformation of the second oxide bridge. In short, the relationships cited suggest that conversion to the olefin acetate involves the change: $-C-O-C-C- \rightarrow -COCOCH_3 + C{=}C-$ and that the reaction with acetic anhydride and *p*-toluenesulfonic acid involves formation of the olefin acetate and Friedel–Crafts acetylation of the double bond.

Ketone 104 shows a carbonyl stretching band at 5.79 μ which we now attribute to the presence of a 6-keto group. Compound A retains this band (5.78 μ) and has additional bands attributable to an acetate carbonyl group (5.72 μ), a conjugated double bond (6.13 μ), and a $\Delta^{\alpha,\beta}$-keto group (6.00 μ). The latter function is clearly indicated also by ultraviolet absorption in ethanol at 249 mμ (16,200).



The constants furthermore correspond closely with those observed for cyclohexane-1,3-dione enol ethyl ether, λ^{EtOH} 249 mμ (18,700),[7] and dimedone enol ethyl ether, λ^{EtOH} 250 mμ (19,200)[7]; λ^{Chf} 6.03, 6.15 μ.[8] On this evidence compound A is regarded as the 1,3-diketone cyclic enol ether **2**, with a primary acetoxy function and a 6-keto group. Ketone 104 (**1**) and compound B (**3**) are thus cyclic acetals of 3,4-seco-3-al-4,5-diols (the stereochemistry is discussed later). Formula **4** for the olefin acetate is supported by the presence in the infrared spectrum of bands at 3.27 (weak) and 13.74 (medium) μ characteristic of a disubstituted *cis* double bond. These bands, as expected, do not appear in the spectrum of compound A; the ultraviolet maximum of compound A (249 mμ) is consistent with its formulation as an α,β-disubstituted $\Delta^{\alpha,\beta}$-ketone, since the maximum calculated[9] from the value for the β,β-disubstituted cyclohexane-1,3-dione enol ethyl ether is 247 mμ (249 less 12-10).

Hydrogenation of the olefin acetate **4** gave the crystalline dihydride acetate **5**, and acid hydrolysis gave an alcohol (**6**) which was liquid but which on acetylation gave the crystalline acetate **5**. Unlike the alcohol from the olefin acetate, the alcohol **6** showed no tendency to cyclize. Oxidation of the alcohol **6** with a limited amount of chromic acid in pyridine gave a crude product showing aldehyde bands at 3.68(w) and 5.74(s) μ, in addition to a carbonyl band at 5.83 μ. Further oxidation with chromic acid in acetic acid gave a crude product characterized as an acid by broad infrared bands at 3.1–3.9 and 5.80 μ. The alcoholic function of **6** is thus shown to be primary. If the substance is indeed an α-hydroxymethyl ketone, treatment with base should eliminate the hydroxymethyl group by reverse aldolization. Both the alcohol and the crystalline acetate **5** when refluxed with methanolic potassium hydroxide gave a product showing no hydroxyl or acetate bands in the infrared spectrum and of composition consistent with the expected formula **7**, and this substance was converted by Huang-Minlon reduction[10] into a substance which should be 4-oxacholestane (**11**). The structure of the latter compound was established by synthesis from 4,5-seco-Δ^3-cholestene-5-one (**8**), prepared according to Clayton, Henbest and Smith[11] (see also ref. 5). Ozonization to the ketoaldehyde **9** followed by reduction with lithium aluminum hydride gave a diol (**10**) which on treatment with benzenesulfonyl chloride in warm pyridine was cyclized to 4-oxacholestane (**11**), shown by m.p. and infrared comparison to be identical with the product of degradation of ketone 104. It will be noted that the reverse aldolization of **5** to **7** establishes the presence of a (somewhat hindered) keto group at C_6.

That the 3,5-oxide bridge in ketone 104 extends to the α-side of C_5 was established by the following synthesis of desoxoketone 104 (**22**). The starting material, cholestane-3β,4β,5α-triol (**18**), was pre-

(7) E. G. Meek, J. H. Turnbull and W. Wilson, *J. Chem. Soc.*, 2891 (1953).

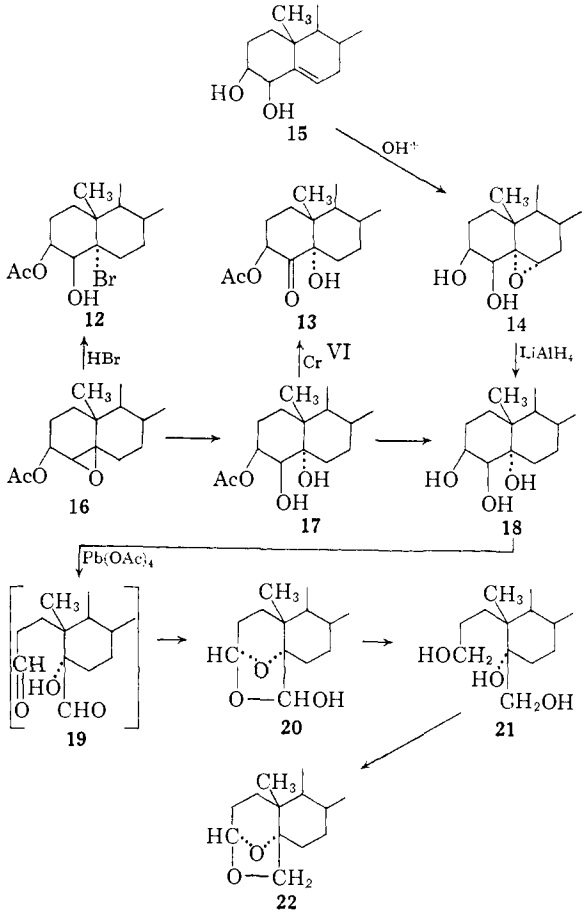
(8) K. Nakanishi, T. Goto and M. Ohashi, *Bull. Chem. Soc. Japan*, in press.

