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.

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

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

BY LOUIS F. FIESER, KOJI NAKANISHI[1] AND WEI-YUAN HUANG[2]

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).

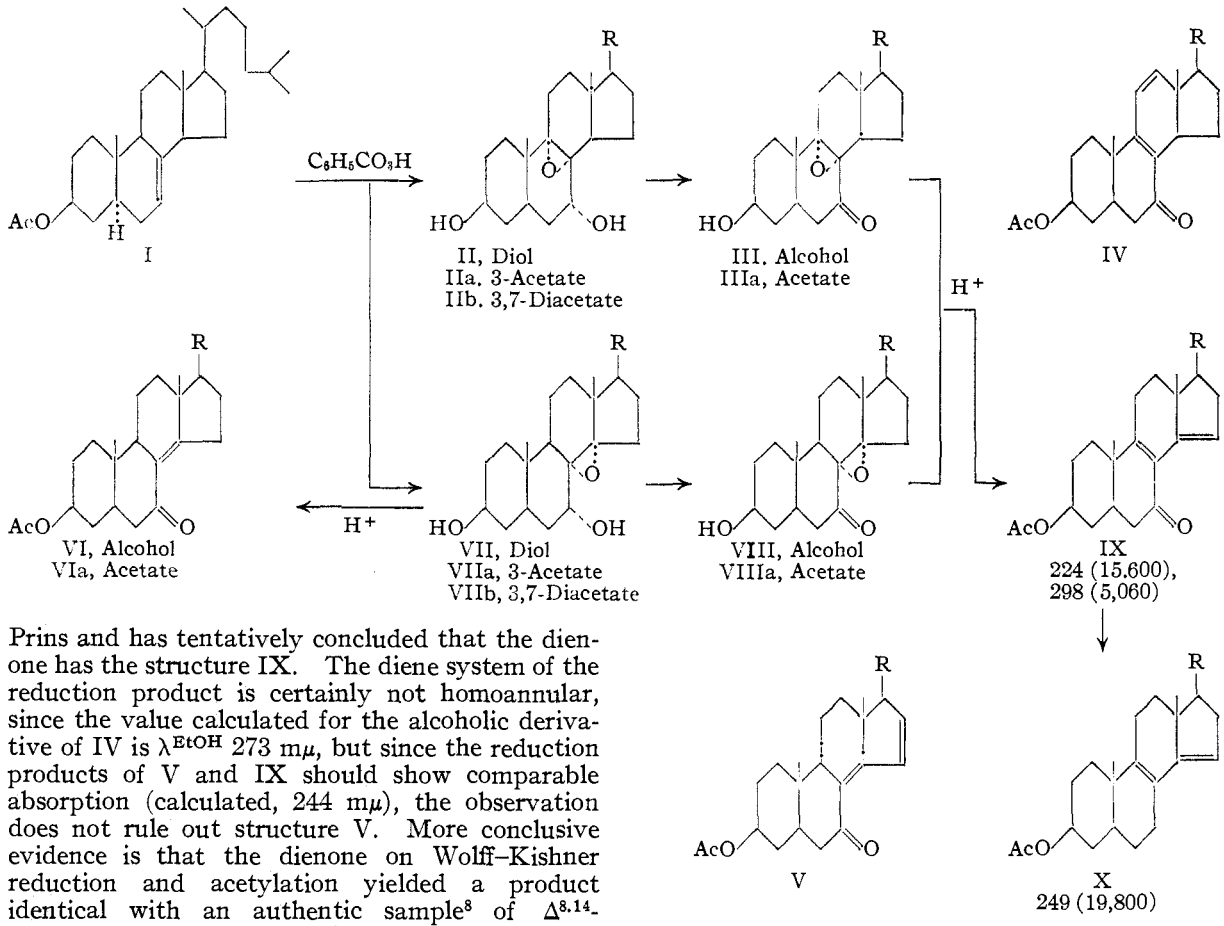
(6) O. Wintersteiner and M. Moore, *ibid.*, **65**, 1507 (1943).

(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.



