[CONTRIBUTION NO. 121 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Conversion of Hecogenin and Manogenin into Derivatives of Allopregnane-12,20-dione

BY GEORGE P. MUELLER, ROBERT E. STOBAUGH AND ROBERT S. WINNIFORD

RECEIVED MAY 8, 1952

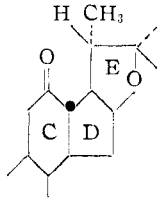
Hecogenin and manogenin have been converted to the corresponding 16-dihydroallopregnene-12,20-diones, the preparation and properties of which are discussed. 3β-Acetoxy-16-allopregnene-12,20-dione was converted through the oxide and bromohydrin to 3β-acetoxy-17α-hydroxyallopregnane-12,20-dione. Both 16-dehydro derivatives yielded the corresponding pregnanes. Δ^4-Hecogenone has been prepared.

Hecogenin and manogenin were both obtained by the procedures of Marker and his colleagues[1] from *Agave toumeyana*. Although several other steroidal sapogenins were also isolated, 9(11)-dehydrohecogenin and 9(11)-dehydromanogenin[2] were particularly difficult to separate from the parent sapogenins. Wagner's group noted that the melting points of these sapogenins are not depressed by the corresponding dehydrogenins as impurities. Chromatographic separation was possible, but there is much overlapping of the two bands. Where a pure sample of either the parent or dehydrogenin was desired we found the application of Girard reagent effective. This reacts more rapidly with the non-conjugated C-12 carbonyl compounds, and the derivatives formed are hydrolyzed more rapidly than those of the sapogenins with conjugated ketone groups. This method was applied independently by Callow, *et al.*,[3] in their isolation of hecogenin from *Agave sisalana*.

In anticipation of the eventual synthesis of progesterone derivatives, Δ^4-hecogenone was prepared by bromination of hecogenone, treatment with sodium iodide and subsequent dehalogenation, a method previously developed for allopregnane derivatives.[4]

Both the acetate IV and the butyrate V of pseudohecogenin were suitable for oxidation and hydrolysis to the corresponding 16-dehydroallopregnane derivatives, but the fortuitous crystallization of hecone diacetate VI enabled us to study its reactions with greater care. Hydrolysis in methanolic potassium carbonate gave 39% of VII while the use of *t*-butyl alcohol afforded 76% of the same product. On the other hand, sublimation of hecone diacetate induced deacylation at C-16 only in low yields. Adsorption and elution of VI from an alumina column resulted in 81% of VII, the best yield obtained.

The relative ease of deacylation of the hecone structure by acid[5] or alkali, both ionic reactions, as opposed to a smooth *cis* elimination in pyrolysis suggests a *trans* relationship between the hydrogen at C-17 and the C-16 acyl group. The behavior toward acids, alkalies and alumina is likewise analogous with similar observations in the cardiac glycoside series. Finally, models based on the configuration of the sterols and bile acids at C-20[6] and on Marker's conversion of diosgenin to cholesterol show that accommodation of ring E is possible only with the oxygen atom in the 16β configuration.



The 16-dehydroallopregnenes, VII, XIII, 3β,12β-diacetoxy-16-allopregnene-11,20-dione[7] and 2α,3β-diacetoxy-5,16-pregnadiene-12,20-dione[8] all show maximal absorption at 227–234 mμ and constitute exceptions to the Woodward rule which would predict the value 237–240 mμ. Moreover the extinction coefficients are generally somewhat lower (8000–9000) than those of similar steroids (9000–13,000) not oxygenated at C-12.[9]

A satisfactory explanation of these effects can be based on the premise that the *s-trans* configuration of the α,β-unsaturated carbonyl function is favored both on energetic grounds[10] and by the values of the extinction coefficients which are considerably greater than is usual for the *s-cis* configuration.[11] The molecular models agree in showing far less hindrance between the oxygens at C-12 and C-20 in this conformation than between the C-12 oxygen and the C-21 methyl group in an *s-cis* arrangement. Thus we have in the *s-trans* form two oxygen atoms directly opposed with a small amount of steric interference between them in addition to the electrostatic repulsion existing between like atoms. The resultant strain in the ground state affords somewhat diminished probability, and hence intensity, of absorption, as observed.[11] The more pronounced hypsochromic shift of the absorption maximum, however, results from the increased energy of excitation in going from a ground state, A, to B, where the dipoles of both excited carbon–oxygen systems are opposed. The repulsion is

(1) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith and C. H. Ruof, THIS JOURNAL, **69**, 2167 (1947).

