$\Delta^{8(14)}$-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

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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).

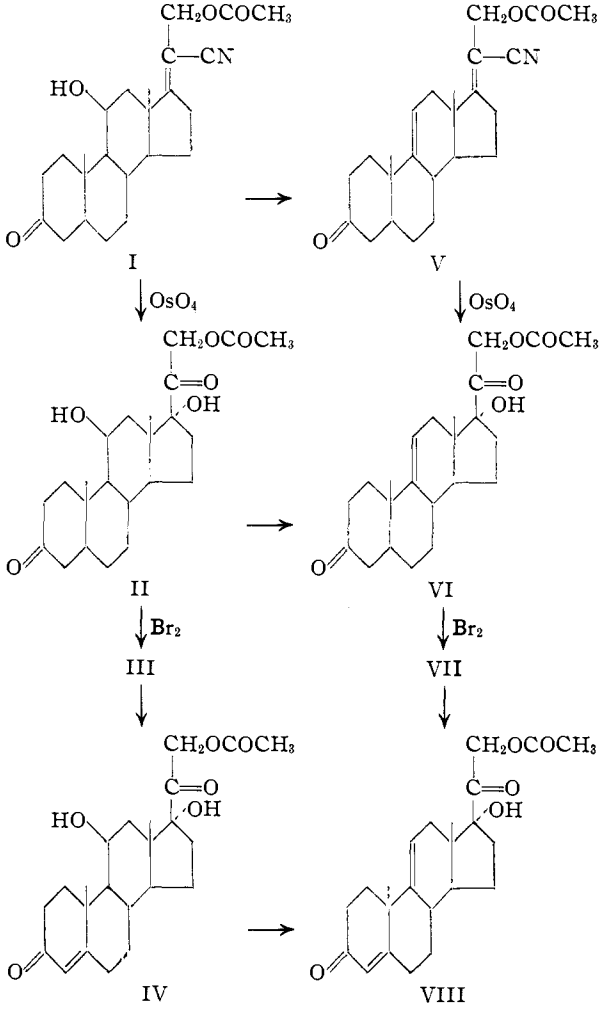
(3) L. H. Sarett in L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 3rd ed., 1949, p. 227.

(4) R. Hirschmann, C. S. Snoddy, Jr., and N. L. Wendler, THIS JOURNAL, **75**, 3352 (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.

increased to the one mole level. Recently the acetylation of an 11β-hydroxy steroid has been reported[7] whereby strong acid catalysis (*inter alia* $HClO_4$) was employed for effecting this conversion. In view of these observations there would appear to be a critical though obscure association between the ease of dehydration of 11β-hydroxy steroids and the nature of the acid employed as a catalyst.



Experimental[8]

20-Cyano-$\Delta^{9(11),17}$-pregnadiene-21-ol-3-one 21-Acetate (V). Method A.—To a solution of 2.0 g. of 20-cyano-17-pregnene-11β,21-diol-3-one 21-acetate (I) in 10.0 ml. of pyridine containing one drop of water was added 1.0 ml. of phosphorus oxychloride and the mixture allowed to stand at room temperature for three days. At the end of this time, 50 ml. of water was added and the organic material extracted with three portions of chloroform. The combined chloroform extracts were washed with 2.5 *N* hydrochloric acid until free of pyridine, then with water and finally the solvent was removed *in vacuo*. The partly crystalline residue was chromatographed over acid-washed alumina and eluted with benzene. The fractions which gave crystalline residues melting in the range 120–129° were combined and recrystallized from ethyl acetate–petroleum ether (b.p. 30–60°) to give 1.01 g. (53%) of the $\Delta^{9(11),17}$-pregnadiene (V), m.p. 124.5–126°. A sample prepared for analysis by recrystallization from ether–petroleum ether (b.p. 30–60°) was obtained as rosettes of heavy needles, m.p. 127–129°, $\lambda_{max}^{CH_3OH}$ 2220 Å., $E_{1\ cm.}^{1\%}$ 413, $[\alpha]^{25}D$ +60.5° (0.94, acetone).[9]

Anal. Calcd. for $C_{24}H_{31}O_3N$: C, 75.56; H, 8.19. Found: C, 75.51; H, 8.20.