Prins and has tentatively concluded that the dienone has the structure IX. The diene system of the reduction product is certainly not homoannular, since the value calculated for the alcoholic derivative of IV is λ^{EtOH} 273 mμ, but since the reduction products of V and IX should show comparable absorption (calculated, 244 mμ), the observation does not rule out structure V. More conclusive evidence is that the dienone on Wolff–Kishner reduction and acetylation yielded a product identical with an authentic sample[8] of $\Delta^{8,14}$-cholestadiene-3β-yl acetate (X). Since it has been demonstrated that a $\Delta^{7,9(11)}$-diene-12-one undergoes Wolff–Kishner reduction without disturbance of the original diene system,[11] the isolation of X shows definitely that the compound in question is the $\Delta^{8,14}$-diene-7-one IX.

Wintersteiner and Moore[6] reported that the dienone exhibits strong end absorption below 240 mμ, but independent measurements by the Ciba group[10] and by us reveal the presence of a strong band at 223–224 mμ; our characterization of the dienone is: λ^{EtOH} 224 mμ (15,600), 298 mμ (5,060). The two-banded spectrum seems to be associated with the presence of a cross-conjugated system. Two comparable compounds are described in a recent communication from the Pfizer Laboratories.[12] An ergostatetraenyl acetate with a chromophoric system of double bonds at the 6,7-, 8,14- and 9,11-positions (formula II in the Communication) showed absorption bands in ether at 232.5 mμ (17,800) and 287.5 mμ (6,600); the first band is close to that calculated for the $\Delta^{6,8(14)}$-dienic system (244 mμ in EtOH) and the second is that expected for the homoannular diene system in ring C (288 mμ in EtOH). An ergostatetraene-3β-ol-11-one acetate (V) with double bonds at the 6,7-, 8,9- and 14,15-positions also has a two-banded spectrum: λ^{Ether} 233 mμ (15,200), 326 mμ (8,900). The second maximum agrees with that calculated (324 mμ in ethanol) for the $\Delta^{6,8}$-diene-11-one system; the more intense maximum at shorter wave length is comparable to the intense band at 224 mμ of the dienone under present investigation. We are at a loss to account for these short wave length bands. In the case at hand the low-intensity band at 298 mμ is perhaps attributable to carbonyl absorption, intensified beyond that characteristic of compounds with fully isolated carbonyl groups.

The research groups at Mexico City[13] and at Glasgow[14] have reported substances of the pregnane and 22,23-dibromoergosterol series that were originally formulated as $\Delta^{8,11}$-diene-7-ones but for which the alternate $\Delta^{8(14),15}$-diene-7-one formulation has more recently been suggested.[15] The absorption characteristics: λ^{EtOH} 225 mμ (18,000), 297 mμ (6,000) are so close to those of the dienone here discussed as to strongly suggest that the substances are also cross-conjugated dienones of the type IX.

Experimental

Oxidation of Δ^7-Cholestenyl Acetate to 8α,14α-Oxidocholestane-3β,7α-diol 3-Acetate (VIIa)[6] and 8α,9α-Oxidocholestane-3β,7α-diol 3-Acetate (IIa) (K.N.).—To a solution of 14.2 g. (2.08 equiv.) of perbenzoic acid in 300 cc. of chloroform, 20.9 g. of Δ^7-cholestenyl acetate was added: the solid soon dissolved and the solution was let stand in the dark at 3° for 8 days, when the perbenzoic acid was all con-

(11) L. F. Fieser, S. Rajagopalan, E. Wilson and Max Tishler, THIS JOURNAL, **73**, 4133 (1951).

(12) C. D. Laubach, E. C. Schreiber, E. J. Agnello, E. N. Lightfoot and K. J. Brunings, *ibid.*, **75**, 1514 (1953).

(13) J. Romo, G. Stork, G. Rosenkranz and C. Djerassi, *ibid.*, **74**, 2918 (1952).

(14) R. Budziarek, R. Stevenson and F. S. Spring, *J. Chem. Soc.*, 4874 (1952).

(15) A. J. Lemin, G. Rosenkranz and C. Djerassi, THIS JOURNAL, **75**, 1745 (1953).

sumed. The solution was washed with soda solution and with water, dried and the solvent evaporated. The residual yellow sirup afforded crystals from methanol, and two crystallizations from this solvent gave 12 g. of platelets of the 8α,14α-oxide VIIa, m.p. 122–123°, α_D +5.5° Chf; this material corresponds in constants to that of Wintersteiner and Moore,[5] but experiments cited below show that it contained a small amount of the 8α,9α-oxide. Processing of the mother liquor gave 1.5 g. more material, m.p. 119–120°.

