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

Synthesis of $\Delta^{3(5)}$-A-Norcholestene-2-one[1]

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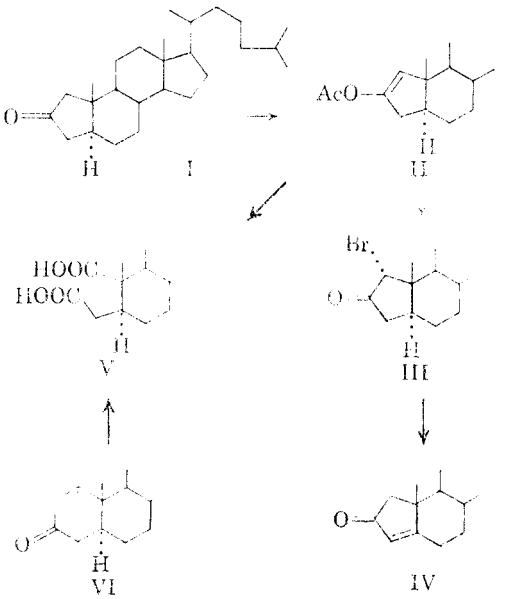
A-Norcholestane-2-one was converted into the Δ^1-enol acetate and, in turn, to the 1α-bromo-A-norcholestane-2-one. Dehydrobromination of the bromoketone with lithium chloride in dimethylformamide yielded $\Delta^{3(5)}$-A-norcholestene-2-one. The bromoketone also was converted *via* the bromohydrin and 1β,2β-epoxide to A-norcholestane-2β-ol, thus establishing the configurations of the epimeric alcohols in this series. The enol lactone 3-oxa-Δ^5-A-norcholestene-2-one, upon reaction with methylmagnesium iodide, yielded the expected bicyclo[3.2.1]octane derivative which, upon base treatment, was converted in small yield to $\Delta^{3(5)}$-A-norcholestene-2-one.

During the past three years, various laboratories have investigated the preparation of A-nor analogs of biologically active steroidal materials,[3-8] and it has been found that the derivative of hydrocortisone is inactive[6] but that A-norprogesterone is an anti-androgen.[9] In the preparation of A-norenones it was found that direct ring contraction of an unsaturated 6-membered ketone proceeded well, whereas the introduction of unsaturation into a saturated 5-membered ketone *via* the usual bromination and dehydrobromination procedures led to complications. For example, Jacobs and Takahashi[3] found that direct bromination of A-norchlorestane-2-one (I) proceeded slowly and only



when the reaction was allowed to continue to the dibromo stage was a pure product obtained.[9a] The dibromide could be converted to the desired enone system by dehydrobromination to a 3-bromo-3-ene compound followed by hydrogenolysis of the bromine. In the course of investigations in this Laboratory pertaining to the chemistry of A-norsteroids, a more direct conversion of a saturated to an unsaturated ketone has been achieved.

The first step in the synthesis involved the preparation of the enol acetate II of A-norcholestane-2-one (I). The use of acetic anhydride or isopropenyl acetate under normal conditions for enol acetylation left the ketone unchanged. When isopropenyl acetate was used under special forcing conditions, enol acetylation occurred slowly, and after three days reaction time the Δ^1-enol acetate II was obtained in 50% yield and 45% of the starting material was recovered. The direction of the enolization was established in two ways. First, in the n.m.r. spectrum of II the band at 4.58 τ due to the olefinic proton was a singlet, suggesting no adjacent protons for spin–spin coupling,[10] a result expected of a Δ^1- but not a Δ^3-structure. Second, oxidation of II yielded 1,3-secocholestane-1,3-dioic acid (V). The acid was identical with the secodiacid obtained from the oxidation of Δ^1-cholestene-3-one (VI) by the procedure of Tamm and Albrecht.[11] The formation of the Δ^1-enol acetate using isopropenyl acetate is of interest since normally this reagent gives the enol acetate resulting from the loss of a proton from the less hindered side of a ketone.[12,13] A similar result is found with the 16-ketoandrostane derivatives[14,15] and it is suggestive that as in normal steroids the stereochemistry of the ring juncture exerts a strong influence on the direction of enolization.

Bromination of the enol acetate gave 1-bromo-A-norcholestane-2-one (III) in 96% yield. When III was heated with collidine, it was recovered unchanged. However, when III was allowed to react with lithium chloride in dimethyl formamide,[16] a facile dehydrobromination occurred and $\Delta^{3(5)}$-A-norcholestene-2-one (IV) was obtained in 92%

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(2) General Electric Co. Fellow in Chemistry, 1958–1959.

