of displacement reactions at the ester and amide bond be provided. Finally, it is pointed out that the present study has been one of a kinetic nature which has presumed, in each case, a displacement of the thiol from the thiol ester carbonyl group. This assumption is felt to be quite safe on the grounds that thiol esters are much less prone to alkyl–sulfur cleavage than are oxygen esters prone to alkyl–oxygen cleavage[25b] and that valerolactone shows no tendency to undergo alkyl–oxygen cleavage. Korte and Cristoph have found no evidence for alkyl–S cleavage in the basic and acidic hydrolysis of a number of γ-butyro and δ-valerothiolactones.[44] It has also been observed that δ-thiolvalerolactone yields with liquid ammonia only δ-thiolvaleramide.[27] It should also be pointed out that in certain cases water may be involved in the transition state as a nucleophile. This is possible in reactions which are first order in the basic species (*i.e.*, general base-assisted water solvolysis) but very unlikely for the higher order reactions. Investigation of this possibility is being pursued.

Acknowledgments.—This work was supported by grants from the National Institutes of Health and the National Science Foundation.

(44) F. Korte and H. Christoph, *Ber.*, **94**, 1966 (1961).

[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY, EAST LANSING, MICH.]

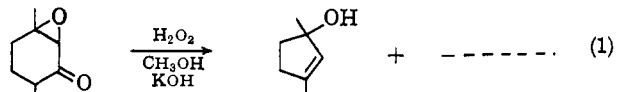
Rearrangements of 4,5-Oxidocholestane-3-one

BY WILLIAM REUSCH AND RONALD LEMAHIEU

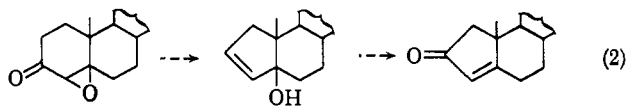
RECEIVED NOVEMBER 3, 1962

The α- and β-epoxides derived from Δ⁴-cholestene-3-one are rearranged by methanolic base to 4-methoxy-Δ⁴-cholestene-3-one (IV). An isomer previously believed to be IV has been identified as 3-methoxy-Δ²-cholestene-4-one (VI). These isomeric enol ethers and the diosphenol V were reduced by hydrogen iodide in refluxing acetic acid to cholestane-4-one. Oxidation of the epoxyketones II and III with alkaline hydrogen peroxide gave, respectively, the lactone acids VIII and X.

Base-catalyzed rearrangements of piperitone oxide and related α,β-epoxyketones were first reported by Treibs[1] and have recently been confirmed by the precise and thorough study of House and Gilmore.[2] Since piperitone oxide was observed to undergo a Favorskii ring contraction, we felt that this rearrangement might provide a convenient route to nor-steroids. In particular, a remarkable oxidative modification described by Treibs (eq. 1)[1d,3] seemed especially appropriate for this purpose (eq. 2).



(1)



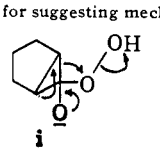
(2)

This paper reports the results from a study of the base-catalyzed reactions of β-(II) and α-(III) 4,5-oxidocholestane-3-one. These steroid isomers are found to differ from the previously reported cases[1,2] in that reaction with methanolic base is much slower and ring contraction does not occur. The major product from both the α- and β-isomers was 4-methoxy-Δ⁴-cholestene-3-one (IV), m.p. 136–138°. This structural assignment rests upon the elemental analysis, infrared spectrum ($\lambda_{max}^{CCl_4}$ 5.97, 6.25μ), ultraviolet spectrum ($\lambda_{max}^{C_2H_5OH}$ 255 mμ, log ε 4.1), n.m.r. (OCH_3 at 6.48 τ), hydrolysis to the diosphenol V and conversion *via* the corresponding ethylene-thioketal to cholestane-4-one. In addition to the above evidence, an isomeric enol ether previously regarded as IV[4] has been shown to have structure VI.