(9) L. F. Fieser and M. Fieser, "Steroids," Reinhold Publishing Corp., New York, N. Y., 1959, p. 19.

(10) Huang-Minlon, THIS JOURNAL, **71**, 3301 (1949).

(11) R. B. Clayton, H. B. Henbest and M. Smith, *J. Chem. Soc.*, 1982 (1957).

pared by a procedure based on the work of Plattner, Heusser and Kulkarni.[12] Δ^4-Cholestene-3-one was reduced with sodium borohydride to a mixture in which the 3β-ol predominates, the mixture on reaction with monoperphthalic acid gave a mixture consisting largely of the 4β,5β-oxides, and this on hydrolysis with perchloric acid in tetrahydrofuran gave a mixture from which the pure triol **18** could be isolated without difficulty. Proof of structure

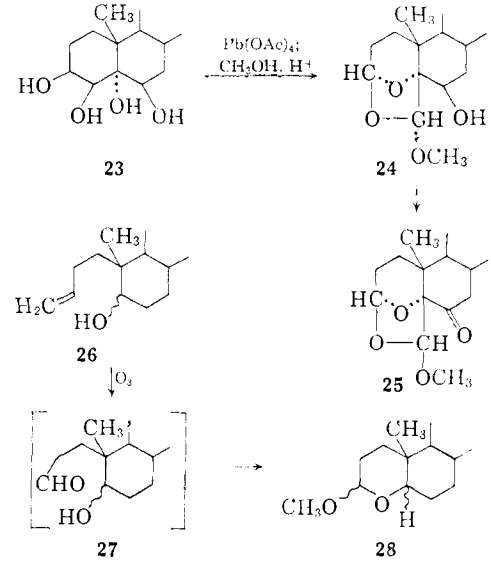


and configuration was important not only because the intermediates were mixtures but because when heated with acetic anhydride in the presence of either pyridine or sodium acetate the substance formed only a monoacetate. One piece of evidence supporting formula **18** was obtained by preparation of an identical triol from the difficultly accessible 4β,5β-oxidocoprostane-3β-ol 3-acetate (**16**)[13] by perchloric acid cleavage and saponification. The direction of cleavage was established by cleavage of the oxide acetate **16** with hydrobromic acid in acetone to give a bromohydrin which on acetylation (Ac_2O–Py) gave a monobromo diacetate and which therefore is the diaxial 5α-bromo-4β-ol (**12**) and not the diaxial 4β-bromo-5α-ol. Perchloric acid cleavage must then yield the acetate **17**. That this monoacetate contains a free secondary alcoholic group was established by oxidation to a ketone (**13**); triol **18** therefore must have two secondary alcoholic functions, one of which for some unknown reason is resistant to acetylation.

Triol **18** was also obtained (in very low over-all yield) by reaction of Δ^1-cholestene-3β,4β-diol[13] (**15**) with monoperphthalic acid in ether to give, after considerable recrystallization, the oxide **14**, m.p. 195.5–198°, α_D −39°, and reduction with lithium aluminum hydride. The course of this reduction shows that the substance is the 5α,6α-oxide, as formulated. On reaction of the unsaturated diol **15** with perbenzoic acid in chloroform, Rosenheim and Starling obtained an oxide, m.p. 173–174°, α_D +3.9°. The specific rotations of cholestane and its 3β-ol and 3β,5α-diol are +25, +22 and +20°, and introduction into each substance of a 4β-hydroxyl group gives compounds of nearly the same rotations: +29, +20 and +20°. Hence comparison with cholesterol α-oxide, α_D −46°, the β-oxide (+10°) and α,β-oxide (−15°) suggests that the previously reported substance is probably the β- or α,β-oxide.

On cleavage of cholestane-3β,4β,5α-triol (**18**) with lead tetraacetate the initially formed hydroxy dialdehyde **19** cyclized spontaneously to the dioxidic alcohol **20**. This on reduction with lithium aluminum hydride gave the triol **21**, which was then oxidized with a limited amount of *t*-butyl chromate to transform the more reactive primary alcoholic group to an aldehydic function. The product (**22**) proved to be identical with desoxoketone 104. The 3,5-oxide bridge is thus shown to extend to the α-side of C_5 because in the synthesis the oxide bridge is derived from an original 5α-hydroxyl group.

Perchloric acid cleavage of cholestane-3β,4β-diol-5α,6α-oxide (**14**) gave the tetrol **23**, which was investigated briefly as a possible starting point for the synthesis of ketone 104. Cleavage with lead tetraacetate and subsequent methylation



gave the methyl ether alcohol **24**, which could be oxidized to the 6-ketone **25**. The sequence was not extended because of the difficulty in obtaining starting material. However, the ether **24**, like the related alcohol **20**, showed characteristic

(12) Pl. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta*, **32**, 265, 1070 (1949).

(13) O. Rosenheim and W. W. Starling, *J. Chem. Soc.*, 377 (1937).