Method B.—A solution of 8.95 g. of the cyanopregnene acetate (I) in 112 ml. of a 1:4 concentrated hydrochloric acid–glacial acetic acid mixture was heated under reflux for 20 minutes. At the end of this time, an additional 58 ml. of the hydrochloric acid–acetic acid mixture was added and refluxing continued for an additional 20 minutes. The final reaction mixture was concentrated *in vacuo* to a volume of *ca.* 15 ml., 125 ml. of water added and the organic material extracted with three portions of ether. The combined ether extracts were washed with water, 5% aqueous sodium bicarbonate solution, with saturated salt solution and finally dried over sodium sulfate and the solvent removed *in vacuo* to give a light brown oily residue, weight 8.07 g. The residue was dissolved in 20 ml. of acetic anhydride, 5.0 ml. of pyridine added and the solution heated at 70–72° for one-half hour. The mixture was concentrated *in vacuo* to about one-half the original volume, cooled and the excess acetic anhydride decomposed by adding 150 ml. of water with cooling and occasional swirling. The oily product which separated was isolated as described above and weighed 7.98 g. This crude product was chromatographed over 430 g. of acid-washed alumina. The fractions eluted with 9:1 benzene–petroleum ether (b.p. 30–60°) and with benzene

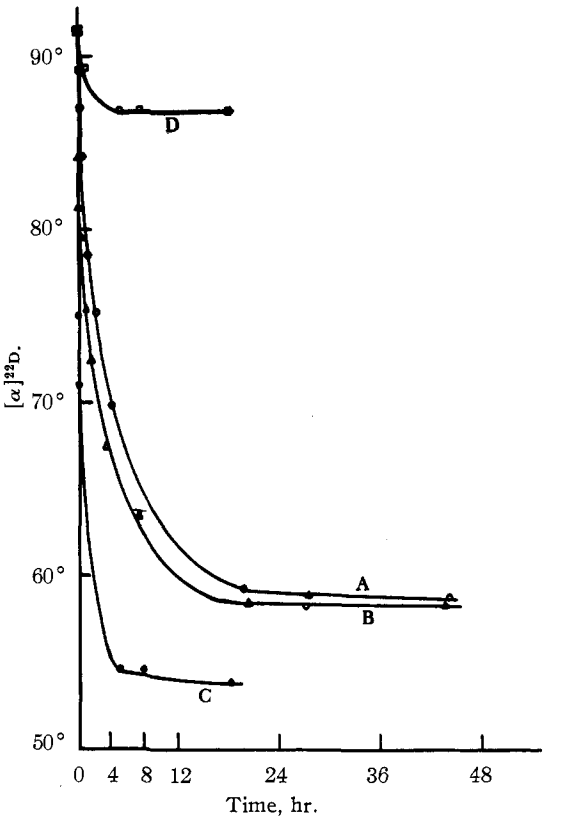


Fig. 1.—Specific rotation of solutions of pregnane-11β,17α,21-triol-3,20-dione 21-acetate (II) in: A, 0.0097 *N* HBr in acetic acid; C, 0.01 *N* HBr in chloroform; B, 0.01 *N* HBr in acetonitrile; D, 0.01 *N* *p*-toluenesulfonic acid in acetic acid. The points on the ordinate correspond to the specific rotation of the triol-dione in the respective pure solvents.

(7) E. P. Oliveto, C. Gerold, L. Weber, H. E. Jorgensen and E. B. Hershberg, Abstr. of the Meeting-in-miniature, North Jersey Section of the American Chemical Society, Newark, N. J., Jan. 26, 1953; also *Arch. Biochem. Biophys.*, **43**, 234 (1953).

(8) All melting points were taken on a micro hot-stage.

(9) The ΔM_D value for the 9,11-double bond in systems bearing the cortical side chain deviates markedly from the ΔM_D value given by D. H. R. Barton and W. Klyne (*Chem. & Ind.*, 755 (1948)) for this grouping. The deviations may presumably be attributed to vicinal effects. A similar though less marked deviation was also observed for $\Delta^{9(11)}$-dehydrotigogenin (ref. 4).

and which melted in the range 120–129° were combined, weight 3.83 g. One recrystallization from ether–petroleum ether (b.p. 30–60°) gave 3.14 g. (37%) of colorless plates, m.p. 127–129°, undepressed on admixture with material prepared by method A.