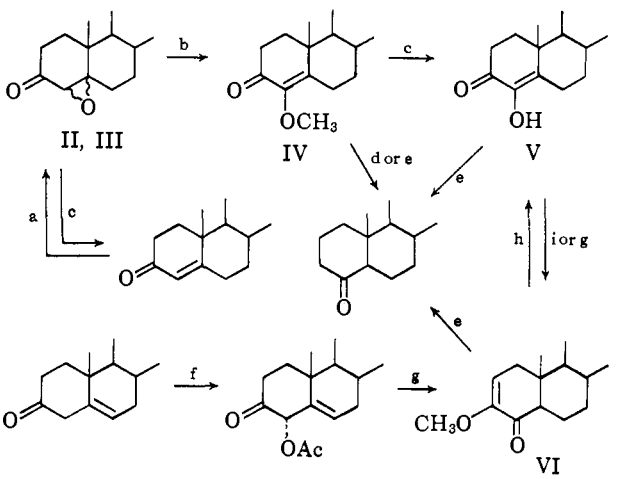
(1) (a) W. Treibs, *Ber.*, **63**, 2423 (1930); (b) **64**, 2178, 2545 (1931); (c) **65**, 163, 1314 (1932); (d) **66**, 610, 1483 (1933).

(2) H. House and W. Gilmore, *J. Am. Chem. Soc.*, **83**, 3972 (1961).

(3) We wish to thank Professor D. H. R. Barton for calling this unusual reaction to our attention and for suggesting mechanism i.



i



(a) CH_2OH, H_2O_2, NaOH at 0°
(b) CH_3OH, NaOH at reflux
(c) HCl, dioxane at reflux
(d) 1, ethanedithiol + BF_3; 2, H_3O^+; 3, Raney nickel
(e) HI in acetic acid at reflux
(f) $Pb(OAc)_4$ in acetic acid
(g) BF_3 in methanol at reflux
(h) HCl, 95% ethanol
(i) $(CH_3)_2SO_4$, CH_3OH, NaOH

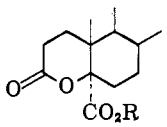
The reaction of 4-α-acetoxy-Δ⁵-cholestene-3-one with refluxing methanolic boron trifluoride yields a $C_{28}H_{46}O_2$ enol ether,[4] m.p. 149°, which is readily hydrolyzed to diosphenol V, and exhibits a n.m.r. spectrum having a pair of overlapping doublets at 4.55 τ (characteristic of C=C*H*—CH_2—) with an area roughly one third that of the OCH_3 group at 6.51 τ. The assignment of structure VI to this substance is supported by the infrared ($\lambda_{max}^{CCl_4}$ 5.95, 6.12 μ) and ultraviolet[5] ($\lambda_{max}^{C_2H_5OH}$

(4) L. F. Fieser and R. Stevenson, *J. Am. Chem. Soc.*, **78**, 1409 (1956). Shortly after this paper was submitted for publication, we discovered that identical structural assignments were made by B. Camerino, B. Patelli and R. Sciaky, *Gazz. chim. ital.*, **92**, 709 (1962). These workers have also prepared the testosterone, analogs of IV and VI.

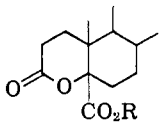
(5) The enhanced bathochromic influence of the α-methoxyl group in enone VI (+37 mμ) as contrasted with that for enone IV (+12 mμ) requires further comment. We suggest that for maximum effect the bonding plane of the oxygen be parallel to the enone chromophore. This condition is easily satisfied when the α-substituent is a hydroxyl group (ii), and diosphenol V($\lambda_{max}^{C_2H_5OH}$ 278, log ε 4.1) exhibits a bathochromic increment of +35 mμ for this substituent. Coplanarity of the methoxyl group in IV, however, is prevented by crowding of the O-methyl with either the carbonyl oxygen or the C-6 methylene group, and a much smaller substituent effect is ob-

263 mμ, log ε 3.8) spectra. Since IV is not changed in any respect by an equivalent treatment with methanolic boron trifluoride, it cannot be an intermediate in the formation of VI. Although diosphenol V[6] does not react with ethereal diazomethane, a refluxing alkaline solution of dimethyl sulfate slowly converted V to the enol ether VI. Isomer VI was also the major product from treatment of V with refluxing methanolic boron trifluoride.[4]