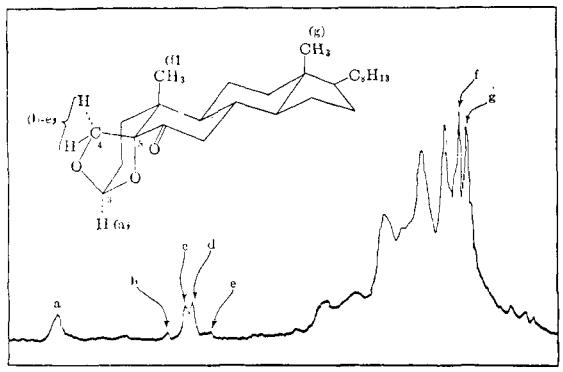


Fig. 1.—N.m.r. spectrum of ketone 104 in cycles per sec.: a, 34 (3α-H); b, 86, c, 94, d, 97, and e, 105 (two hydrogens at C_4 in different electronic circumstances; J = 8 c.p.s., δH = 7.5 c.p.s.); f, 226 (10-CH_3); g. 229 (13-CH_3).

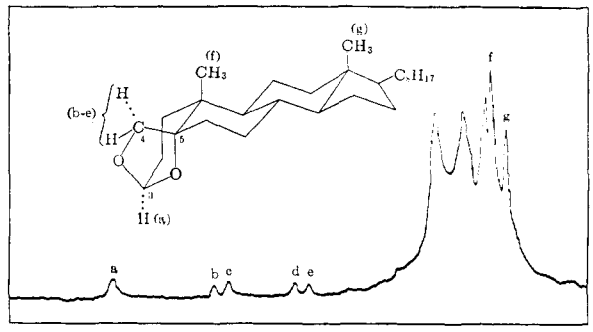


Fig. 2.—N.m.r. spectrum of desoxoketone 104 in cycles per sec.: a, 36 (3α-H); b, 86, c, 93.5, d, 125, e, 132.5 (two hydrogens at C_4; J = 7.5 c.p.s., δH = 38 c.p.s.); f, 222 (10-CH_3); g, 229 (13-CH_3).

strong infrared bands in the fingerprint region like ketone 104. The 4-oxacholestane or 4-oxacoprostane derivative **28** was synthesized by borohydride reduction of 4,5-seco-Δ^3-cholestene-5-one (**8**) to a crude alcohol **26**, ozonization (**27**), and methylation.

The nuclear magnetic resonance spectra of ketone 104 and its desoxo derivative are recorded in Figs. 1 and 2, with the assignments indicated in the legends. Of particular interest are the four peaks (b-e) associated with the protons of the 4-methylene group. Two at lower field (b, c) reflect resonances of one hydrogen, and two at higher field (d, e) are associated with the other. We shall designate these hydrogens according to their original configurations in cholesterol; thus the one directed more or less to the rear (dotted bond) is the 4β-H. This hydrogen is at a distance of 2.44 Å. from each of two hydrogens of the angular methyl group, and it is 2.36 Å. distant from the 1β-H; in desoxoketone 104 the 4β-hydrogen is not close enough to either hydrogen at C_6 for interaction. The 4α-hydrogen is, in the ketone, free from H-interactions, and in the desoxo compound it probably is too far from the 6β-H (2.9 Å.) and from the 6α-H (2.5 Å.) for significant effect. Hence reduction of the 6-keto group would not appear to alter the H-environment of either proton at C_4. On the other hand, the carbonyl oxygen atom is closer to the 4α-H than to the 4β-H by about 0.5 Å., and hence the peaks at higher field (d, e) that shift to lower frequencies on passing from the desoxo compound to the ketone would appear to be associated with the 4α-H. On the other hand, in view of the stronger H-environment on the rear side, the 4β-H would be expected to give rise to the peaks of higher frequency.

A point of interest is that, of the dioxidic substances studied, those which like ketone 104 have a bridging 4-methylene group show a characteristic infrared band (in chloroform solution) at 6.72 μ (1489 cm.$^{-1}$). Substitution in the methylene bridge of a hydroxyl (**20**) or methoxyl group (**25**) wipes out this band. The band is attributable to a scissoring vibration of the 4-methylene group and is comparable to bands near 1467 cm.$^{-1}$ for *n*-alkanes and near 1455 cm.$^{-1}$ for a CH_2 in a five-membered ring.[14] Typical 6-ketosteroids show a carbonyl stretching vibration at 1714–1706 cm.$^{-1}$,[15] but in the case of the 6-ketones of the present investigation the position of the band is shifted to 1730–1724 cm.$^{-1}$ (5.78–5.80 μ). This abnormal position of the carbonyl band is characteristic not only of the dioxidic compounds **1** and **3**, but also of the monoöxidic compounds **2**, **4** and **5**. With even the simple substance formulated as 4-oxacholestane-6-one (**7**) the carbonyl band is shifted to 1736 cm.$^{-1}$ (5.76 μ). In the 5α-configuration the bond extending from C_5 to oxygen is equatorial to ring B, and hence there may be some dipole interaction between this bond and the carbonyl group analogous to that noted with α-haloketones in which the halogen is equatorial.[16]

The formation by oxidation of a substance of the unusual structure established for ketone 104 is a remarkable reaction. Although it seemed unlikely that any of the normal oxidation products[17] is an intermediate to the abnormal one, the point was tested by oxidation of Δ^5-cholestene-3-one, cholesterol α- and β-oxide, and 6β-hydroxy-Δ^4-cholestene-3-one under conditions used for preparation of ketone 104, but none of them yielded this substance. Ketone 104 has a hydrogen atom at C_3 and two hydrogens at C_4, and presumably these three hydrogens are those originally present in cholesterol. Since the chief normal reaction involves attack of the hydrogen at C_3, the reaction producing ketone 104 would appear to be of a different type. Indeed evidence to this effect is that the yield of the ketone is increased from 1 to 4% by raising the temperature of initial oxidation from 20–40 to 100°.[5]