(3) T. L. Jacobs and N. Takahashi, *J. Am. Chem. Soc.*, **80**, 4865 (1958).

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(8) B. Fuchs and H. J. E. Loewenthal, *Tetrahedron*, **11**, 199 (1960).

(9) L. J. Lerner, A. Bianchi and A. Borman, *Proc. Soc. Exp. Biol. Med.*, **163**, 172 (1960).

(9a) By n.m.r. spectroscope, the crystalline dibromide has been shown to be a 1,3 rather than a 3,3, dibromoketone.

(10) Although the spin–spin coupling constant varies with the dihedral angle (M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959)), the dihedral angle of about 90° needed for a zero coupling constant did not appear reasonable from examination of models.

(11) Ch. Tamm and R. Albrecht, *Helv. Chim. Acta*, **43**, 768 (1960).

(12) R. B. Moffett and D. I. Weisblat, *J. Am. Chem. Soc.*, **74**, 2183 (1952).

(13) W. S. Johnson, I. A. David, H. C. Dehm, R. J. Highet, E. W. Warnhoff, W. D. Wood and E. T. Jones, *ibid.*, **80**, 661 (1958).

(14) J. Fishman and C. Djerassi, *Experientia*, **16**, 138 (1960).

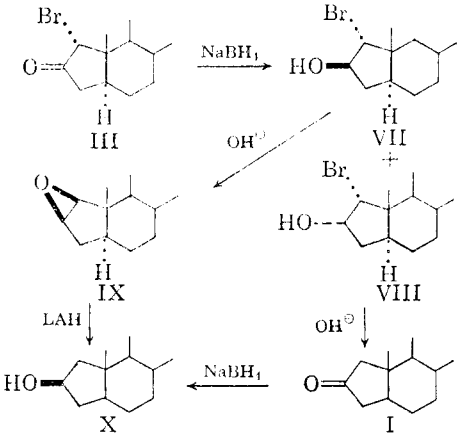
(15) J. Fajkos and J. Joska, *Coll. Czech. Chem. Comm.*, **25**, 2863 (1960); **26**, 1118 (1961).

(16) R. P. Holysz, *J. Am. Chem. Soc.*, **75**, 4432 (1953).

yield. Such a rearrangement upon dehydrohalogenation by this reagent is well known,[17,18] but it was necessary to establish that the bromine was at C_1 as expected. This fact was readily established in that in the n.m.r. spectrum of III the band at 6.27 τ due to the proton on the bromine bearing carbon atom was a singlet as expected for the 1-bromo-2-ketone structure with no adjacent protons available for spin–spin coupling.

The configuration of the bromine atom in III should be 1α since in the bromination of the enol acetate of a 16-keto-steroid the α-isomer is formed.[14,15] Such a configuration places the 1-bromine atom in a Ψ-axial conformation since ring A must be present as a half-chair conformation.[14,15] In agreement with the Ψ-axial conformation was the finding of a shift of +9 cm.$^{-1}$ in the infrared and +22 mμ in the ultraviolet for the carbonyl absorption as compared with the parent ketone.[14,15] Also, it was found that the bathochromic shift of the first extremum of the positive Cotton curve was 33 mμ,[19] a value in line with the recent work of Fishman and Djerassi.[14] These results clearly establish the Ψ-axial conformation and, in turn, the 1α-configuration of the bromine atom in III.

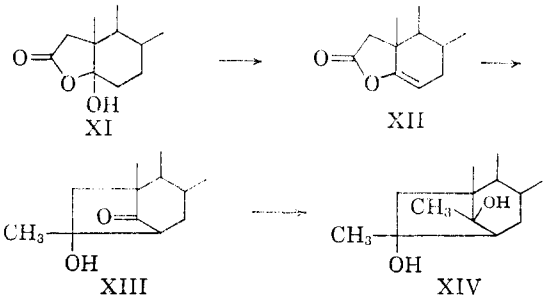
With the establishment of the stereochemistry of the bromoketone, it was possible to settle the problem as to the configuration of the epimeric 2-A-norcholestanols. In 1959, Shoppee and Sly,[20] using arguments based upon molecular rotational differences, concluded that the isomer which formed a precipitate with digitonin was 2α. Recently, Fuchs and Loewenthal,[8] using conformation arguments, arrived at an opposite conclusion. In the present work, starting with the bromoketone II, it was found that reduction with sodium borohydride gave a mixture of bromohydrins VII and VIII. The mixture was not separated but treated briefly