On chromatography of the combined mother liquor material on alumina, 20:1 and 9:1 petroleum ether–ether mixtures eluted small amounts of solid fractions, m.p. 100–101° and 100–110° (no ultraviolet absorption) that were not further investigated. Then 1:1 petroleum ether–ether eluted a total of 1 g. of solid material that when crystallized from methanol melted in the range 125–135°. Rechromatography of this evident mixture failed to effect a separation. However, when a solution of the material in a small volume of ether was let evaporate spontaneously, crystals of two distinct forms were observed: needles (m.p. 120–130°), which climbed up the walls of the flask, and flakes (m.p. 135–140°), which separated at the bottom. The two were separated mechanically and each crop was recrystallized in the same way and further fractionation was conducted by the triangulation scheme. Two crystallizations of the needles from methanol gave 100 mg. of VIIa. Two crystallizations of the purified flakes from methanol afforded 440 mg. of the 8α,9α-oxide IIa, m.p. 146.5–147.5°, α_D +26.0° Chf. The analytical sample, recrystallized again from methanol, melted at 148–149° (Wintersteiner and Moore[6]: m.p. 146°, α_D +27.6°).

Anal. Calcd. for $C_{29}H_{48}O_4$ (460.67): C, 75.60; H, 10.50. Found: C, 75.52; H, 10.68.

8α,9α-Oxidocholestane-3β-ol-7-one 3-acetate (IIIa) was obtained on oxidation of 100 mg. of IIa in 3 cc. of acetic acid with 29 mg. of chromic anhydride in 1 cc. of 80% acetic acid (24 hr. at 25°). Dilution with water gave a crystalline precipitate that on crystallization from methanol yielded 70 mg. of the 7-ketone, m.p. 176–177°, α_D −33.4° Chf; no depression in m.p. on admixture with an authentic sample.[7]

Oxidation of Crude VIIa.—A solution of 1.59 g. of the above material, m.p. 122–123°, in 30 cc. of acetic acid was treated at 25° with a solution of 457 mg. of chromic anhydride in 40 cc. of 80% acetic acid and the solution let stand overnight. Dilution with water precipitated a solid (1 g., m.p. 120–125°) that was chromatographed. Petroleum ether–ether (4:1) eluted material that when crystallized from methanol afforded 150 mg. of 8α,9α-oxidocholestane-3β-ol-7-one 3-acetate, m.p. 177–178°, α_D −33.8° Chf, identified by mixed m.p. determination and comparison of the infrared spectra. Elution with 3:2 petroleum ether–ether then gave a total of 700 mg. of 8α,14α-oxidocholestane-3β-ol-7-one 3-acetate, which when crystallized once from methanol had the constants: m.p. 139–140°, α_D −73.5° Chf

Action of Lithium Aluminum Hydride on 8α,14α-Oxidocholestane-3β,7α-diol 3-Acetate (W.-Y. H.).—Refluxing of the 3-acetate (1.78 g.) with excess reagent in tetrahydrofuran for 5 hr. resulted merely in deacetylation to the diol VII (1.12 g., m.p. 187–188°). The recrystallized sample, m.p. 188–189°, α_D +8.6° (*c* 2.10), λ^{Chf} 2.9 μ, and its diacetate, m.p. 164–165°, α_D −12.7° Chf (*c* 3.31), corresponded to the description of Wintersteiner and Moore[6] and were identified by mixed m.p. determinations.

8α,14α-Oxidocholestane-3β-ol-7-one (W.-Y. H.) (VII) obtained by saponification of the 3-acetate VIIa (200 mg.) with potassium carbonate (0.15 g.) in aqueous methanol at room temperature (24 hr.), crystallized from aqueous methanol in thin prismatic plates (100 mg.), m.p. 177–178°, α_D −81.2° Chf (*c* 2.02), λ^{Chf} 2.95, 5.89 μ.

Anal. Calcd. for $C_{27}H_{44}O_3$ (416.62): C, 77.83; H, 10.65. Found: C, 78.09; H, 10.71.

Attempts to oxidize this monoalcohol to the diketone with dichromate and with chromic anhydride led only to amorphous material, even after chromatography.