In a study of the chromic acid oxidation of secondary aliphatic alcohols to ketones, Mosher[18] has discovered that the main products are often accompanied by very small amounts of products of rearrangement. Thus methyl-*n*-amylcarbinol yielded 0.03% of *n*-amyl acetate, and ethyl-*sec*-butylcarbinol yielded 1% of *sec*-butyl alcohol. Mosher suggested that the reaction

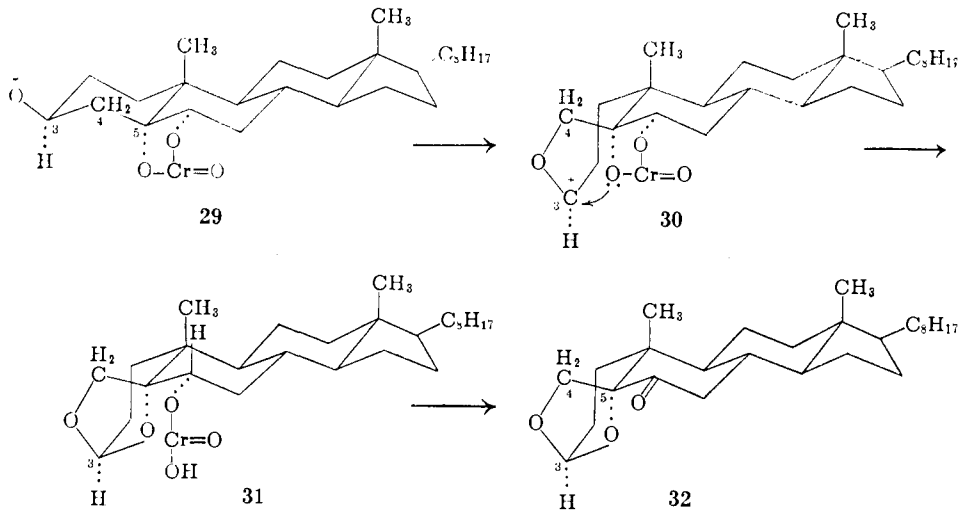
(14) S. A. Francis, *J. Chem. Phys.*, **19**, 942 (1951); R. N. Jones and A. R. Cole, THIS JOURNAL, **74**, 5648 (1952); K. Nakanishi, T. Goto and M. Ohashi, *Bull. Chem. Soc. Japan*, **30**, 403 (1957).

(15) L. F. Fieser and M. Fieser, ref. 9, p. 170.

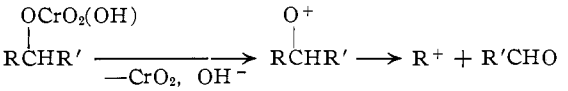
(16) E. J. Corey, THIS JOURNAL, **75**, 2301 (1953); R. N. Jones, D. A. Ramsey, F. Herling and K. Dobriner, *ibid.*, **74**, 2828 (1952).

(17) L. F. Fieser, *ibid.*, **75**, 4377, 4388 (1953).

(18) W. A. Mosher and E. O. Langerak, *ibid.*, **71**, 286 (1949); Dr. Mosher has kindly informed us of more recent results.



involves formation and rearrangement of an intermediate with an electron deficient oxygen or an equivalent chromate ester



A mechanism along similar lines which may be applicable to the case at hand involves the intermediates **29–32**. Attack of the double bond of cholesterol, in part at least, prior to oxidation of the alcoholic group has been observed in another instance (formation of epicholesterol).[17]

Acknowledgments.—This work was supported by grants from the National Cancer Institute of the National Institutes of Health (CY1696, C6 Endo), Research Corporation, and the Higgins Fund of Harvard University. We are indebted to Drs. Max Tishler and Malcolm L. Brown of Merck and Co. for preparation of a generous batch of ketone 104.[6]

Experimental[19]

Ketone 104, m.p. 123.5–124.5°; α_D −37.6, −36.6°; λ^{Chf} 5.80, 6.72w, 8.98, 9.82, 10.07, 11.08 μ.

Olefin Acetate (4).—A mixture of 1 g. of ketone 104 (1), 15 ml. of acetic anhydride and 1 g. of aluminum chloride was heated for 4 hr. in a vessel surrounded by the vapor of boiling xylene. Decomposition of the cooled mixture with ice and extraction with ether gave a yellow oil which gradually crystallized, and crystallization from methanol gave 880 mg. of rectangular prisms, m.p. 114–114.5°. Chromatography of the mother liquor afforded 40 g. more, m.p. 113–114°. Further crystallization afforded prisms, m.p. 115–116°; λ^{CS_2} 3.27w, 5.73s (acetate carbonyl), 5.79s (keto carbonyl), 6.03m, 8.14s (C–O), 9.47s, 13.73m μ.

5β-Acetoxymethyl-4-oxacoprostane-6-one (5).—A solution of 800 mg. of **4** in 25 ml. of acetic acid was hydrogenated at room temperature in the presence of 60 mg. of platinum oxide (50 min.). The recovered product was an oil but it separated from methanol to give cubical crystals, m.p. 107° (640 mg.). Recrystallization from methanol afforded plates, m.p. 108–109°, α_D −5°; λ^{CS_2} 5.73s, 8.09s, 9.40m, 9.58m μ.

Anal. Calcd. for $C_{29}H_{48}O_4$ (460.68): C, 75.60; H, 10.50. Found: C, 75.42; H, 10.64.

5β-Hydroxymethyl-4-oxacoprostane-6-one (6).—A solution of 100 mg. of **5** in 3 ml. of methanol containing 3 drops of concd. hydrochloric acid was refluxed for 3 hr. and worked up by dilution and ether extraction. The recovered product was an oil; λ^{CS_2} 2.78, 5.84s, 9.18m, 9.33m, 9.67m μ. Acetylation of a 50-mg. sample (1 ml. each of pyridine and acetic anhydride, 4 hr. at 24°) and crystallization from methanol gave 30 mg. of plates, m.p. 104–105°, undepressed on admixture with **5**.

