[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

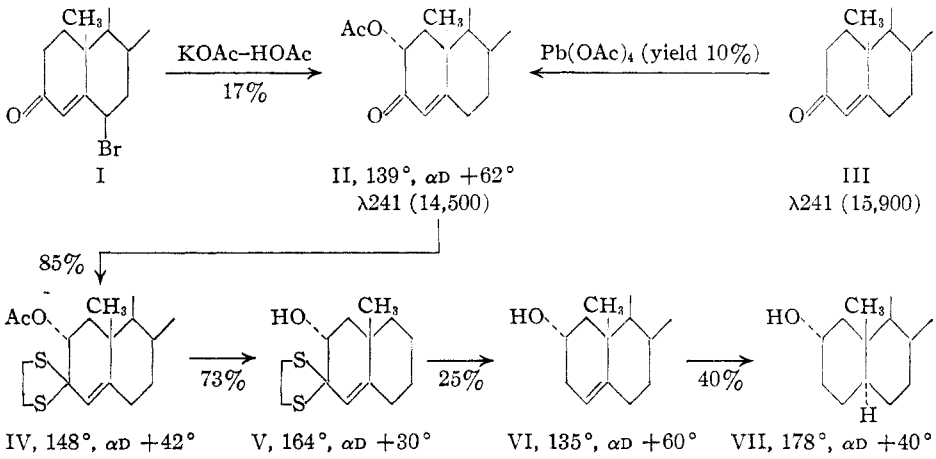
Rearrangement of 6β-Bromo-Δ⁴-cholestene-3-one to 2α-Acetoxy-Δ⁴-cholestene-3-one[1]

BY LOUIS F. FIESER AND MIGUEL A. ROMERO[2]

RECEIVED APRIL 23, 1953

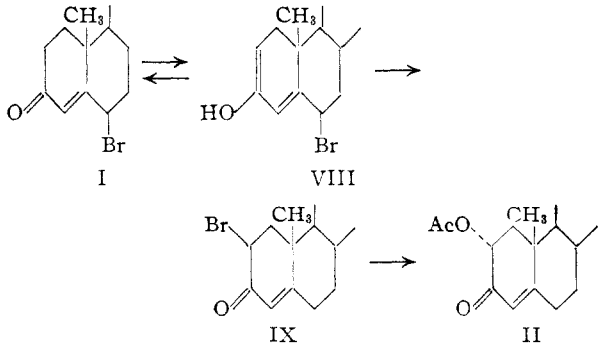
A substance obtained by Rivett and Wallis by acetolysis of 6β-bromo-Δ⁴-cholestene-3-one (I) is shown to be identical with the 2-acetoxy-Δ⁴-cholestene-3-one obtained by Seebeck and Reichstein by oxidation of cholestenone with lead tetraacetate. The 2-acetoxy group was shown to be α-oriented (II) by degradation to the known cholestane-2α-ol (VII). To explore further the acetolysis of 2α-bromocholestanone (X) to heterocholestenone (XIV), effected by Butenandt at 200°, we studied the action of potassium acetate and acetic acid on X at the reflux temperature. One product was shown to consist of a complex of 2α- and 4α-acetoxycholestane-3-one (XV); another was identified as 2,3-secocholestane-2,3-dioic acid (XVI). Mechanisms are suggested for both rearrangements.

From the mixture resulting from refluxing 6β-bromo-Δ⁴-cholestene-3-one (I) with potassium acetate in acetic acid, Rivett and Wallis[3] isolated in 8.5% yield a substance, isomeric with the known 6β-acetoxy-Δ⁴-cholestene-3-one, which they assumed to be the 6α-acetoxy epimer. However, authentic 6α-acetoxy-Δ⁴-cholestene-3-one, recently described by one of us,[4] differs from the Rivett and Wallis acetate. We prepared some of their product and the corresponding alcohol and observed that the alcohol has the properties of a diosphenol: positive ferric chloride test[3] and formation of a yellow enolate salt. We then noted that the acetate of Rivett and Wallis is close in melting point (139°) and rotation (α_D +62°) to an acetate (m.p. 142°, α_D +65.5°) that Seebeck and Reichstein[5] obtained in small amounts by oxidation of cholestenone (III) with lead tetraacetate. Direct comparison of samples made in the two ways indeed established their identity.