8α,14α-Oxidocholestane-3,7-dione (W.-Y. H.).—A solution of 367 mg. of 8α,14α-cholestane-3β,7α-diol and 340 mg. of sodium dichromate dihydrate in 5 cc. of acetic acid was left at 25° for 46 hr. and the crude product was adsorbed onto 10 g. of alumina. Petroleum ether–benzene eluted a little material forming soft prisms from methanol, m.p. 110–135°. Then a series of five similar fractions were obtained by elution with benzene, and then benzene–ether (14:1 to 4:1); each on crystallization from methanol gave amorphous material, but recrystallization from ether–petroleum ether gave long prisms melting in the range 135–141°. Recrystallization of the combined prisms gave 71 mg. of the 7α,8α-oxido-3,6-diketone, m.p. 140–141°, α_D −70.0° Chf (*c* 1.21), λ^{Chf} 5.87 μ.

Anal. Calcd. for $C_{27}H_{42}O_3$ (414.61): C, 78.21; H, 10.21. Found: C, 78.05; H, 10.43.

Treatment of the diketone with 5% methanolic hydrochloric acid at 23° gave a yellow product showing λ^{EtOH} 262 mμ.

The mother liquor material remaining from crystallization of the above product was submitted to reoxidation and afforded a product identified as **8α,9α-oxidocholestane-3,7-dione** (mixed m.p. with sample described below), m.p. 180° (chloroform–methanol), α_D −11.1° Chf (*c* 1.16), λ^{Chf} 5.88 μ.

Anal. Calcd. for $C_{27}H_{42}O_3$ (414.61): C, 78.21; H, 10.21. Found: C, 78.60; H, 10.30.

The substance evidently was derived from a little 8α,9α-oxide in the starting material.

8α,9α-Oxidocholestane-3,7-dione was obtained readily from 8α,9α-oxidocholestane-3β-ol-7-one 3-acetate (130 mg.) by saponification with aqueous methanolic potassium hydroxide (15 hr., 25°) to the free alcohol (m.p. 159–160°, λ^{Chf} 2.95, 5.88 μ) and oxidation in benzene–acetic acid with excess chromic acid (25°). Crystallized from methanol, the diketone melted at 179–181°, α_D −13° Chf (*c* 1.15), and did not depress the m.p. of a sample previously described.[7]

$\Delta^{8,14}$-Cholestadiene-3β-ol-7-one 3-Acetate (IX)[8] (K. N.).—This dienone was obtained in better yield than reported[8] and without chromatography by conducting the acetolysis in a more dilute solution. A solution of 465 mg. of 8α,14α-oxidocholestene-3β-ol-7-one 3-acetate (VIIa) in 50 cc. of 95% ethanol containing 2.5 cc. of 36% hydrochloric acid was refluxed 3 hr. and diluted to the point of saturation. The solid that separated (m.p. 136–137°) was reacetylated and the product crystallized twice from methanol (crystallization was difficult until seed had been obtained); 230 mg. of slightly yellowish, fine needles, m.p. 172–174.5°, α_D −14.5° Chf (*c* 1.51), λ^{EtOH} 224 mμ (15,600), 298 mμ (5,060); Wintersteiner and Moore: m.p. 166°, α_D −17.6°, λ^{EtOH} 297 mμ (4,800).

Anal. Calcd. for $C_{29}H_{44}O_3$ (440.64): C, 79.07; H, 10.07. Found: C, 79.22; H, 10.44.

The dienone was obtained readily from Δ^7-cholestenyl acetate (41.8 g.) by perbenzoic acid oxidation, chromic acid oxidation of the resulting crude mixture, and acetolysis of the mixture of 8,9- and 8,14-oxido-7-ketones; yield 11.3 g.

Reduction of 570 mg. of the dienone acetate with lithium aluminum hydride, followed by acetylation, gave material from which no crystalline product could be obtained on chromatography. The sirup (470 mg.) showed strong absorption at 247.5 mμ.

Attempts to convert the dienone into an enol acetate and to isolate products of reaction with bromine, N-bromosuccinimide, ethylene glycol, ethanedithiol and selenium dioxide all failed to afford definite products. Osmium tetroxide gave a trace of solid product showing absorption at 255 mμ.