A solution of 150 mg. of chromic anhydride in 4 ml. of pyridine was added to a solution of 100 mg. of **6** in 1 ml. of pyridine and the solution was let stand at 22° for 1 hr. Extraction with ether afforded a semi-solid residue, λ^{CS_2} 3.69w and 5.74s (aldehyde), 5.82s (ketone) μ. Further oxidation with chromic acid in acetic acid gave a crude product characterized as an acid by a very broad band centering at 3.5 μ and a strong broad band at 5.79 μ.

Compound A (2) by B. K. B.—A mixture of 5 g. of ketone 104, 75 ml. of acetic anhydride and 2.3 g. of *p*-toluenesulfonic acid was shaken occasionally at room temperature until the solid had all gone into solution (10–20 min.), let stand for 120 hr., and then decomposed with cold dil. sodium carbonate solution. The glassy precipitate was extracted with ether and the product crystallized from petroleum ether; it separated in fine white needles, m.p. 147–148°. The mother liquor when chromatographed furnished 1.31 g. of olefin acetate, m.p. 115–116°, and 2.01 g. of compound A, m.p. 147–148°, eluted by 1:3 petroleum ether–benzene (total yield 67%). Recrystallization from methanol gave fine needles, m.p. 147–148°, α_D −57°, λ^{EtOH} 249 mμ (16,200); λ^{CS_2} 5.73, 5.79, 6.00, 6.13, 8.15, 8.43 μ.

Anal. Calcd. for $C_{31}H_{48}O_5$ (500.69): C, 74.36; H, 9.66. Found: C, 74.66; H, 9.52.

When the reaction mixture was refluxed no crystalline products were obtained. When it was heated 1.5 hr. on the steam-bath the yield of **2** was 29%; when the reaction was conducted at room temperature for only 72 hr. the yield was 48%.

The dioxime was obtained by refluxing a solution of 30 mg. of **2**, 40 mg. of hydroxylamine hydrochloride and 0.05 ml. of pyridine in 2 ml. of methanol for 1 hr. and adding a few drops of water. The product which separated after three crystallizations from methanol afforded small plates, m.p. 119–120°, completely transparent at 125°, λ^{EtOH} 246 mμ (15,490).

Anal. Calcd. for $C_{31}H_{50}O_5N_2$ (530.73): C, 70.15; H, 9.50; N, 5.28. Found: C, 69.73; H, 9.37; N, 4.91.

The **disemicarbazone** when prepared similarly and crystallized three times from methanol melted at 193–195°; λ^{EtOH} 234–235 mμ (14,520), 269–270 mμ (22,130).

Anal. Calcd. for $C_{33}H_{56}O_6N_6$ (632.83): C, 62.63; H, 8.92; N, 13.28. Found: C, 63.17; H, 9.08; N, 12.64.

(19) Experiments by T. G., except as noted; infrared values all by T. G. Melting points are uncorrected. Specific rotations are measured in chloroform unless otherwise stated, *c* 1–2, maximum error ±2°. Infrared spectra in CS_2 or $CHCl_3$ taken in a 0.4-mm. cell with a Perkin–Elmer model 21 spectrophotometer; s = strong, m = medium, w = weak, no indication = strong. Ultraviolet spectra taken in 95% ethanol in a 1-cm. quartz cell with a Cary spectrophotometer. Recovery from an ethereal extract: solution washed 2–3 times with water, with saturated sodium bicarbonate solution, and with saturated salt solution, dried over sodium sulfate and the solvent removed in vacuum.

Compound B (3), by B. K. B.—A mixture of 120 mg. of compound A and a solution of 0.3 ml. of 96% sulfuric acid in 5 ml. of methanol was refluxed for 2 hr., cooled, diluted with ice and water, and the oil that precipitated was extracted with ether and chromatographed. A solid eluted by 3:1 and 1:1 petroleum ether–benzene, m.p. 120–123°, 35 mg. (32%), after three crystallizations from methanol formed fine needles, m.p. 124.6–125°, α_D −74.6° Chf (*c* 1.41); λ^{Chf} 5.81, 6.72$_m$, 7.36$_m$, 8.99, 9.45, 9.70, 10.07, 10.92, 11.10 μ; negative ferric chloride and tetranitromethane tests, no ultraviolet absorption.

Anal. Calcd. for $C_{29}H_{46}O_3$ (458.66): C, 75.94; H, 10.11. Found: C, 75.81; H, 10.27.

The same product was obtained in lower yield by the action of boron fluoride in methanol at 25°.

B-Dioxime.—A solution of 60 mg. of B, 90 mg. of hydroxylamine hydrochloride and 0.2 ml. of pyridine in 4 ml. of methanol was refluxed for 15 min., when considerable solid had separated. This was brought into solution with ethanol and refluxing continued for 2 hr., when the solution was diluted slightly and let cool. Three recrystallizations of the product (60 mg., m.p. 215–217°) from ethanol gave needles, m.p. 218.8–219.2°.

Anal. Calcd. for $C_{29}H_{48}O_4N_2$ (488.69): C, 71.27; H, 9.90; N, 5.73. Found: C, 71.31; H, 9.93; N, 5.64.