with methanolic potassium hydroxide and 46% of A-norcholestanone (I) and 25% of the epoxide IX were obtained. The epoxide, which must possess a 1β,2β-configuration since it was derived from a 1α-bromo derivative,[21] was allowed to react with lithium aluminum hydride and the resulting mixture of 1β- and 2β-hydroxy derivatives separated by the use of digitonin. The same 2β-isomer was obtained by direct reduction of A-norcholestanone with sodium borohydride. These results show that the isomer precipitated with digitonin is the 2β, a conclusion in agreement with that originally made by Marker[22] and reaffirmed by Fuchs and Loewenthal[8] and in disagreement with the assignment made by Shoppee and Sly.[20] The finding of a 94% yield of the 2β-isomer on reduction of A-norcholestanone with sodium borohydride as compared to the formation of a 50:50 mixture of α- and β-isomer when the ketone was reduced with sodium in 2-propanol illustrates the hindered nature of the ketone. The extremely high specificity in the hydride reduction is to be expected in view of the about equal energy content of the two isomers and the relative importance of "steric approach control"[23] in the hydride reduction of similarly substituted steroids.

When A-norcholestenone (IV) was reduced with lithium in liquid ammonia the ratio of the A/B *cis* to A/B *trans* product was about 4:1. Weisenborn and Applegate[5] have reduced A-nortestosterone under similar conditions and have found about equal amounts of the *cis* and *trans* isomers. Although in terms of energy the percentage differences obtained with these two norsteroids is not large, it does appear that here is another example where long range conformational forces are operative.[24]

An initial approach tried for the preparation of A-norcholestenone (IV) was patterned after the methylmagnesium iodide–enol lactone sequence employed so successfully in the synthesis of cholestenone.[25] In a manner similar to that described by Jacobs and Takahashi,[3] the lactol XI, derived from hydroxymethylenechlolestenone, was dehydrated to yield the enol lactone XII. When XII was allowed to react with 0.5–1.0 mole excess of methylmagnesium iodide, a one-mole addition product was obtained.



The infrared spectrum of the product possessed the expected band at 3.0μ (hydroxyl) and also a band at 5.88 μ. That this latter band was due to the presence of a ketonic function and not the original enolic double bond which absorbed at the same position was readily shown by the absence of any

(17) J. J. Beereboom and C. Djerassi, *J. Org. Chem.*, **19**, 1196 (1954).

(18) M. E. Kuehne, *J. Am. Chem. Soc.*, **83**, 1492 (1961).

(19) We wish to thank Professor Djerassi for kindly determining the optical rotatory dispersion curve.

(20) C. W. Shoppee and J. C. P. Sly, *J. Chem. Soc.*, 345 (1959).

(21) L. F. Fieser and R. Ettorre, *J. Am. Chem. Soc.*, **75**, 1700 (1953).

(22) R. E. Marker, O. Kamm, D. M. Jones and L. W. Mixon, *ibid.*, **59**, 1363 (1937).

(23) W. G. Dauben, E. J. Blanz, Jr., J. Jiu and R. A. Micheli, *ibid.*, **78**, 3752 (1956).

(24) D. H. R. Barton, F. McCapra, P. J. May and F. Thudium, *J. Chem. Soc.*, 1297 (1960), and earlier papers.

(25) G. I. Fugimoto, *J. Am. Chem. Soc.*, **73**, 1856 (1951); G. I. Fugimoto and J. Prager, *ibid.*, **75**, 3259 (1953).

vinyl proton absorption in the n.m.r. spectrum, a negative test with tetranitromethane and no end absorption in the ultraviolet. In view of previous work on homologous analogs[26,27] and the above spectral properties, the bicyclo[3.2.1] structure XIII was assigned to the product. When the enol lactone XII was allowed to react with three moles of Grignard reagent, both the ketol XIII and the derived diol XIV were obtained. Treatment of ketol XIII with methanolic potassium hydroxide under conditions which work well in the cholestenone preparation left the material unchanged. When the reaction time was extended, the desired enone IV was formed in about 25% yield as shown by the spectrum of the crude reaction mixture. It was not possible to isolate the A-norcholestenone in pure form but it could be characterized by formation of the 2,4-dinitrophenylhydrazone.