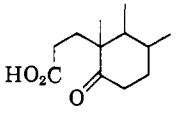
The hydrolysis of IV to V proceeds much slower than for the isomeric enol ether VI. Since our initial attempts to effect this transformation under mild conditions were unsuccessful, we treated IV with a refluxing acetic acid solution of hydriodic acid. The product of this reaction was not the expected diosphenol, but cholestane-4-one. This remarkable reaction has been duplicated using enol ether VI and the diosphenol V as reactants; the latter compound is undoubtedly a common intermediate.[7]



VIII, R = H
IX, R = CH_3

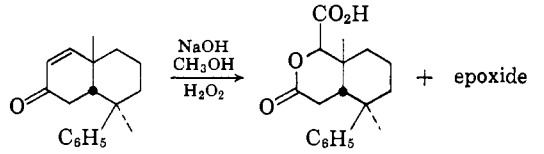


X, R = H
XI, R = CH_3



XII

Oxidation of epoxy ketones II and III with alkaline hydrogen peroxide solutions gave respectively the lactone acids VIII and X rather than the A-nor-enols (equation 2) anticipated by analogy with piperitone oxide.[1d] Windaus[8] and Tschesche[9] reported VIII among the products of permanganate oxidation of Δ^4-cholestene-3-one, but cited no evidence for this structural assignment. Both VIII and X have now been degraded to the well known keto acid XII[8,10] by oxidation with lead tetraacetate and sodium bismuthate, respectively.[11] This, coupled with the infrared spectra of the acids and their methyl esters lends strong support to the structures proposed here.[12] Since VIII and X are stereoisomers, the rearrangement must have



proceeded with either retention or inversion of configuration at C-5. We prefer the former possibility from mechanistic considerations[13] and tentatively assign configurations VIII and X to the isomers.

The differences in the reactions of the steroidal epoxy ketones described in this paper, as contrasted with piperitone and carvenone oxides,[1d,2] are paralleled in the chemistry of isophorone oxide reported by House and Gilmore.[2] This suggests that an α-alkyl substituent may be necessary for the Favorskii ring contraction of α,β-epoxyketones. We are now investigating the corresponding 2-alkyl-4,5-oxido-3-ketosteroids with this possibility in mind.

Experimental

Melting points were determined on a Kofler hot-stage. The infrared spectra were measured with a Perkin–Elmer model 21 spectrophotometer. The ultraviolet spectra were determined with a Beckman DK-2 spectrophotometer. The microanalyses were performed by Spang Microanalytical Lab., Ann Arbor, Mich. The n.m.r. spectra were determined in carbon tetrachloride solution using a Varian Associates, A-60, high resolution spectrometer.

4-Methoxy-Δ^4-cholestene-3-one (IV). From II. A.—A solution of 4β,5β-oxidocholestane-3-one[14] (II, m.p. 117.5–118.5°, 200 mg.) in methanol (25 ml.) was treated with 4 *N* sodium hydroxide (2 ml.) at reflux for 24 hr. Dilution with water followed by 24 hr. at 5° gave a solid (180 mg.) which was crystallized from aqueous methanol to give IV as needles (140 mg.), m.p. 133–135°, $\lambda_{max}^{CCl_4}$ 5.97 and 6.25 μ, $\lambda_{max}^{C_2H_5OH}$ 255 mμ (log ε 4.1), $[\alpha]^{28}D$ +87.5° (*c* 0.56 g./100 ml., $CHCl_3$); n.m.r. 6.48 (OCH_3), 8.83, 9.08, 9.12, 9.30 τ (no vinyl hydrogen). An analytical sample, m.p. 136–138°, was prepared by crystallization from petroleum ether.

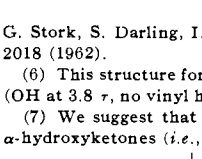
Anal. Calcd. for $C_{28}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.52; H, 11.39.

B.—A similar reaction employing sodium methoxide instead of the hydroxide gave, after 24 hr. at reflux, a 50% conversion to IV and a 50% recovery of II.