Compound C, probably a polymorphic form of B since the infrared spectra and specific rotations are practically the same, resulted from the treatment of C with acids. A solution of 0.3 ml. of 96% sulfuric acid in 5 ml. of methanol was added to a solution of 305 mg. of compound A in 15 ml. of methanol and the solution was let stand at room temperature for 16 hr. and worked up as before. The solid eluate, m.p. 110–112° (70 mg.) after four crystallizations from methanol, formed microcrystals, m.p. 110.6–111.6°, α_D −77.2° Chf, infrared spectrum identical with that of B.

Anal. Calcd. for $C_{29}H_{46}O_4$ (458.66); C, 75.94; H, 10.11. Found: C, 75.81; H, 10.11.

The same product resulted in low yield from treatment of A with methanolic hydrochloric acid at 25°; sulfuric acid in dioxane at 87° gave both B and C.

4-Oxocholestene-6-one (7).—A solution of 550 mg. of the saturated acetoxymethyl derivative **5** in 27.5 ml. of hot methanol was treated with 6 ml. of Claisen alkali and let cool to 22° and stand overnight. The solution was diluted with ether, washed with water, dried and evaporated and the residual solid crystallized from methanol to give long needles, m.p. 140–142° (380 mg.), α_D +30°; λ^{CS_2} 5.77$_s$, 8.94$_m$, 9.20$_m$, 9.33$_m$ μ (no OH band).

Anal. Calcd. for $C_{26}H_{44}O_3$ (388.61): C, 80.35; H, 11.41. Found: C, 80.39; H, 11.33.

Treatment of a methanol solution of the hydroxymethyl compound with Claisen alkali also afforded **7**, m.p. and mixed m.p. 139–141°.

4-Oxacholestane (11).—A mixture of 100 mg. of **7**, 400 mg. of potassium hydroxide, 90 mg. of 95% hydrazine, 1 ml. of ethanol and 4 ml. of triethylene glycol was heated in an oil-bath under reflux at 120° for 20 min. and the condenser was removed and the bath temperature raised to 200° and held there for 1 hr. The slightly dark solution was poured into water and the product collected by ether extraction and chromatographed on 1.5 g. of alumina. Petroleum ether eluates afforded 50 mg. of solid, which on crystallization from ether–methanol gave prisms, m.p. 94–95°, α_D +48°; λ^{CS_2} 9.08, 9.20 μ.

Anal. Calcd. for $C_{26}H_{46}O$ (374.63): C, 83.35; H, 12.38. Found: C, 83.00; H, 12.43.

Synthesis of 11.—Ozonized oxygen (0.1 millimole per minute) was passed into a solution of 1 g. of 4,5-seco-Δ^3-cholestene-5-one[5,11] (**8**) in 20 ml. of petroleum ether at 0° for 1 hr. and the solution was added to a solution of 0.5 g. of lithium aluminum hydride in 30 ml. of absolute ether at room temperature. The solution was refluxed for 30 min., excess reagent was decomposed with water and 10% sulfuric acid (80 ml.), and the crude 3,5-secocholestane-3,5β-diol (**10**) was used in the next step without purification. A solution of 0.5 g. of the diol in 4 ml. of pyridine was treated at about 90° with 0.8 ml. of benzenesulfonyl chloride, added by drops. After heating for 10 min. on the steam-bath, water was added and the product extracted with ether. The residual oil was adsorbed onto 15 g. of alumina and petroleum ether eluates afforded 100 mg. of solid product, which when crystallized from methanol afforded long prisms of **11**, m.p. 93.5–95.5°, undepressed on admixture with material obtained by degradation.

3-Methoxy-4-oxacholestane (28).—Sodium borohydride (200 mg.) was added to a solution of 1 g. of 4,5-seco-Δ^3-cholestene-5-one (**8**) in 5 ml. of ether and 5 ml. of methanol and the mixture was let stand at 22° for 1 hr. Evaporation of the ethereal extract gave a crude solid unsaturated alcohol (**26**), 0.5 g. of which in 20 ml. of chloroform was ozonized as above at 20° for 40 min. The ozonized solution was evaporated to 2 ml. at reduced pressure and room temperature, a solution of 200 mg. of sodium bisulfite in 5 ml. of water was added, and the mixture was heated on the steam-bath for 1 hr. (the purpose of this operation was to destroy any peroxidic material present; the hydroxyaldehyde **27** apparently had cyclized spontaneously). Ether extraction gave an oily product, and this was refluxed with 5 ml. of methanol containing 10 drops of concd. sulfuric acid. Ether extraction gave an oily product which was chromatographed on 10 g. of alumina. Petroleum ether–benzene (5:1) eluates gave 40 mg. of an oily product which crystallized after standing for some time. Crystallization from ether–methanol gave 20 mg. of needles, m.p. 89–92°; λ^{CS_2} 8.88, 9.48, 9.67, 11.25 μ.

Anal. Calcd. for $C_{27}H_{45}O_2$ (404.65): C, 80.14; H, 11.96. Found: C, 79.87; H, 11.84.

Cholestane-3β,4β,5α-triol (18). (a) Preparation.—Ten grams of Δ^4-cholestene-3-one, reduced with sodium borohydride in ether–methanol, gave 10 g. of an α,β-mixture of Δ^4 cholestene-3-ols, m.p. 118–123°. This material was treated in ether with 1.2 equivalents of monoperphthalic acid at room temperature for 2 days. The solution was decanted from precipitated phthalic acid and the solution was washed neutral, dried and evaporated. A solution of 6 g. of the residual oily oxide mixture in 60 ml. of tetrahydrofuran was treated with 18 ml. of 30% perchloric acid at 22° for 7 hr. Addition of water precipitated a filterable solid. This was digested with about 10 ml. of ether and the undissolved material collected. Crystallization from aqueous methanol gave 2 g. of material melting at 205–208°. Further crystallization from acetone afforded plates, m.p. 215–216°, α_D +20°. The analytical sample was dried at 110° in vacuum for 10 hr.