Acknowledgment.—The authors are indebted to David Chan and David A. Lightner for their assistance during the course of this work.

Experimental[28]

2-Acetoxy-Δ^1-A-norcholestene (II).—A solution of 6.10 g. (16.3 mmoles) of A-norcholestane-2-one (I)[29] [λ_{max}^{EtOH} 292 mμ, $\nu_{max}^{CS_2}$ 1733 cm.$^{-1}$], 1.0 g. of *p*-toluenesulfonic acid and 100 ml. of redistilled isopropenyl acetate was heated in an apparatus which consisted of a small unpacked column connected to a condenser and in the unpacked column was placed a well which contained ethanol and which was capped with a reflux condenser. In this manner, the acetone which formed was removed and the isopropenyl acetate returned to the reaction flask. The solution was heated under reflux for 72 hours and additional isopropenyl acetate added from time to time to maintain a volume of not less than 75 ml. At the end of the reflux period, the solution was cooled to room temperature, solid sodium bicarbonate added and the mixture concentrated under reduced pressure. The residue was dissolved in ether and the ethereal solution washed, successively, with sodium bicarbonate, water and saturated salt solution. The ether was removed and the residual brown oil chromatographed on alumina (Act. III). Elution with petroleum ether gave 3.40 g. (50.8%) of crystalline enol acetate. Further elution with benzene yielded 2.81 g. (46.2%) of unreacted A-norcholestane-2-one.

The crude enol acetate, m.p. 80–85°, was recrystallized twice from 95% ethanol; m.p. 87–88°, $[\alpha]^{25}D$ +52.6° (*c* 1.22, chf.), $\nu_{max}^{CS_2}$ 1750 and 1250 cm.$^{-1}$.

Anal. Calcd. for $C_{28}H_{46}O_2$ (414.65): C, 81.10; H, 11.18. Found: C, 80.84; H, 10.88.

1α-Bromo-A-norcholestane-2-one (III).—A solution of 631 mg. (1.52 mmoles) of enol acetate II in 30 ml. of carbon tetrachloride, stirred magnetically while cooled in an ice-salt-bath, was treated dropwise over a period of 5 minutes with 242 mg. (1.52 mmoles) of bromine in chloroform. The stirred solution remained colorless until about 80% of the bromine solution had been added and after this point the bromine color was discharged slowly. The resulting light yellow solution was concentrated under reduced pressure and the residual yellow sirup was crystallized from ethanol; yield 660 mg. (96%), m.p. 90–95°. The bromoketone III was recrystallized twice from ethanol; m.p. 97–98°, $[\alpha]^{25}D$ + 77° (*c* 1.04, chf.), λ_{max} 313 mμ (ε 113), $\nu_{max}^{CS_2}$ 1742 cm.$^{-1}$. The optical rotatory curve (solvent MeOH) showed a peak at 348 mμ (+850) and a trough at 302 mμ (−125).

Anal. Calcd. for $C_{26}H_{43}OBr$ (451.45): C, 69.16; H, 9.60; Br, 17.70. Found: C, 69.33; H, 9.46; Br, 17.86.

$\Delta^{3(5)}$-A-Norcholestene-2-one (IV).—A solution of 1.32 g. (2.92 mmoles) of bromoketone III and 500 mg. of anhydrous lithium chloride in 20 ml. of dimethylformamide[15] was heated under nitrogen for 24 hours at 150°. The light yellow solution was cooled, diluted with water and kept for 1 hour in an ice-bath. The crystalline precipitate was filtered, washed with water and dried; yield 1.0 g. (92%), m.p. 75–80°. Recrystallization of the product from ethanol yielded the $\Delta^{3(5)}$-A-norcholestene-2-one in two crystalline modifications: prisms, m.p. 87.0–88.0°; needles, m.p. 96.0–97.0°, λ_{max}^{EtOH} 236 mμ (ε 15,600), $\nu_{max}^{CS_2}$ 1705 and 1620 cm.$^{-1}$, $[\alpha]^{25}D$ −14.6° (*c* 1.41, chf.) [lit.[3] m.p. 96–97°, $[\alpha]D$(chf) −143°]. The reported optical rotation[3] must be a typographical error. The optical rotatory dispersion curve (solvent dioxane) showed a trough at 325 mμ (−1140) and a peak at 300 mμ (+ 1500).[19]

Anal. Calcd. for $C_{26}H_{42}O$ (370.63): C, 84.26; H, 11.42. Found: C, 84.37; H, 11.26.