By degradation of their product to 2,3-secocholestane-2,3-dioic acid, Seebeck and Reichstein established that the substance is a 2-acetoxy derivative of cholestenone. We have now found that it is, specifically, 2α-acetoxy-Δ⁴-cholestene-3-one (II). Thus condensation with ethanedithiol to an ethylenethioketal (IV), hydrolysis (V), desulfurization to a cholestenol (VI) and hydrogenation gave a saturated alcohol corresponding in properties (m.p. 178°, α_D +40.5°) to cholestane-2α-ol[6,7] (m.p. 180°, α_D +36°) and not to cholestane-2β-ol[6,7] (m.p. 155°, α_D +33°).

The only evidence that can be presented regarding the mechanism of the rearrangement of I to II is the negative finding that 6α-acetoxy-Δ⁴-cholestene-3-one was recovered unchanged when submitted to the same treatment and therefore is not an intermediate in the reaction. Possibly the rearrangement proceeds through the enol VIII, which undergoes double α,γ-shift of bromine (concerted) and ketonization to IX; the final step would then be displacement at C_2 with inversion. That 6β-bromo-Δ⁴-cholestene-3-one (I) can react in the form of the homoannular dienol VIII is evidenced by the fact that I on bromination yields 2,6α-dibromo-Δ⁴-cholestene-3-one.[8]



The rearrangement, involving transfer of a functional group from C_6 to C_2 is just the reverse of the remarkable rearrangement of 2α-bromocholestanone[9] (X) to heterocholestenone (XIV), dis-

(1) In agreement with Drs. Romo, Rosenkranz and Sondheimer of Syntex, S.A., this paper was submitted simultaneously with one by these authors (p. 4712) reporting independent discovery of the same rearrangement.

(2) Fellow of the Camille and Henry Dreyfus Foundation.

(3) D. E. A. Rivett and E. S. Wallis, *J. Org. Chem.*, **15**, 35 (1950).

(4) L. F. Fieser, THIS JOURNAL (paper I), **75**, 4377 (1953).

(5) E. Seebeck and T. Reichstein, *Helv. Chim. Acta*, **27**, 948 (1944).

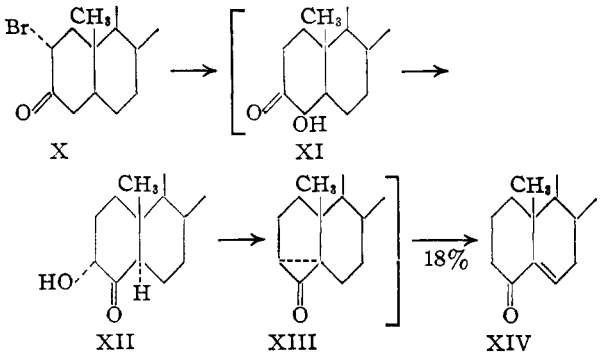
(6) L. Ruzicka, Pl. A. Plattner and M. Furrer, *ibid.*, **27**, 524 (1944).

(7) Configurations: A. Fürst and Pl. A. Plattner, *ibid.*, **32**, 275 (1949).

(8) C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and T. Pataki, THIS JOURNAL, **72**, 4534 (1950).

(9) For configuration, see E. J. Corey, *ibid.*, **75**, Oct. 5 (1953); L. F. Fieser and W.-Y. Huang, *ibid.*, **75**, Oct. 5 (1953).

covered by Butenandt.[10] The reaction, conducted in a mixture of potassium acetate and acetic acid at 200°, affords in low yield a product unequivocally established to be Δ⁵-cholestene-4-one (XIV).