Anal. Calcd. for $C_{27}H_{48}O_3 \cdot {}^1/_2H_2O$ (429 66): C, 75.50; H, 11.50. Found: C, 75.50, 75.67; H, 11.40, 11.81.

3-Acetate (17).—A solution of 40 mg. of the triol in 0.5 ml. of pyridine and 0.5 ml. of acetic anhydride was let stand overnight at 22°. Dilution with ice-water precipitated a solid which on crystallization from methanol gave plates, m.p. 196–199°, α_D +6°; λ^{CS_2} 2.90$_m$, 5.73 μ.

Anal. Calcd. for $C_{29}H_{50}O_4$ (462.69): C, 75.28; H, 10.89. Found: C, 75.34; H, 10.90.

The monoacetate was also the product when the solution was heated on the steam-bath for 30 min. or when sodium acetate was used as the basic catalyst.

(b) **From Coprostane-3β-ol-4β,5β-oxide 3-Acetate (16).**—Prepared by the method of Plattner, *et al.*,[12] the sample consisted of needles, m.p. 91–92°, α_D −14°. A solution of 100 mg. of **16** in 2 ml. of tetrahydrofuran was treated with 0.3 ml. of 30% perchloric acid at 22° for 4 hr. and extracted with ether. The solid product on crystallization from methanol gave plates of the triol 3-acetate, m.p. 198.5–200.5°; a mixture with the above sample (a) melted at 197.5–200.5°. Saponification of the acetate from **16** and crystallization of the product from methanol gave slender needles of the triol **18**, m.p. 209–213°, α_D +22°.

(c) **From Δ^5-Cholestene-3β,4β-diol.**—A solution of 100 mg. of the 5α,6α-oxide **14** (below) in 5 ml. of ether was added to a solution of 50 mg. of lithium aluminum hydride in 5 ml. of ether and let stand at 22° for 3 hr. After addition of water and dilute sulfuric acid, extraction with ether and two crystallizations of the product from aqueous methanol gave slender needles, m.p. 200–203°. Acetylation in pyridine at 22° and crystallization of the product from methanol afforded plates, m.p. 190–195°, α_D +4°. Mixed m.p. and infrared comparison indicated identity with the acetate described in (a).

3β-Acetoxycholestane-5α-ol-4-one (13).—A solution of 100 mg. of cholestane-3β,4β,5α-triol 3-acetate (**17**) in 2 ml. of benzene was mixed with a solution of 100 mg. of sodium dichromate dihydrate in 2 ml. of acetic acid and the mixture was let stand at 28° for 10 hr. and then heated at about 50°

for 2 hr. The product recovered by dilution and ether extraction was an oil, but a solution in 0.5 ml. of methanol deposited aggregates of small needles (40 mg.). On recrystallization the product melted at 178–182°; λ^{CS_2} 2.90 (OH), 5.73 (ester carbonyl), 5.80 μ (keto group).

Anal. Calcd. for $C_{29}H_{48}O_4$ (460.67): C, 75.60; H, 10.50. Found: C, 75.82; H, 10.41.

5α-Bromocholestane-3β,4β-diol 3-Acetate (12).—A solution of 130 mg. of coprostane-3β-ol-4β,5β-oxide 3-acetate (**16**) in 6 ml. of acetone was treated with 0.26 ml. of 48% hydrobromic acid and kept at 30° for 45 min. Addition of water gave a filterable precipitate which on crystallization from methanol afforded 80 mg. of small prisms, m.p. 143–144.5° dec., α_D +18°. The substance is very sensitive to heat and decomposes somewhat even at room temperature.

Anal. Calcd. for $C_{29}H_{49}O_3Br$ (524.59): C, 66.40; H, 9.41. Found: C, 67.37; H, 9.64.

Acetylation in pyridine (24 hr. at 22°) gave the **3,4-diacetate,** which crystallized from methanol in plates, m.p. 148.5–150.5°, α_D +24°.

Anal. Calcd. for $C_{31}H_{51}O_4Br$ (566.63): C, 65.69; H, 9.09. Found: C, 65.82; H, 9.23.

Cholestane-3β,4β-diol-5α,6α-oxide (14).—A solution of 4 g. of Δ^5-cholestane-3β,4β-diol (m.p. 176°) in 150 ml. of ether was treated with 31.5 ml. of an ethereal solution of 1.1 mol. equiv. of monoperphthalic acid and let stand at 22° for 72 hr. The solution was decanted, washed until neutral, dried and concentrated eventually in 30 ml., after collecting successive crops of precipitate. Crystallization from methanol gave 2.82 g. of crystals, m.p. 184–186°. After several recrystallizations from methanol the oxide **14** was obtained as aggregates of prisms, m.p. 195.5–198°, α_D −39°.

Anal. Calcd. for $C_{27}H_{46}O_3$ (418.64): C, 77.46; H, 11.08. Found: C, 77.59; H, 11.17.

5α-Hydroxy-3,4-secocholestane-3,4-diol Cyclic Acetal-(20).—Cholestane-3β,4β,5α-triol (1.5 g.) was added to a solution of 2 g. of lead tetraacetate in 100 ml. of acetic acid at 22°. After a few hours long needles began to separate and these were found by infrared analysis to consist of a molecular compound of the reaction product **20** and acetic acid. The mixture was let stand overnight and then diluted with water and worked up by ether extraction. Evaporation of solvent left a solid which on crystallization from methanol gave 1.4 g. of needles, m.p. 134–135.5°, α_D −15°; λ^{CS_2} 2.94$_m$ (with a small band at 2.80), 9.07, 9.27, 9.82, 10.14, 10.38, 10.77, 10.92, 11.07 μ.