From III.—A solution of 4α,5α-oxidocholestane-3-one[15] (III, m.p. 118–121°, 23 mg.) in methanol (3 ml.) containing 0.25 ml. of 4 *N* sodium hydroxide was refluxed for 24 hr. Dilution with water (3 ml.) followed by 3 hr. at 0° gave 24 mg. of a crude solid which was crystallized twice from aqueous methanol to give 17 mg. of IV, m.p. 135–137°. A mixture melting point with the material from the previous preparation was undepressed.

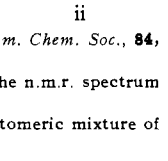
3-Methoxy-Δ^2-cholestene-4-one (VI).—A solution of 4α-acetoxy-Δ^5-cholestene-3-one[16] (m.p. 155–157°, 700 mg.) in methanol (35 ml.) containing freshly distilled boron trifluoride etherate (0.7 ml.) was refluxed 1 hr. Dilution with water followed by cooling (5°) overnight gave 460 mg. of crude product which was crystallized from petroleum ether and twice from methanol to give 120 mg. of VI, needles, m.p. 148–149°; $\lambda_{max}^{CCl_4}$ 5.95, 6.12 and 9.07 μ; $\lambda_{max}^{C_2H_5OH}$ 263 (log ε 3.8); n.m.r. 4.55 (center of a quartet due to C=CH) and 6.51 (OCH_3) τ (peak areas ~ 3:8). This material is presumed to be identical with the product

served. In order for an α-methoxyl group to attain coplanarity, the enone[e] chromophore must not bear a *cis*-β-alkyl substituent, a condition met by compounds VI, iii and iv.



iii, α-isomer, $\lambda_{max}^{C_2H_5OH}$ 267.5 mμ

iv, β-isomer, $\lambda_{max}^{C_2H_5OH}$ 262 mμ

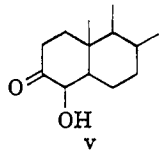


ii

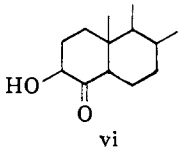
G. Stork, S. Darling, I. Harrison and P. Wharton, *J. Am. Chem. Soc.*, **84**, 2018 (1962).

(6) This structure for the diosphenol is confirmed by the n.m.r. spectrum (OH at 3.8 τ, no vinyl hydrogens).

(7) We suggest that the reduction proceeds *via* a tautomeric mixture of α-hydroxyketones (*i.e.*, v and vi).



v



vi

Reductive removal of the least hindered hydroxyl group (that in vi) then leads to the observed product. In support of this proposal, α-hydroxycyclohexanone has been reduced to cyclohexanone under similar conditions. It is worth noting that hydrogen iodide reduction of epoxyketone II gives Δ^4-cholestene-3-one.

(8) A. Windaus, *Ber.*, **39**, 2008 (1906).

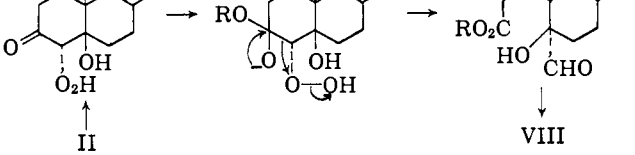
(9) R. Tschesche, *Ann.*, **498**, 185 (1932).

(10) R. B. Turner, *J. Am. Chem. Soc.*, **72**, 579 (1950).

(11) Isomer X is recovered unchanged from treatment with lead tetraacetate under conditions which permit the conversion of VIII to XII. Vigorous oxidation with sodium bismuthate is necessary for the degradation of X. Stereochemical arguments based upon this difference in reactivity are unfortunately lacking in rigor.

(12) We are pleased to acknowledge a private communication from Professor R. Ireland in which a similar rearrangement is reported.

(13) Opening of the epoxide ring by nucleophilic attack at C-5 is less likely than attack at C-4, which must also be the initial step in the formation of enol ether IV. We offer the following mechanism as a rationale for this rearrangement, but hasten to point out that other explanations are possible.



II VIII

(14) Prepared by the method of J. Shaw and R. Stevenson, *J. Chem. Soc.*, 3549 (1955).

(15) The α-oxide was prepared by photosensitized oxidation of Δ^4-cholestene-3β-ol. We wish to thank Professor Alex Nickon for detailed instructions concerning this preparation.