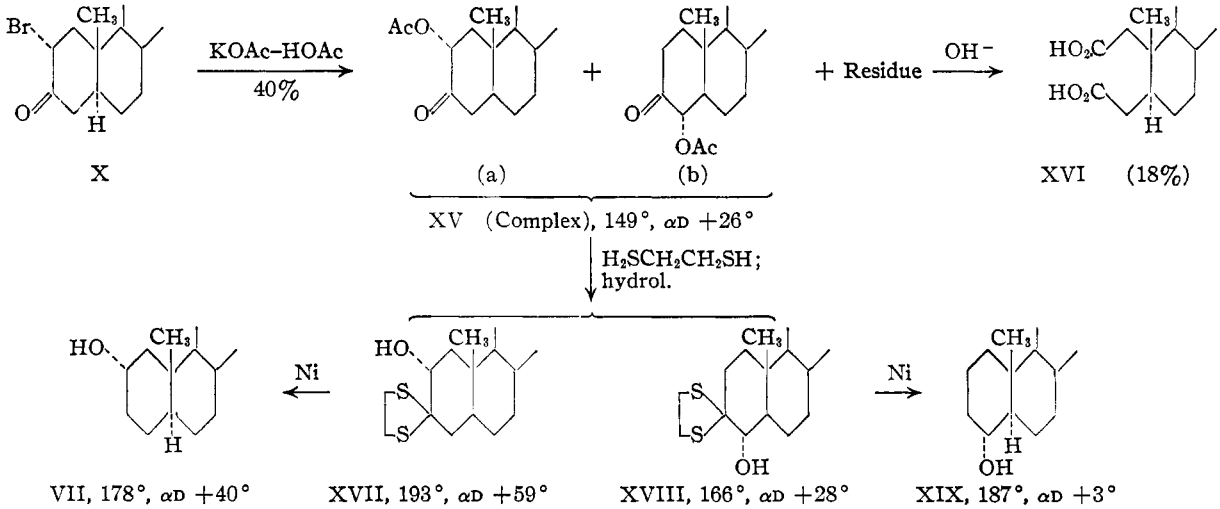


X XI XII XIII XIV

Butenandt suggested that the reaction may proceed by migration of bromine to C_4, hydrolysis to XI, isomerization to the ketol XII (here assumed to be the 3α-ol), dehydration to the *i*-steroid XIII, and isomerization. In the hope of clarifying the curious rearrangement further, we studied the action of potassium acetate and acetic acid on 2α-bromocholestanone at the reflux temperature instead of 200° and isolated, in yield about twice that reported for heterocholestenone, a substance of constant melting point having the composition of an acetoxycholestanone; as will be shown presently, the substance appears to be a complex (XV) containing the 2α- and 4α-acetoxy 3-ketones. Saponification of the oily residue from the mother liquor of XV afforded a substance identified as 2,3-secocholestane-2,3-dioic acid[11] (XVI). The complex could not be resolved into its components by either crystallization or chromatography. Condensation with ethanedithiol gave a mixture that tended to form gels and that could not be separated into the components. Desulfurization of this mixture with Raney nickel and saponification gave a mixture that could be separated by chromatography. The only product strongly adsorbed on alumina was identified as cholestane-4α-ol (XIX); early eluates yielded cholestane, evidently derived from the derivative of 2α-acetoxycholestane-3-one. Saponification of the ethylenethioketal mixture from the complex (XV) afforded a mixture of ethylenethioketal alcohols (XVII and XVIII) that were separable by chromatography. Although each substance separated from methanol–acetone in well-formed crystals, these appeared to contain solvent that could not be eliminated by drying at a temperature low enough to avoid decomposition. The two substances, however, are characterized by the cholestanols that they afford on desulfurization. One was identical with cholestane-2α-ol (VII), obtained in the series of experiments described above. The other corresponded in melting point and rotation to cholestane-4α-ol (XIX), as described by Barton and Rosenfelder,[12] and comparison of the samples established their identity.

The evidence, although indirect, shows that low-temperature acetolysis of 2α-bromocholestanone effects transformation to 2α- and 4α-acetoxycholestanone. Although neither substance has been isolated as such and shown to be a precursor of heterocholestenone, the relative yields are such as to suggest that both substances probably function as precursors. Thus the by-product that affords the diacid XVI in 18% yield in the low-temperature reaction undoubtedly is produced in yield at least this high when the acetolysis is conducted at 200°. The mechanism postulated by Butenandt assumes intermediate hydrolysis to free alcohols (XI, XII) in the acetic acid–potassium acetate medium, but the present evidence indicates that the key intermediates are ketol acetates and not free ketols. An alternate mechanism is that the acetyl group of 4α-acetoxycholestane-3-one (XVb) migrates to C_3 (XX), as demonstrated in an analogous instance,[13] and that, at a high temperature, the enol XXI suffers 1,4-elimination of acetic acid to give XXII, the enol of heterocholestenone (XIV).