The lower melting dipmorphic form was obtained by slow crystallization from ethanol at room temperature and the higher melting form was obtained by rapid crystallization at ice temperatures. The lower melting form after melting at 87–88° resolidifies and remelts at 96–97°.

The 2,4-dinitrophenylhydrazone was prepared and recrystallized from ethyl acetate–ethanol; m.p. 193–195° (sealed capillary), λ_{max}^{chf} 392 mμ (ε 32,000) [lit.[3] m.p. 191–193°].

1,3-Secocholestane-1,3-dioic Acid (V).—A solution of 100 mg. of 2-acetoxy-Δ^1-A-norcholestene (II) and 100 mg. of chromium trioxide in 20 ml. of acetic acid and 1 ml. of benzene was allowed to stand for 18 hours at room temperature. The excess chromium trioxide was destroyed by addition of methanol, the solvents removed at reduced pressure and the residue dissolved in ether. The ethereal solution was washed with water and extracted with sodium bicarbonate. The bicarbonate solution was acidified with hydrochloric acid, extracted with ether and the ether extract washed with water and dried. The solvent was evaporated and the residue crystallized from ether–petroleum ether; m.p. 223–226°, yield 20 mg., $[\alpha]^{25}D$ +9.8° (*c* 0.55, chf.) [lit.[11] m.p. 221–222°, $[\alpha]D$ 13°]. Upon admixture with an authentic sample prepared from Δ^1-cholestene-3-one,[11] the m.p. was not depressed and the infrared spectra of the two samples were identical. Loewenthal reports a mixture of 1,3-secocholestane-1,3-dioic acid and 2,4-secocholestane-2,4-dioic acid melts at 205°.[30]

The dimethyl ester was prepared and crystallized from methanol; m.p. 50–51°, $[\alpha]^{25}D$ +13.5 ±2° (*c* 0.57, chf.); the infrared spectrum was identical with an authentic sample and a sample kindly supplied by Dr. H. J. E. Loewenthal.[31]

Sodium Borohydride Reduction of 1α-Bromo-A-norcholestane-2-one (III).—To a well-stirred solution of 0.50 g. (1.1 mmoles) of bromoketone III in 30 ml. of ethanol was added a solution of 100 mg. of sodium borohydride in 20 ml. of ethanol. The resulting solution was allowed to stir for 1 hour at room temperature, the excess hydride decomposed with dilute hydrochloric acid and mixture extracted with ether. The ethereal extract was washed with water, sodium bicarbonate, saturated sodium chloride solution and dried. The solvent was removed under reduced pressure and the sirupy residue (477 mg., 94%) partially solidified on standing. The product could not be recrystallized satisfactorily although a portion of it could be obtained as a solid by allowing a hexane solution to stand in a refrigerator; the solid melted from 115–118°, $[\alpha]^{20}D$ +7° (*c* 1.22 chf.). The infrared spectrum of the crude reaction product demonstrated the absence of any carbonyl-containing material and the mixture was used directly in the next reaction.

Anal. Calcd. for $C_{26}H_{45}OBr$ (453.47): C, 68.79; H, 9.93. Found: C, 69.04; H, 9.70.

Conversion of Mixed Bromohydrins VII and VIII to 1β,2β-Epoxy-A-norcholestane (IX) and A-Norcholestane-2-one (I).—A solution of 270 mg. (0.59 mmole) of mixed bromohydrins VII and VIII (crude product from above reaction) and 0.3 g. of potassium hydroxide in 30 ml. of methanol was refluxed for 46 hours. The reaction mixture was diluted with water and extracted with ether. The ether extracts

(26) G. I. Fugimoto and K. D. Zwahlen, *J. Org. Chem.*, **25**, 445 (1960).

(27) W. S. Johnson, J. A. Korst, R. A. Clement and J. Dutta, *J. Am. Chem. Soc.*, **82**, 614 (1960).

(28) All chromatographies were conducted with Woelm neutral alumina. All analyses were performed by the Microanalytical Laboratory, University of California.

(29) A. Windaus and O. Dalmer, *Ber.*, **53**, 162 (1919); A. Windaus, *Ann.*, **532**, 63 (1938).

(30) H. J. E. Loewenthal, private communication.