(16) Prepared by lead tetraacetate oxidation of Δ^5-cholestene-3-one according to L. Fieser and R. Stevenson, *J. Am. Chem. Soc.*, **76**, 1731 (1954).

obtained by Fieser and Stevenson[4]; m.p. 150–151°; $\lambda_{max}^{CHCl_3}$ 5.91, 6.06, 9.00 μ; $\lambda_{max}^{C_2H_5OH}$ 263 (log ϵ 3.7).

Attempted Rearrangement of IV with Boron Trifluoride.—A solution of 4-methoxy-Δ^4-cholestene-3-one (IV, 200 mg.) in methanol (20 ml.) containing boron trifluoride etherate (1 ml.) was refluxed for 1 hr. Dilution with water followed by cooling to 0° gave a solid which was crystallized from aqueous methanol to give 170 mg. of recovered IV, m.p. 135°, identified by mixture melting point and infrared spectrum.

4-Hydroxy-Δ^4-cholestene-3-one (V).—A solution of 4α-acetoxy-Δ^5-cholestene-3-one (200 mg.) in 95% ethanol (10 ml.) containing 0.5 ml. of concd. hydrochloric acid was refluxed for 3 hr. The mixture was diluted with water, and after cooling at 0° deposited a yellowish solid which was crystallized twice from methanol to give 100 mg. of V, m.p. 145–147°, $\lambda_{max}^{C_2H_5OH}$ 278 (log ϵ 4.1), n.m.r. 3.8 τ (broad).

Hydrolysis of Enol Ether IV.—A solution of 4-methoxy-Δ^4-cholestene-3-one (IV, 200 mg.) in dioxane (25 ml.) containing concd. hydrochloric acid (2 ml.) was refluxed for 24 hr. Water was added to the cooled solution and the resulting yellowish solid was crystallized from methanol to give 100 mg. of V, m.p. 144–146°, identified by mixture melting point and infrared spectrum. The conditions required for hydrolysis of IV are much more severe than those reported[4] and found for the hydrolysis of 3-methoxy-Δ^2-cholestene-4-one (VI).

Methylation of 4-Hydroxy-Δ^4-cholestene-3-one (V).—A solution of diosphenol V (700 mg.) and sodium hydroxide (200 mg.) in methanol (100 ml.) was treated with dimethyl sulfate (2.7 g) and refluxed for 24 hr. Water was then added until a cloudiness persisted and the reaction mixture was cooled to 0°. The infrared spectrum of the resulting solid product (650 mg.) indicated that a mixture of unreacted diosphenol and the enol ether VI had been produced. Chromatography of 200 mg. of this mixture on neutral alumina (activity I) gave 80 mg. of VI, m.p. 146–147°, eluted with benzene and identified by mixture melting point and infrared spectrum. Elution with ether gave 100 mg. of unreacted V.

Diosphenol V does not react with ethereal diazomethane.

Conversion of Enol Ether IV to Cholestane-4-one.—A solution of 4-methoxy-Δ^4-cholestene-3-one (IV, 100 mg.) in acetic acid (0.5 ml.) was treated with ethanedithiol (0.4 ml.) and boron trifluoride etherate (0.4 ml.) and permitted to stand at room temperature for 15 hr. The reaction mixture, which at this point consisted of two phases, was shaken with a mixture of ether and water, and the ether extracts were washed with dilute sodium bicarbonate, dried and evaporated to yield a heavy oil. This oil was taken up in 25 ml. of ethanol containing 1.5 ml. of 20% hydrochloric acid and the solution was warmed on a steam-bath for 10 min. Dilution with water followed by extraction with ether gave a semisolid material which was dissolved in 15 ml. of abs. ethanol and refluxed over Raney nickel (0.3 g.) for 6 hr. Removal of the catalyst by filtration, dilution with water and extraction with ether resulted, after the usual work-up techniques, in the isolation of 70 mg. of a crude solid. Two crystallizations from aqueous methanol gave pure cholestane-4-one, m.p. 97–98°, identified by mixture melting point and comparison of the infrared spectrum with authentic material.[17]

Reduction of Enol IV by Hydrogen Iodide.—A solution of 4-methoxy-Δ^4-cholestene-3-one (IV, 200 mg.) in glacial acetic acid (15 ml.) containing 0.5 ml. of 47% hydriodic acid was refluxed for 1 hr. After dilution with water, the reaction mixture was extracted with ether and the ether extracts washed, decolorized and dried over magnesium sulfate. The extracts yielded 180 mg. of a crude solid which, when crystallized from aqueous methanol, gave cholestane-4-one (100 mg.), m.p. 96–97°, identified by mixture melting point and infrared spectrum.