The present results afforded an explanation of



X (a) (b) XVI (18%)

XV (Complex), 149°, α_D +26°

$H_2SCH_2CH_2SH$; hydrol.

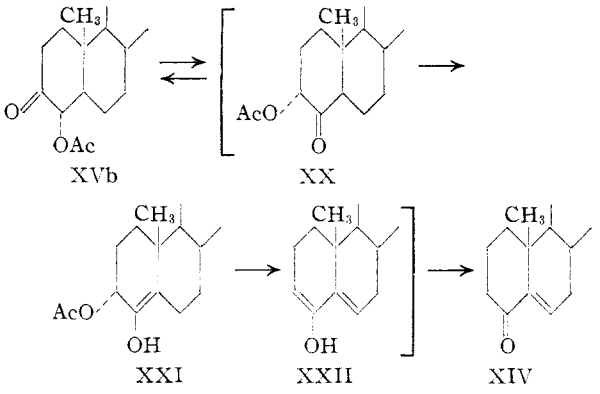
VII, 178°, α_D +40° XVII, 193°, α_D +59° XVIII, 166°, α_D +28° XIX, 187°, α_D +3°

(10) A. Butenandt and A. Wolff, *Ber.*, **68**, 2093 (1935); A. Butenandt and G. Ruhenstroth-Bauer, *ibid.*, **77**, 397 (1944).

(11) A. Windaus and Cl. Uibrig, *ibid.*, **47**, 2384 (1914).

(12) D. H. R. Barton and W. J. Rosenfelder, *J. Chem. Soc.*, 1048 (1951).

(13) Δ⁵-Cholestene-4α-ol-3-one acetate is isomerized by acid-washed alumina to Δ⁵-cholestene-3β-ol-4-one acetate.



some curious transformations reported[14] for a substance prepared[15] by the action of sodium acetate in acetic acid on 2α-bromocholestanone and described as 2-acetoxycholestanone (m.p. 146°). The substance corresponds to the product (m.p. 149°) now shown to be the complex XV, and the transformation products appear to have been derived from one or the other component or both. Thus one degradation afforded a product identified as cholestane-4α-ol (XIX); another gave a substance regarded as "cholestane-1-ol" of melting point (166°) close to that of a mixture of pure cholestane-4α-ol and cholestane-2α-ol.

Experimental

Δ⁴-Cholestene-2α-ol-3-one Acetate (II).—6β-Bromo-Δ⁴-cholestene-3-one (I, m.p. 129.5–130°) was prepared by dehydrobromination of 5α,6β-dibromocholestane-3-one as described in the literature.[16] The 6β-bromo derivative (14.5 g.) was treated with potassium acetate in acetic acid as described by Rivett and Wallis[3] except that the refluxing was conducted under nitrogen. The yield of white plates of II, m.p. 137–138°, was 2.3 g. (16.6%). Physical constants found for fully purified material were as follows: m.p. 139–140°, α_D +62° Chf, λ^{EtOH} 240 mμ (14,500), λ^{Chf} 5.74, 5.89, 6.15 μ.

Oxidation of Δ⁴-cholestenone with lead tetraacetate was conducted as described by Seebeck and Reichstein[5] except that the solvent used was 95% acetic acid instead of acetic acid–acetic anhydride; the change was attended with lowering of the yield to 6.5%. The reaction product melted at 137–138° and a mixture with the above sample showed no depression in m.p.

Ethylenethioketal of Δ⁴-Cholestene-2α-ol-3-one Acetate (IV).—A solution of 1 g. of the ketone II in 30 cc. of acetic acid was treated at 25° with 2.5 cc. each of ethanedithiol and boron fluoride etherate, when the product promptly began to separate. In 5 min. a small amount of water was added and the solid was collected and crystallized three times from methanol–chloroform. The yield of white needles, m.p. 147–148°, α_D +42.3° Chf, was 1.0 g. (85.5%).