(31) B. Fuchs and H. J. E. Loewenthal[8] report m.p. 57–58°, $[\alpha]D$ +29°, but the sample supplied to us by Dr. Loewenthal had m.p. 51.5–52.5°, $[\alpha]D$ +12.5 ± 2° (0.16 chf.).

were washed with water, dilute hydrochloric acid, water, saturated sodium chloride solution and dried. The ether was evaporated and the crystalline residue (180 mg., 82%) was chromatographed on alumina (Act. III). Elution with petroleum ether gave 55 mg. (25%) of crystalline 1β,2β-epoxy-A-norcholestane (IX), m.p. 95–98°. The material was recrystallized twice from methanol; m.p. 102–104°, $[\alpha]^{20}D$ +16° (*c* 0.67, chf.).

Anal. Calcd. for $C_{26}H_{42}O$ (372.61): C, 83.80; H, 11.90. Found: C, 83.28; H, 11.88.

Further elution with benzene yielded 100 mg. (45%) of crystalline A-norcholestane-2-one (I). The ketone was recrystallized from ethanol; m.p. 98–100°, $[\alpha]^{20}D$ +150° (*c* 1.10, chf.), no depression in m.p. when admixed with an authentic sample; the infrared spectrum was identical with that of an authentic sample.

A-Norcholestane-2β-ol (X). (a) From A-Norcholestane-2-one (I).—A solution of 0.50 g. (1.34 mmoles) of A-norcholestane-2-one in 25 ml. of 95% ethanol was allowed to react with a solution of 100 mg. of sodium borohydride in 10 ml. of ethanol. The solution was stirred for 2 hours at room temperature, diluted with aqueous hyrochloric acid and extracted with ether. The ethereal extract was washed with water, saturated salt solution and dried. The solvent was evaporated and the white crystalline residue chromatographed on alumina (Act. III). Elution with petroleum ether–benzene (1:4) afforded 472 mg. (94%) of crystalline stanol, m.p. 100–105°. After two recrystallizations from aqueous ethanol the A-norcholestane-2β-ol was obtained as long, white blades, m.p. 110–112°, $[\alpha]^{25}D$ +23° (*c* 0.97, chf.).

Anal. Calcd. for $C_{26}H_{46}O$ (374.63): C, 83.35; H, 12.38. Found: C, 83.55; H, 12.29.

In order to establish the homogeneity of the material, a sample was recrystallized three times from ethanol and once from petroleum ether and the melting point did not change. Furthermore, a sample was purified as the digitonide and recrystallized from methanol–ether; m.p. 108–110°.

The acetate was prepared by refluxing 80 mg. (0.214 mmole) of the stanol in 5.0 ml. of acetic anhydride for 30 minutes. The excess reagent was removed under reduced pressure and the crystalline residue recrystallized twice from ether–methanol; yield 60 mg. (68%), m.p. 75–77°, $[\alpha]^{25}D$ +20° (chf.).

Anal. Calcd. for $C_{28}H_{48}O_2$ (416.25): C, 80.70; H, 11.62. Found: C, 80.45; H, 11.30.

The physical properties of the isomer which forms a precipitate with digitonin found in this present work differs from those reported by Shoppee and Sly.[20] These latter workers report: m.p. 128°, [α] +38° for the alcohol and m.p. 80°, [α] +1° for the acetate. These workers also report the following properties for the non-digitonin-precipitable isomer: m.p. 120° (solvate), [α] +28°; acetate, m.p. 93°, [α] +25°.

The two isomers were prepared following the procedure of Marker[22] using sodium and isopropyl alcohol reduction of the ketone. From 0.220 mg. (0.59 mmole) of A-norcholestane-2-one there was obtained 105 mg. of the digitonin-precipitable isomer (m.p. 100–105°) and from the filtrate from the ditonin precipitation reaction there was obtained the epimer, m.p. 125–128° (solvate), $[\alpha]^{20}D$ +29° (*c* 0.86, chf.).

(b) From 1β,2β-Epoxy-A-norcholestane (IX).—To a stirred solution of 38 mg. (0.10 mmole) of the epoxide in 10 ml. of anhydrous ether was added a slurry of 100 mg. of lithium aluminum hydride. The mixture was stirred at room temperature for 2 hours, ethyl acetate added to decompose the excess hydride and the solution diluted with water. The mixture was extracted with ether and the ethereal solution processed in the usual fashion to yield 35 mg. of the crude stanol mixture. The material was purified through the digitonide and recrystallized from methanol–ether; yield 27 mg. (71%), m.p. 105–108°, no depression when admixed with material prepared above, $[\alpha]^{25}D$ +20° (*c* 1.02, chf.); the infrared spectrum was identical with material prepared above. Oxidation yielded A-norcholestane-2-one, m.p. 100–102°.