Anal. Calcd. for $C_{27}H_{46}O_3$ (418.64): C, 77.46; H, 11.08. Found: C, 77.39; H, 11.13.

3,4-Secocholestane-3,4,5-triol (21).—A solution of 1.3 g. of the acetal **20** in 5 ml. of ether was added to a solution of 0.5 g. of lithium aluminum hydride in 10 ml. of ether and the mixture was worked up after standing at 22° for 5 hr. Crystallization of the solid product from aqueous methanol gave 1.14 g. of needles, m.p. 114–116°.

Anal. Calcd. for $C_{27}H_{50}O_3$ (422.67): C, 76.72; H, 11.92. Found: C, 76.93; H, 12.15.

3,4-Secocholestane(3α,5α)(3β,4)-dioxide = Desoxoketone 104 (22).—A solution of *t*-butyl chromate was prepared by addition of 1 g. of chromic anhydride in portions with ice cooling to 2.2 g. of *t*-butyl alcohol and dilution with benzene to a volume of 20 ml.; the benzene solution was separated from a small aqueous layer and dried. Eight ml. of this solution was added to a suspension of 1 g. triol **21** in 20 ml. of benzene. The mixture was let stand at 22° for 48 hr. The solution then was shaken with 5 ml. of water containing 1.5 g. of sodium bisulfite and 20 ml. of 10% sulfuric acid until the color changed from brown to green. The yellowish organic layer was separated and processed as usual. On chromatography of the oily product on 20 g. of alumina, 4:1 petroleum ether–benzene eluates gave 260 mg. of an oil of infrared spectrum identical with that of desoxoketone 104, but it could not be induced to crystallize. This was rechromatographed on 10 g. of alumina and 9:1 petroleum ether–benzene and gave fractions which were oils but which when digested with methanol gave 80 mg. of crystals, m.p. 51–53°; a mixture with desoxoketone 104 melted at 51–56° and the infrared and n.m.r. spectra were identical; λ^{Chf} 6.74, 9.02, 9.87, 10.08, 11.10 μ.

Cholestane-3β,4β,5α,6β-tetraol (23).—A solution of 0.17 g. of cholestane-3β,4β-diol-5α,6α-oxide (**14**) in 13 ml. of tetrahydrofuran was treated with 0.8 ml. of 30% perchloric acid at 22° for 8 hr. Dilution with water gave a white precipitate which was washed well and crystallized from aqueous methanol and then from aqueous acetone. It separated as a microcrystalline powder, m.p. 173–176° (sample dried in vacuum at 110° for 15 hr.).

Anal. Calcd. for $C_{27}H_{48}O_4$ (436.65): C, 74.26; H, 11.08. Found: C, 74.62; H, 11.19.

4-Methoxy-4,5,6β-trihydroxy-3,4-secocholestane-3-ol Cyclic Acetal (24).—The crude tetraol **23** (550 mg.) was added to 30 ml. of acetic acid containing 0.05 mole of lead tetraacetate and the mixture worked up. Ether extraction gave a solid residue, which was refluxed for 2 hr. with 5 ml. of methanol containing 10 drops of concd. hydrochloric acid. Ether extraction gave a crude solid which was dissolved in 10 ml. of benzene and 20 ml. of petroleum ether and chromatographed on 12 g. of alumina. Ether eluates afforded 190 mg. of needles which on recrystallization from petroleum ether afforded needles, m.p. 118–120°, α_D −43°; λ^{Chf} 2.80$_w$, 9.02$_s$, 9.22$_s$, 10.25$_s$, 10.37$_s$, 11.08$_s$ μ.

Anal. Calcd. for $C_{28}H_{48}O_4$ (448.66): C, 74.95; H, 10.78; CH_3O, 6.92. Found: C, 74.47; H, 10.89; CH_3O, 7.09.

4-Methoxy-4,5-dihydroxy-3,4-secocholestane-3-ol-6-one Cyclic Acetal (25).—A solution of 50 mg. of sodium dichromate dihydrate in 0.5 ml. of acetic acid was added to a solution of 110 mg. of **24** in 1.5 ml. of benzene and 2 ml. of acetic acid with ice cooling. The mixture was let stand at 22° for 5 hr., and ether extraction gave an oil which solidified. Crystallization from petroleum ether afforded prisms, m.p. 120–121.5°, α_D −23°, λ^{CS_2} 5.80, 9.04, 9.20, 9.80, 9.97, 10.31 (broad), 11.05 μ.

Anal. Calcd. for $C_{28}H_{46}O_4$ (446.65): C, 75.29; H, 10.38. Found: C, 75.15; H, 10.44.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Reactions of Ketone 104

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Several transformations of the ketone are now interpretable on the basis of the structure **1**. Typical reactions involve acetolysis to the unsaturated acetoxy ketone **2** and electrophilic attack of the double bond to give products **3**, **9** and **10**.

Following elucidation of the structure of ketone 104 as 3,4-secocholestane-6-one-(3α,5α)(3β,4)-dioxide (**1**),[2] it is possible to interpret a series of transformations encountered (B. K. B.) in an early search for a clue to the structure. The key intermediate to most of the products is the previously described[2] olefin acetate **2**, obtainable in good yield by heating the ketone **1** with acetic anhydride and aluminum chloride at a temperature

(1) See notes 2 and 3 of preceding paper, ref. 2.

(2) L. F. Fieser, T. Goto and B. K. Bhattacharyya, THIS JOURNAL, **82**, 1700 (1960).