Anal. Calcd. for $C_{31}H_{50}O_2S_2$ (518.71): C, 72.06; H, 9.71; S, 12.36. Found: C, 71.59; H, 9.80; S, 12.40.

Ethylenethioketal of Δ⁴-Cholestene-2α-ol-3-one (V).—A solution of 0.9 g. of the acetate IV in 30 cc. of methanol containing 0.1 g. of potassium hydroxide was refluxed for 1 hr. and diluted with water. The alcohol V separated in crystalline form and crystallization from methanol–acetone gave 600 mg. (73%) of needles, m.p. 163–164°, α_D +30° Chf, λ^{Chf} 2.9 μ.

Anal. Calcd. for $C_{29}H_{48}OS_2$ (476.70): C, 73.07; H, 10.15. Found: C, 73.29; H, 10.12.

(14) L. Ruzicka, Pl. A. Plattner and M. Furrer, *Helv. Chim. Acta.*, **27**, 727 (1944).

(15) L. Ruzicka, Pl. A. Plattner and R. Aeschbacher, *ibid.*, **21**, 866 (1938).

(16) E. Dane, Y. Wang and W. Schulte, *Z. physiol. Chem.*, **245**, 80 (1936); see also L. Ruzicka, W. Bosshard, W. H. Fischer and H. Wirz, *Helv. Chim. Acta*, **19**, 1147 (1936).

Δ⁴-Cholestene-2α-ol (VI).—Desulfurization of V was accomplished by refluxing 500 mg. of material with 2.5 g. of Raney nickel in 40 cc. of acetone for 1.5 hr. The solution was filtered and evaporated, and the residue on two crystallizations from petroleum ether–benzene afforded 100 mg. (25%) of needles, m.p. 134–135°, α_D +60° Chf, λ^{Chf} 2.9 μ.

Anal. Calcd. for $C_{27}H_{46}O$ (386.64): C, 83.87; H, 11.99. Found: C, 83.25; H, 11.75.

Cholestane-2α-ol[6,7] (VII).—The cholestenol (50 mg.) was hydrogenated in acetic acid (12 cc.) over platinum catalyst: one mole of hydrogen was consumed in 4 hr. The filtered solution was evaporated under vacuum and the residue crystallized from acetone. The substance formed thin needles (20 mg., 40%), m.p. 177–178°, α_D +40.5° Chf, λ^{Chf} 2.9 μ.

Anal. Calcd. for $C_{27}H_{48}O$ (388.65): C, 83.43; H, 12.45. Found: C, 83.77; H, 12.59.

Acetolysis of 2α-Bromocholestane-3-one: Complex XV.—A solution of 10 g. of 2α-bromocholestanone (m.p. 168–170°) and 70 g. of potassium acetate in 350 cc. of acetic acid was refluxed in a nitrogen atmosphere for 6 hr., the slightly yellow solution was poured into water and the product extracted with ether. The extract, washed well with water and with bicarbonate solution and dried, left on evaporation an oily residue that afforded a solid when processed with methanol. Two recrystallizations from methanol–acetone gave 3.8 g. (40%) of thin white needles of constant m.p. 147–149°, α_D +25.7° Chf, λ^{Chf} 5.84, 8.0 μ.

Anal. Calcd. for $C_{29}H_{48}O_3$ (444.67): C, 78.32; H, 10.87. Found: C, 78.64; H, 10.71.

A product of the same properties was isolated in the same yield when the reaction mixture was chromatographed. All attempts to effect separation of the components were unsuccessful.

2,3-Secocholestane-2,3-dioic Acid (XVI).—About 5 g. of residual oil from the methanol mother liquor remaining after removal of the crystalline complex was dissolved in 125 cc. of methanol containing 3 g. of potassium hydroxide and the solution was refluxed for 2 hr., diluted with water, acidified and extracted with ether. The washed and dried extract was evaporated to dryness and the residue taken up in petroleum ether. Colorless crystals slowly separated and after several days a first crop of acid was collected and the solution concentrated to half its volume and let stand to deposit a second crop. The total product (m.p. 165–180°) on two crystallizations from benzene afforded 1.5 g. (18%) of white plates, m.p. 197–199°. Purification through the methyl ester (solvated, m.p. 60–61°, α_D +18° Chf) gave acid of m.p. 197.5–199°, α_D +32° Chf. This did not depress the m.p. of an authentic sample,[17] m.p. 193–196.5°, α_D +27.3° Chf.