A-Norcoprostane-2-one. (a) From Hydrogenation of $\Delta^{3(5)}$-A-Norcholestene-2-one.—A solution of 200 mg. (0.54 mmole) of unsaturated ketone and 0.3 g. of potassium hydroxide in 30 ml. of methanol was hydrogenated over 5% palladium-on-charcoal. After absorption of 1 mole equivalent of hydrogen, the catalyst was filtered, the base neutralized with acetic acid and the product crystallized from methanol–ether; yield 133 mg. (67%), m.p. 100–102°, $[\alpha]^{25}D$ −46° (*c* 1.08, chf.) [lit.[3] m.p. 102–103°, $[\alpha]^{28}D$ −43° (chf.)].

(b) From Lithium–Ammonia Reduction of $\Delta^{3(6)}$-A-Norcholestene-2-one.—A solution of 0.28 g. (0.75 mmole) of A-norcholestenone in 20 ml. of anhydrous ether was added to 75 ml. of liquid ammonia. During a 30-minute period, 0.50 g. of lithium was added, the deep blue solution stirred for an additional 20 minutes, an aqueous solution of ammonium chloride added and the ammonia allowed to evaporate. The residue was dissolved in ether, the ethereal solution washed and dried and the solvent evaporated. The residual oil (0.25 g.) was found to contain 20% of starting unsaturated ketone by examination of the ultraviolet and infrared spectra. The crude product was dissolved in petroleum ether and chromatographed on alumina (Act. III). Elution with petroleum ether gave 0.15 g. of crude saturated ketone, $[\alpha]^{20}D$ +2° (*c* 1.45 Chf.). This value corresponds to a mixture of 77% A-norcoprostanone and 23% of A-norcholestanone; the values are most likely accurate to within 5%. Recrystallization of the fraction from ethanol yielded 40 mg. of pure A-norcoprostanone, m.p. 105–107°, $[\alpha]^{20}D$ −43° (*c* 0.92 chf.). From the mother liquor there was obtained 60 mg. of less pure material.

Further elution with benzene yielded 70 mg. of A-norcholestenone plus a small amount of alcohol.

The Reaction of Enol Lactone XII with Methylmagnesium Iodide. (a) One-mole Addition Product (XIII).—To a well stirred solution of 0.713 g. (1.92 mmoles) of enol lactone XII[3] in 20 ml. of 1:1 benzene–ether there was added 2 mole equivalents of methylmagnesium iodide in 5 ml. of ether. The reaction mixture was allowed to stir for 1 hour, an excess of 10% hydrochloric acid added and the ether layer separated. After the usual workup, the 685 g. of residual yellow oil was chromatographed on alumina (Act. III). Elution with petroleum ether yielded 130 mg. of an oil which was not investigated and elution with 1:1 ether–petroleum ether gave 359 mg. of crystalline product, the infrared spectrum of which indicated the presence of a small amount of starting material. The solid was recrystallized twice from petroleum ether to yield 166 mg. (22.8%) of XIII, m.p. 117–118°, $[\alpha]D$ +40° (*c* 1.17, chf.); $\nu_{max}^{CS_2}$ 1700, 3415 and 3570 cm.$^{-1}$; negative tetranitromethane test.

Anal. Calcd. for $C_{26}H_{44}O_2$ (388.61): C, 80.35; H, 11.41. Found: C, 79.89; H, 11.44.

(b) Two-mole Addition Product (XIV).—In a similar manner as described above with the exception that the enol lactone was added to the Grignard reagent, 0.540 mg. (1.45 mmoles) of enol lactone XII was allowed to react with 3 mole equivalents of methylmagnesium iodide. Elution with petroleum ether gave 333 mg. (56.5%) of XIV which was recrystallized from acetone; m.p. 101–102°, $[\alpha]^{25}D$ +63° (*c* 2.67, chf.).

Anal. Calcd. for $C_{27}H_{48}O_2$ (404.65): C, 80.14; H, 11.96. Found: C, 79.96; H, 11.86.

Further elution with petroleum ether–benzene 1:1 gave 140 mg. of XIII, m.p. 115–117°, no depression upon admixture with monoaddition product prepared above.