Reduction of Enol Ether VI.—A solution of 3-methoxy-Δ^2-cholestene-4-one (100 mg.) in glacial acetic acid (15 ml.) was treated with 0.5 ml. of 47% hydriodic acid at reflux for 30 min. A work-up similar to that described in the preceding preparation gave cholestane-4-one (55 mg.), m.p. 95–96°.

Reduction of Diosphenol V.—A solution of 4-hydroxy-Δ^4-cholestene-3-one (V, 200 mg.) in glacial acetic acid (15 ml.) was treated with 0.5 ml. of 47% hydriodic acid at reflux for 30 min. Cholestane-4-one (80 mg.), m.p. 95–96°, was isolated by the usual work-up.

Reduction of II by Hydrogen Iodide.—A solution of 4β,5β-oxidocholestane-3-one (II, 200 mg.) in glacial acetic acid (20 ml.) containing 47% hydriodic acid (1 ml.) was refluxed for 30 min. After dilution with water and extraction with ether, a white solid (170 mg.) was obtained which after two crystallizations from aqueous methanol gave needles, m.p. 78–79°, identified as Δ^4-cholestene-3-one by mixture melting point and infrared spectrum.

Reduction of α-Hydroxycyclohexanone by Hydrogen Iodide.—A solution of α-hydroxycyclohexanone (1.0 g., Aldrich Chem. Co.) in acetic acid (40 ml.) was refluxed 1 hr. with 47% hydriodic acid (2 g.). Neutral products were isolated by diluting the reaction mixture with water, extraction with ether and a strong basic wash of the combined ether extracts. A light yellow oil (420 mg.) was thus obtained. This material was identified as cyclohexanone on the basis of the infrared spectrum (traces of cyclohexenone were also present), retention time on a 20% silicone column (6 ft.) at 100°, and preparation of a DNP, m.p. 158–159° (after chromatography on alumina), which was identical with an authentic sample.

5α-Carboxy-4-Oxacholestane-3-one (VIII).—A solution of 4β,5β-oxidocholestane-3-one (II, 200 mg.) in methanol (25 ml.) was heated to reflux while 30% hydrogen peroxide (1.6 ml.) and 4 *N* sodium hydroxide (1 ml.) were added simultaneously. After refluxing for 24 hr., the reaction mixture was diluted with water and extracted with ether; 10 mg. of neutral material was thus obtained. Acidification of the aqueous portion followed by ether extraction yielded 180 mg. of acidic material which was crystallized from aqueous methanol to give a white solid, m.p. 213–215°, $\lambda_{max}^{C_4Cl_6}$ 5.72 and 5.87 μ.

A methyl ester (IX) was prepared by reaction with diazomethane; m.p. 152–154°, $\lambda_{max}^{CCl_4}$ 5.72 and 5.76 μ.

Anal. Calcd. for $C_{28}H_{46}O_4$: C, 75.29; H, 10.38. Found: C, 75.11; H, 10.49.

These properties compare favorably with those reported by Windaus[8] and Tschesche[9] for VIII, m.p. 217–218°, methyl ester m.p. 148–149°.

Compound VIII may also be obtained as a by-product from the epoxidation[14] of Δ^4-cholestene-3-one by acidification and extraction of the basic aqueous filtrate.