In another experiment (W.-Y. H) 595 mg. of dienone (m.p. 162–164°) in chloroform at 3° consumed one mole of perbenzoic acid in 42 hr. Crystallization of the product from methanol gave 297 mg. of an *unidentified product* in the form of pale yellowish crystals, m.p. 149–150°. Two recrystallizations from chloroform–methanol gave colorless prisms, m.p. 160–161°, α_D +4.3° Chf (*c* 2.50), λ^{Chf} 2.99, 5.83, 6.00, 6.19, 8.0 μ, λ^{EtOH} 244 mμ (8,100).

Anal. Calcd. for $C_{29}H_{46}O_5$ (474.66): C, 73.38; H, 9.77. Found: C, 73.31; H, 9.89.

This substance was recovered unchanged after treatment with acetic anhydride in pyridine (48 hr. at 25°). Treatment with acetic anhydride and *p*-toluenesulfonic acid gave a yellow oil, λ^{EtOH} 230, 305 mμ. Hydrolysis with potassium hydroxide in aqueous methanol or with boron fluoride in methanol gave no crystalline product. Reduction with lithium aluminum hydride gave an amorphous product that was unsaturated to tetranitromethane and showed no infrared absorption in the carbonyl region.

The mother liquors from the perbenzoic acid oxidation afforded a small amount of a second substance: fine yellow needles from methanol, m.p. 150–151°, λ^{EtOH} 224, 318 mμ (E 1 g./l. 26.8, 5.6); found: C, 81.71; H, 9.71.

$\Delta^{8(14)}$-Cholestene-3β-ol-7-one (VI) from VIIa (K. N.).—A solution of 400 mg. of VIIa and 1 cc. of 36% hydrochloric acid in 20 cc. of 95% ethanol was refluxed for 3 hr. and diluted to saturation. The product separated as colorless needles and after recrystallization from methanol melted at 129–130° (240 mg.), λ^{EtOH} 261 mμ (8,800), λ^{Chf} 3.0, 6.03, 6.31 μ.

Anal. Calcd. for $C_{27}H_{44}O_2$ (400.62): C, 80.94; H, 11.07. Found: C, 80.91; H, 10.97.

The acetate, m.p. 141–142°, α_D −53.3° Chf (*c* 1.25), did not depress the m.p. of an authentic sample.[7]

Wolff–Kishner Reduction of $\Delta^{8,14}$-Cholestadiene-3β-ol-7-one 3-Acetate (IX) (W.-Y. H.).—Reduction of 1 g. of dienone by the Huang-Minlon procedure at 200° gave a crude product that separated as a solid on dilution of the cooled reaction mixture. This material absorbed at 248 mμ and the infrared spectrum indicated the absence of a carbonyl group; it was acetylated and the acetate chromatographed. Fractions eluted by petroleum ether–benzene (7:3 and 1:1) crystallized from ether–methanol to give elongated prisms melting in the range 90–95°. The combined crystallizate (300 mg.) on two recrystallizations from ether–methanol afforded **$\Delta^{8,14}$-cholestadiene-3β-yl acetate (X)**, m.p. 100–101°, λ^{EtOH} 249 mμ (19,800), α_D −19.3° Chf (*c* 2.22), no depression in m.p. on admixture with an authentic sample,[8] m.p. 99–99.4°.

CAMBRIDGE, MASSACHUSETTS

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

$\Delta^{9,(11)}$-Dehydro Cortical Steroids. Synthesis of $\Delta^{9,(11)}$-Anhydro-17-hydroxycorticosterone Acetate

BY R. P. GRABER, A. C. HAVEN, JR., AND N. L. WENDLER

RECEIVED MAY 28, 1953

The formation of several functionally substituted $\Delta^{9,(11)}$-dehydrosteroids including the synthesis of $\Delta^{9,(11)}$-anhydro-17-hydroxycorticosterone acetate is described.