Ethylenethioketals (XVII and XVIII) of Cholestane-2α-ol-3-one and Cholestane-4α-ol-3-one.—Addition of 0.5 cc. of ethanedithiol and 1 cc. of boron fluoride etherate to a solution of 500 mg. of complex XV in acetic acid caused prompt separation of a white solid. After 5 min. the paste was diluted with a little methanol and the product collected. Crystallization from ethanol gave a gelatinous product that dried to an amorphous powder (480 mg., 82%), m.p. 150–175°. Chromatography failed to effect separation of the mixture.

Desulfurization of 300 mg. of this material with Raney nickel in refluxing ethanol (5 hr.) gave material that could not be obtained crystalline but that afforded a solid product on saponification. On chromatography of the crude product (180 mg.) on alumina, petroleum ether eluted a series of fractions that afforded a total of 100 mg. (45%) of **cholestane**, m.p. 78–80°, undepressed on admixture with an authentic sample. Petroleum ether–benzene (3:2) eluted a solid that on crystallization from methanol–acetone afforded 40 mg. (18%) of **cholestane-4α-ol** (see below), m.p. 186–187°, α_D +3° Chf.

Although the ethylenethioketal mixture could not be separated as the acetate, two components were isolated after saponification. Thus 450 mg. of acetate, m.p. 150–175°, was refluxed for 8 hr. in aqueous methanol (50 cc.) containing 4% of potassium hydroxide, the solution was diluted, and the solid that precipitated was collected, dried (m.p. 174–176°) and chromatographed.

The 4α-hydroxy derivative XVIII was eluted first, by 3:10 petroleum ether–benzene, and on crystallization from methanol–acetone yielded 170 mg. (41%) of solvated needles,

(17) H. Heymann and L. F. Fieser, *Helv. Chim. Acta*, **35**, 631 (1952).

m.p. 165–166°, α_D +28° Chf, λ^{Chf} 2.9 μ. The sample decomposed when dried for analysis at 60°; another sample was dried for a prolonged period at room temperature but analysis showed that it still contained solvent (carbon 1.6% low).

A next fraction, eluted by 4:10 petroleum ether–benzene on crystallization as above gave short needles, m.p. 175–177° (80 mg.); this appeared to be a mixture of XVII and XVIII, since it gave no depression in m.p. when mixed with either one. The **2α-hydroxy derivative** XVII was then eluted by 1:1 petroleum ether–benzene; crystallization from methanol–acetone gave 80 mg. (19%) of bright plates, m.p. 192–193°, α_D +59° Chf, λ^{Chf} 2.9 μ. This substance also was hydrated and was too sensitive to heat to be dried satisfactorily.

Cholestane-2α-ol (VII) from XVII.—Treatment of 80 mg. of XVII with Raney nickel in refluxing acetone (1.5 hr.) and crystallization of the product from methanol–acetone gave 25 mg. (77%) of cholestane-2α-ol as long needles, m.p. 176–177°, α_D +40° Chf, λ^{Chf} 2.9 μ, undepressed in m.p. on admixture with the sample described above.

Cholestane-4α-ol (XIX) resulted from similar desulfurization of 80 mg. of XVIII. Crystallization from methanol–acetone gave 40 mg. (61.5%) of needles, m.p. 186–187°, α_D +3° Chf. A mixture with the sample described earlier showed no depression in m.p.

Anal. Calcd. for $C_{27}H_{48}O$ (388.65): C, 83.43; H, 12.45. Found: C, 82.89; H, 12.32.

The constants agree with those reported by Barton[12]: m.p. 188–189°, α_D +5° Chf. A mixed melting point comparison kindly done in Dr. Barton's laboratory established the identity of the samples.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

$\Delta^{8,14}$-Cholestadiene-3β-yl-7-one Acetate

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RECEIVED MAY 2, 1953

A reinvestigation of a type of steroid diene-7-one discovered by Stavely and Bollenback and by Wintersteiner and Moore indicates the presence of the cross-conjugated system of formula IX. The principal evidence is that on Wolff–Kishner reduction the ketone yields the B_1-type diene X. A two-banded ultraviolet absorption spectrum appears to be characteristic of this and other steroids having a cross-conjugated chromophore.