5β-Carboxy-4-oxacholestane-3-one (X).—A solution of 4α,5α-oxidocholestane-3-one (49 mg.) in hot methanol (6 ml.) was refluxed while 30% hydrogen peroxide (0.4 ml.) and 4 *N* sodium hydroxide (0.3 ml.) were quickly added. An additional ml. of methanol was added to dissolve a flocculent white solid which formed. After refluxing for 24 hr. the mixture was poured into 15 ml. of cold 3% sodium hydroxide. Ether extraction of this basic mixture gave 3 mg. of a neutral oil, while acidification and extraction of the aqueous portion yielded 40 mg. of a white solid. Several crystallizations of the acidic material from ethyl acetate–cyclohexane and from aqueous methanol gave 11 mg. of material, m.p. 186–192°, which strongly depressed the melting point of the lactone acid VIII reported above. The infrared spectrum of X, $\lambda_{max}^{CCl_4}$ 5.72 and 5.85 μ, was significantly different from VIII in the fingerprint region.

Difficulties in the further purification of X led to the preparation of the corresponding methyl ester XI by reaction with diazomethane. Two crystallizations from aqueous methanol gave lustrous plates, m.p. 116–119°, mixture melting point with IX 102–120°, $\lambda_{max}^{CCl_4}$ 5.70–5.78 μ.

Anal. Calcd. for $C_{28}H_{46}O_4$: C, 75.29; H, 10.38. Found: C, 74.52; H, 10.89.

Oxidation of VIII to XII.—A solution of 5α-carboxy-4-oxacholestane-3-one (VIII, 500 mg.) in benzene (20 ml.) and acetic acid (20 ml.) was treated with lead tetraacetate (1.0 g.) for 80 hours at room temperature. Excess oxidizing agent was destroyed by the addition of a little ethylene glycol; the reaction mixture was then diluted with water and extracted with ether. The yellow oil obtained from the dried ether extracts was crystallized from petroleum ether and gave 320 mg. of solid. Three recrystallizations from petroleum ether–benzene mixtures raised the melting point to 149–150°. A mixture melting point with authentic XII (m.p. 150–151°) prepared[10] by ozonolysis of Δ^4-cholestene-3-one was not depressed, and the infrared spectra of the corresponding methyl esters were identical.

Oxidation of X by Lead Tetraacetate.—A solution of 5β-carboxy-4-oxacholestane-3-one (X, 23 mg.) in benzene (5 ml.) and acetic acid (5 ml.) was treated with lead tetraacetate (75 mg.) for 80 hours at room temperature. A work-up similar to that described in the previous preparation yielded only recovered X (15 mg., m.p. 185–192).

Oxidation of X by Sodium Bismuthate.—A solution of X (15 mg.) in benzene (3 ml.) and acetic acid (3 ml.) was treated with sodium bismuthate (50 mg.) for 24 hours at room temperature followed by 3 hours on the steam-bath. Bismuth was precipitated as the phosphate and the reaction mixture was diluted with water and extracted with ether. The washed and dried ether extracts yielded an oil (14 mg.) which gave a solid upon trituration with petroleum ether. Several crystallizations from a petroleum ether–benzene mixture raised the melting point of this material to 135–140°. Infrared examination of the methyl ester (prepared by reaction with diazomethane) demonstrated we were dealing with a mixture (roughly 50:50) of XII and unreacted X. The oily methyl ester mixture was converted to a 2,4-dinitrophenylhydrazone derivative[18] which was purified by chromatography on alumina. The resulting yellow DNP, m.p. 91–93°, was identical with the corresponding derivative, m.p. 93–96°, prepared from authentic XII.

(17) Cholestane-4-one was prepared by a method devised by G. Stork and W. Reusch: William Reusch, Ph.D. Thesis, Columbia University, 1957.

(18) R. Shriner, R. Fuson and D. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, Inc., New York, N. Y., 1956, p. 11.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, BERKELEY 4, CALIF.]