$\Delta^{9(11)}$-Pregnene-17α,21-diol-3,20-dione 21-Acetate (VI). (a) By Osmium Tetroxide Hydroxylation of V.—A solution of 2.13 g. of the $\Delta^{9(11),17}$-pregnadiene (V) and 1.43 g. of osmium tetroxide in 17.5 ml. of dry benzene and 3.5 ml. of dry pyridine was allowed to stand at room temperature for one day. The mixture was diluted with 25 ml. of chloroform and 0.7 g. of filtercel added followed by the dropwise addition of 7.0 ml. of concentrated hydrochloric acid with vigorous stirring. After stirring for two hours, the curdy precipitate containing oxides of osmium was removed by filtration and the residue washed thoroughly with hot chloroform. The combined filtrates were washed twice with water and then stirred for 1.5 hours with 100 ml. of 5% aqueous potassium carbonate solution. The chloroform layer was separated, washed twice with water and the solvent removed *in vacuo*. The partly crystalline residue was dissolved in 15 ml. of chloroform, 2.0 ml. of pyridine and 2.0 ml. of acetic anhydride were added, and the mixture stored at room temperature overnight. At the end of this period 100 ml. of water was added and the organic material extracted with chloroform. The combined chloroform extracts were washed with water and the solvents removed *in vacuo*. The residue thus obtained was crystallized from chloroform–ether to give 1.57 g. of VI, m.p. 201–205°. A sample prepared for analysis by recrystallization from acetone–ether was obtained as granular prisms, m.p. 207–210.5°, $[\alpha]^{25}D$ +49.1° (1.07, acetone), +55.5° (1.105, acetic acid).

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.15; H, 8.18.

(b) By Dehydration of Pregnane-11β,17α,21-triol-3,20-dione 21-Acetate (II) with Phosphorus Oxychloride in Pyridine.—To a cooled solution of 1.22 g. of pregnane-11β,17α,-21-triol-3,20-dione 21-acetate (II) in 10.0 ml. of dry pyridine was added 0.50 ml. of phosphorus oxychloride and the mixture was allowed to stand at room temperature overnight. At the end of this time the reddish-brown solution was concentrated *in vacuo* at *ca.* 25° to a volume of 5 ml. and 35 ml. of water added slowly with occasional swirling. The solid which separated was extracted with ethyl acetate. The combined ethyl acetate extracts were washed once with water, with 1 *N* hydrochloric acid until free of pyridine, again with water, once with 5% sodium bicarbonate solution, with water and finally with saturated salt solution. The washed extracts were dried and the solvent removed *in vacuo* to give a tan crystalline residue, weight 0.90 g. (77.3%), m.p. 194–205° with softening at 185°. Re-extraction of the combined washes above gave an additional 0.075 g. (6.4%). The two residues were combined and recrystallized from acetone–ether to afford the pregnene-dioldione acetate (VI) as small prisms, weight 0.675 g. (58%), m.p. 202.5–206°, undepressed on admixture with material prepared *via* osmylation of V. The material remaining in the mother liquor was chromatographed on acid-washed alumina. The fractions eluted with ether were combined and recrystallized to give an additional 0.17 g., m.p. 199.5–205°, raising the over-all yield to 73%.

(c) By Hydrogen Bromide Catalyzed Dehydration of Pregnane-11β,17α,21-triol-3,20-dione 21-Acetate (II).—A solution of 1.003 g. of II in 50 ml. of glacial acetic acid containing 0.50 ml. of 0.97 *N* hydrogen bromide in glacial acetic acid was allowed to stand at room temperature. The change in specific rotation of this solution was followed polarimetrically (Fig. 1) and after *ca.* 24 hours had become essentially constant. The acetic acid was then removed *in vacuo* at 25°, the partly crystalline residue treated with 50 ml. of water and the organic material extracted with three portions of ethyl acetate. The combined extracts were washed once with water, twice with 5% aqueous sodium bicarbonate until neutral, again with water and finally with saturated salt solution. The dried solution was filtered and the solvent removed *in vacuo* to give a buff-colored crystalline residue, weight 1.095 g., m.p. 178–195°. Two recrystallizations from ethyl acetate afforded 0.55 g. of VI, m.p. 202–206.5°, undepressed on admixture with material prepared *via* phosphorus oxychloride–pyridine dehydration.