The conversion of 11β-hydroxylated cortical steroids to their $\Delta^{9,(11)}$-anhydro derivatives has been variously described by Reichstein and his associates[1] employing conditions of room temperature dehydration with phosphorus oxychloride in pyridine[1e] as well as with refluxing acetic–hydrochloric acid mixtures.[1a–d] By the latter technique Shoppee and Reichstein[1d] were able to convert corticosterone acetate to $\Delta^{9,(11)}$-anhydrocorticosterone acetate. We wish to report the conversion of certain 11β-hydroxylated steroids and particularly those bearing the 17-hydroxycortical side chain into their respective $\Delta^{9,(11)}$-anhydro derivatives. These conversions have made possible several routes culminating in the synthesis of $\Delta^{9,(11)}$-anhydro-17-hydroxycorticosterone acetate (VIII).

Treatment of 20-cyano-17-pregnene-11β,21-diol-3-one 21-acetate (I)[2] with phosphorus oxychloride in pyridine at room temperature afforded the $\Delta^{9,(11)}$-anhydrocyanopregnene (V) in 50–60% yield. Somewhat lower yields of this compound were obtained under dehydration conditions employing refluxing 1:4 hydrochloric–acetic acid.[1d] Hydroxylation of V employing a slight excess over one mole of osmium tetroxide afforded VI in good yield, with no apparent evidence of involvement of the $\Delta^{9,(11)}$-double bond in the hydroxylation reaction. In this regard it has previously been reported that $\Delta^{9,(11)}$-double bonds in the normal (5β) steroid series are essentially unreactive to osmium tetroxide[3] in contrast to the *allo* series (5α) where hydroxylation proceeds readily.[4] The anhydro derivative (VI) could also be prepared smoothly and in good yield by the direct dehydration of 4,5-dihydro-17-hydroxycorticosterone acetate (II)[3] again employing phosphorus oxychloride in pyridine at room temperature. The relative ease and freedom from side reactions with which the dehydration of II proceeded is noteworthy in view of the recognized lability of the cortical steroid side chain.[5] Bromination of VI followed by dehydrobromination with semicarbazide acetate completed the synthesis of $\Delta^{9,(11)}$-anhydro-17-hydroxycorticosterone acetate (VIII).[6] This substance was also formed in low yield by the direct dehydration of 17-hydroxycorticosterone acetate (IV)[3] with phosphorus oxychloride in pyridine. The low yield of anhydro derivative obtained from IV in the latter manner suggests involvement of the A-ring unsaturated ketone, possibly by way of formation in part of a phosphorylated enolate.

It had been our earlier experience[3] that the hydrogen bromide catalyzed bromination of 4,5-dihydro-17-hydroxycorticosterone acetate (II) gave variable results. It was subsequently observed that II in acetic acid containing catalytic amounts of hydrogen bromide underwent a fairly rapid loss of rotation which after several hours became nearly constant and approached the value for the anhydro derivative VI (Fig. 1). The latter could, in fact, be isolated from such an experiment in good yield. The same room temperature dehydration of II → VI was also observed to occur in chloroform as well as acetonitrile in the presence of small amounts of hydrogen bromide. By employing *p*-toluenesulfonic acid as the catalyst in acetic acid solution, however, no substantial change in rotation corresponding to dehydration was observable even when the concentration of *p*-toluenesulfonic acid was

(1) See for example (a) C. W. Shoppee, *Helv. Chim. Acta*, **23**, 740 (1940); (b) C. W. Shoppee and T. Reichstein, *ibid.*, **24**, 351 (1941); (c) P. Hegner and T. Reichstein, *ibid.*, **26**, 715 (1943); (d) C. W. Shoppee and T. Reichstein, *ibid.*, **26**, 1316 (1943); (e) E. Seebeck and T. Reichstein, *ibid.*, **26**, 536 (1943).

(2) N. L. Wendler, R. P. Graber, R. E. Jones and M. Tishler, THIS JOURNAL, **72**, 5793 (1950); **74**, 3630 (1952).

(3) L. H. Sarett in L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 3rd ed., 1949, p. 227.

(4) R. Hirschmann, C. S. Snoddy, Jr., and N. L. Wendler, THIS JOURNAL, **75**, 3252 (1953).

(5) See for example, L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Co., New York, N. Y., 1949, Chapt. 5; V. R. Mattox, THIS JOURNAL, **74**, 4340 (1952).

(6) Since the completion of this work J. Fried and E. Sabo (*ibid.*, **75**, 2273 (1953)) have described the conversion of 11-*epi*-17α-hydroxycorticosterone to $\Delta^{9,(11)}$-anhydro-17α-hydroxycorticosterone acetate.