The Configuration of B-Norsteroid Derivatives[1,2]

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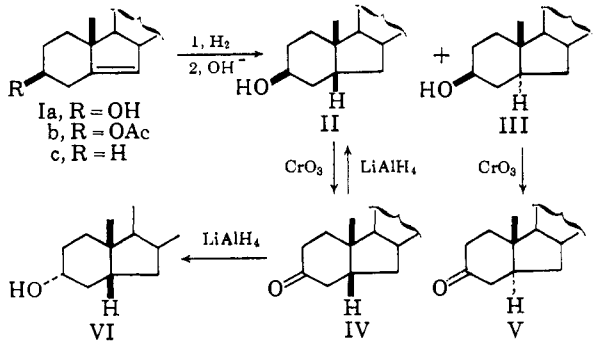
The stereochemical course of the hydrogenation of B-norcholesteryl acetate has been re-examined and it has been found that the major product possesses an A/B *cis* configuration, a result in direct contrast to that found with natural steroids. The epoxide derived from B-norcholesteryl acetate has been shown to possess the α-configuration. Studies of the reaction of the epoxide and its derivatives have permitted the determination of the configuration of "Butenandt diketone" (XIII) and the evaluation of the steric strain present in the B-norsteroid series. The configuration of the four isomeric diols derived from the above dione has been established and the certain reactions of the alcohols have been studied.

In the course of an earlier study of the reactions of B-norcholesterol,[4] it was found that when the modified sterol was hydrogenated in acetic acid mainly one isomer was formed (~75% yield). This major isomer was assigned an A/B *trans* configuration since such an isomer is formed in the similar reaction in the natural sterols.[5] Additional support for this stereochemical assignment was gained by examination of the products formed in the reduction by lithium aluminum hydride of the ketone derived from the hydrogenated alcohol. Subsequently, on the basis of optical rotatory dispersion measurements in this series, Djerassi, Marshall and Nakano[6] suggested that a *cis* arrangement of the A/B ring juncture was more likely. This problem of the nature of the ring juncture has now been re-examined, chemically, and it has been found that, indeed, the *cis* stereochemical assignment of the latter workers is correct.

First, the lithium aluminum hydride reduction of the saturated ketone IV was restudied and it was found that the earlier results were in error. Reduction of IV gave two isomers in a ratio of 3:1. The minor alcohol II was assigned the 3β-configuration since it was identical with the material prepared by hydrogenation of B-norcholesterol which has a 3β-hydroxyl group. In such a reduction of an unhindered ketone the equatorial isomer always is the major product[7] and, thus, the major product of the reduction, the 3α-hydroxyl isomer VI, must possess such a conformation, a conformational arrangement only possible with an A/B *cis* configuration.



To strengthen the optical rotatory argument, it was felt desirable to examine both the A/B *cis* and *trans* isomers in order to ensure no anomaly was present. By careful separation of the saponified hydrogenation products of B-norcholesteryl acetate (Ib) there was isolated in 70% yield the previously obtained major isomer II and, in addition, 15% of the minor isomer III. Oxidation of II and III yielded the corresponding 3-keto derivatives IV and V, the rotatory dispersion curves of which were practically identical with those of coprostanone and cholestanone, respectively.[8] This finding of similarity of optical rotatory dispersion curves in the normal stereoidal ketones and the related B-nor derivatives is most interesting since, as was pointed out by Djerassi,[6] rotatory dispersion would have been expected to be more sensitive to minor conformational alterations than catalytic hydrogenation. After completion of this work, similar stereochemical conclusions were arrived at by three other groups of workers.[9-11]

In view of this decisive influence of a five-membered B-ring on the steric course of hydrogenation, the direction of attack by a chemical reagent on the 5,6-double bond was investigated. It was found that when B-norcholesteryl acetate (Ib) was allowed to react with monoperphthalic acid there was formed in high yield a single epoxide (VIIb), whereas cholesteryl acetate under similar reaction conditions gives rise to a mixture of the α- and β-epoxides. The B-norepoxide VIIb was shown to possess an α-configuration in the following manner. Upon treatment with boron fluoride etherate, the epoxide rearranged to yield a diol monoacetate VIIIb. The related diol VIIIa, obtained upon alkaline saponification of VIIIb, showed the high end absorption in the ultraviolet (ϵ_{205} 10,500) characteristic of a dioxocyclic double bond.[12] Upon oxidation, VIIIb yielded a non-conjugated unsaturated ketone IXb which possessed a single intense band in the infrared at 1730 cm.$^{-1}$, indicating the formation of a cyclopentanone whose absorption coincides with the

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