Investigations of Stavely and Bollenback and of Wintersteiner and Moore led to the discovery of diene-7-one derivatives of the acetates of ergostanol,[3] Δ^{22}-ergostenol,[4] Δ^{22}-stigmastenol[5] and cholestanol[6] of obviously analogous constitution that has not as yet been elucidated. The diene-7-one derivative of cholestanol was obtained by Wintersteiner and Moore by the action of ethanolic hydrochloric acid on the 8α,14α-oxido-7-ketone VIIIa, resulting from chromic acid oxidation of an oxido alcohol (VIIa), formed by perbenzoic acid oxidation of Δ^7-cholestenyl acetate (I). An isomeric oxido alcohol formed in the reaction[6] has now been characterized as the 8α,9α-oxide IIa by oxidation to the corresponding 7-ketone IIIa[7]; evidence of the α-orientation of these substances at positions 7, 8 and 9 has been presented in a recent paper from this Laboratory.[8] The 8α,14α- and 8α,9α-oxidocholestane-3,7-diones were obtained by chromic acid oxidation of either the 3,7-diol or the 3-ol-7-one. Since both the 8α,14α- and 8α,9α-oxido 7-ketones, IIIa and VIIIa, give the same diene-7-one, separation of isomers is not necessary.

We have obtained the diene-7-one derivative of cholestanyl acetate from Δ^7-cholestenyl acetate in 27% yield without purification of any of the intermediates. Incidentally, we found that the 8α,14α-oxide ring is stable to lithium aluminum hydride, since the reagent merely deacetylated VIIa to VII.

The absorption maxima reported for the four steroid diene-7-ones are in the range 297–300 mμ (E 4,800–5,300). Stavely and Bollenback[3] expressed a preference for the homoannular dienic formulation IV, but mentioned in a footnote that Dr. R. B. Woodward had suggested the alternate formulation V. Wintersteiner and Moore[6] felt that formula IV is in better accord with the absorption characteristics but noted that the third formulation IX "deserves preference on chemical grounds." The chemical evidence was that the diene-7-ones on hydrogenation afford $\Delta^{8,14}$-ene-7-ones such as VI. We have found that VI is also obtainable by isomerization of the 8α,14α-oxido-7α-ol VIIa with ethanolic hydrochloric acid. The evidence of hydrogenation now appears inconclusive, since any of the three alternate structures conceivably could afford VI on hydrogenation. The spectrographic evidence is also indecisive. Absorption maxima calculated[9] for IV and for V are 324 mμ and 295 mμ; that for the cross-conjugated system of IX cannot be calculated from available data. Although the observed wave length of absorption agrees well with the value calculated for V, the extinction coefficient is far too low for such a chromophore.

Various reactions of the dienone that might have been diagnostic were tried with negative results. Lithium aluminum hydride reduction, followed by acetylation, gave an apparent mixture that could not be separated but that had a strong absorption band at 247.5 mμ. Dorfman[10] has reported that the same observation has been made by D. A.

(1) Research Fellow studying under the sponsorship of the Institute of International Education as participant in the Japanese Student Program of the Department of the Army and SCAP.

(2) National Institutes of Health predoctoral fellow, 1950–1952.

(3) H. E. Stavely and G. N. Bollenbeck, THIS JOURNAL, **65**, 1285 (1943).

(4) H. E. Stavely and G. N. Bollenback, *ibid.*, **65**, 1290 (1943).

(5) H. E. Stavely and G. N. Bollenback, *ibid.*, **65**, 1600 (1943).

(6) O. Wintersteiner and M. Moore, *ibid.*, **65**, 1507 (1943).

(7) L. F. Fieser, *ibid.*, **75**, 4395 (1953).

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

(9) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 2nd Ed., Reinhold Publ. Corp., New York N. Y., 1949, pp. 184–198.

(10) L. Dorfman, "Ultraviolet Absorption of Steroids," *Chem. Revs.*, in press; we are greatly indebted to Dr. Dorfman for a copy of his manuscript.