The experiment above was repeated employing 0.01 *N* hydrogen bromide in chloroform and 0.01 *N* hydrogen bromide in acetonitrile as the solvents. The yields of VI, m.p. 199–204.5°, were 52 and 50.8%, respectively. However, when 0.01 *N* *p*-toluenesulfonic acid in acetic acid was used, the specific rotation did not change materially in 18 hours and the starting material was quantitatively recovered unchanged.

4-Bromo-$\Delta^{9(11)}$-pregnene-17α,21-diol-3,20-dione 21-Acetate (VII).—To a cooled stirred solution of 1.02 g. (0.00263 mole) of the acetate (VI) in 35 ml. of glacial acetic acid was added dropwise 27.5 ml. (0.00275 mole) of 0.10 *N* bromine in glacial acetic acid over a period of 50 minutes. The reaction mixture was poured into 250 ml. of water and the organic material extracted with three portions of chloroform. The combined chloroform extracts were washed with 5% sodium bicarbonate solution until free of acid, finally with water, and the chloroform removed *in vacuo*. The residue was crystallized from ether to afford 0.515 g. of the bromoketone, m.p. 206–206.5° (dec.). A second crop was obtained by concentrating the mother liquor, weight 0.18 g., m.p. 197.5–198° (dec.). A sample recrystallized for analysis melted at 211.5–212° (dec.), $[\alpha]^{23}D$ +93.1° (0.912, $CHCl_3$).

Anal. Calcd. for $C_{23}H_{31}O_5Br$: Br, 17.10. Found: Br, 16.97.

The combined mother liquors were evaporated to dryness and the residue treated with 0.62 g. of zinc dust in 5 ml. of glacial acetic acid at 90° for 40 minutes. The suspension was filtered, the filtrate diluted with water and the organic material extracted with chloroform. The combined chloroform extracts were worked up as described above to give, after one recrystallization from ether, 0.31 g. of the acetate (VI), m.p. 200.5–204°.

$\Delta^{4,9(11)}$-Pregnadiene-17α,21-diol-3,20-dione 21-Acetate (VIII). (a) By Dehydrobromination of the 4-Bromoketone (VII).—A 0.52-g. sample of the 4-bromoketone (VII) was dissolved in 15 ml. of glacial acetic acid. To this solution was added a solution of 0.435 g. of semicarbazide hydrochloride and 0.50 g. of anhydrous sodium acetate in 1.0 ml. of water and 35 ml. of glacial acetic acid and the mixture heated at 90° under nitrogen for one hour. At the end of this time, the reaction mixture was cooled and 2.0 ml. of 90% pyruvic acid, 0.60 g. of anhydrous sodium acetate and 3.0 ml. of water were added and the mixture heated at 90° for an additional hour. The final reaction mixture was cooled to room temperature, poured into 25 ml. of water and the organic material extracted with chloroform. The combined chloroform extracts were washed with 5% sodium bicarbonate solution until free of acid, finally with water and the solvent removed *in vacuo*. The crude residue was recrystallized from chloroform–ether to give 0.31 g. of the pregnadiene acetate (VIII), m.p. 215–225°. A sample recrystallized from chloroform–ether for analysis melted at 231.5–234.5°, $[\alpha]^{22}D$ +124° (1.04, $CHCl_3$), $\lambda_{max}^{CH_3OH}$ 2400 Å., $E_{1\ cm.}^{1\%}$ 407.

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.47; H, 7.83. Found: C, 71.26; H, 7.78.

(b) By Dehydration of 17α-Hydroxycorticosterone Acetate (IV).—A 1.22-g. sample of 17α-hydroxycorticosterone acetate (IV) was treated with 0.30 ml. of phosphorus oxychloride in 10.0 ml. of dry pyridine as described above for the dehydration of the pregnanetriol acetate (II). Addition of 50 ml. of water to the concentrated reaction mixture caused the separation of a reddish-brown gummy oil which only partly dissolved in the ethyl acetate extracts. The combined extracts were worked up to give a buff-colored partly crystalline residue, weight 0.13 g. Trituration with ether gave 0.055 g. of granular crystals, m.p. 218–225°. Recrystallization from acetone–ether afforded 0.042 g. of micro-needles, m.p. 225–232°, undepressed on admixture with material prepared by dehydrobromination of the 4-bromoketone (VII).

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