(2) R. B. Wagner, R. F. Forker and P. F. Spitzer, *ibid.*, **73**, 2494 (1951).

(3) R. K. Callow, J. W. Cornforth and P. C. Spensley, *Chem. and Ind.*, 699 (1951).

(4) G. Rosenkranz, O. Mancera, J. Gatica and C. Djerassi, THIS JOURNAL, **72**, 4077 (1950).

(5) R. E. Marker, *et al.*, *ibid.*, **63**, 774 (1941).

(6) P. Wieland and K. Miescher, *Helv. Chim. Acta*, **32**, 1922 (1949).

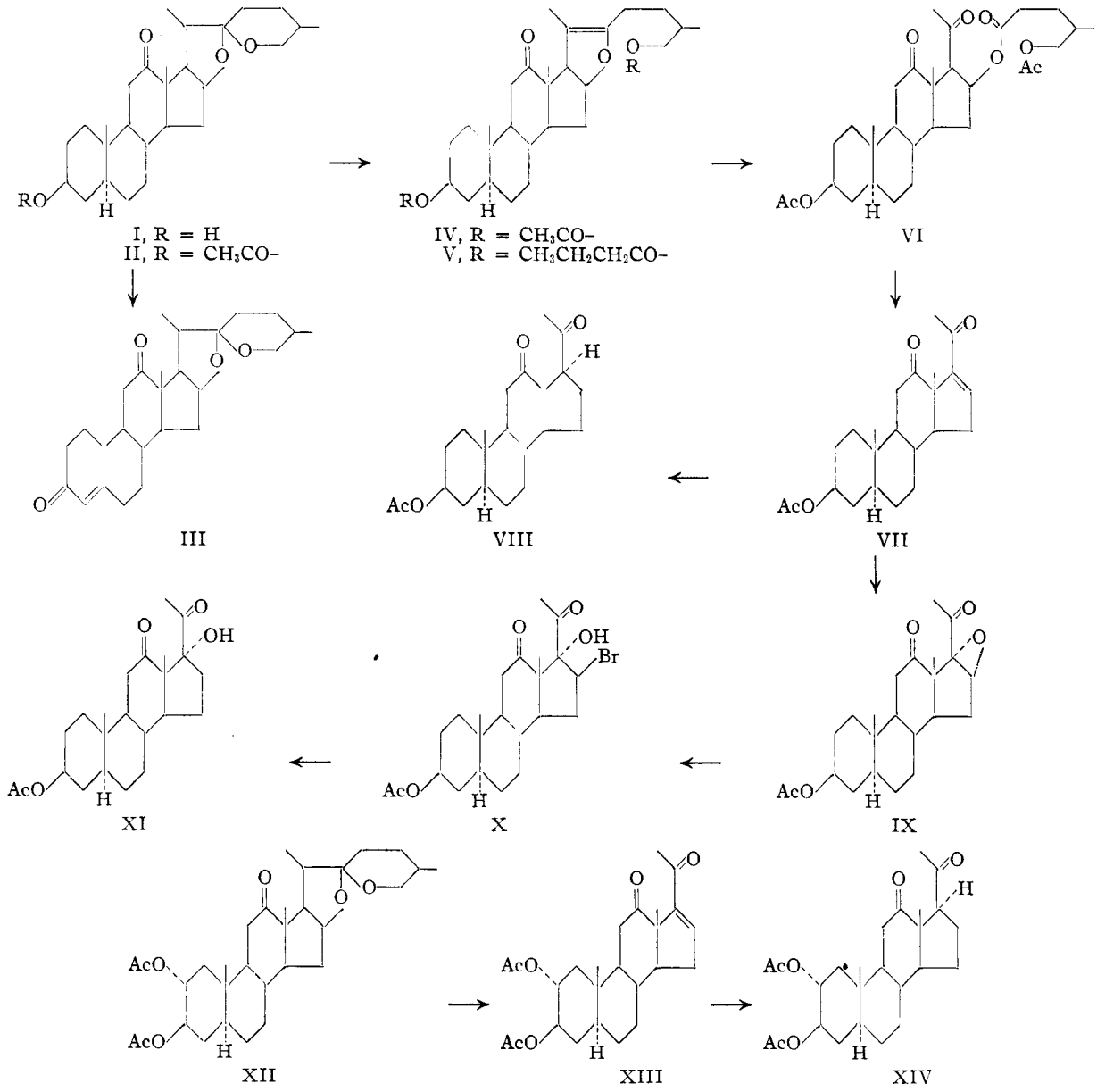
(7) G. P. Mueller, L. L. Norton, R. E. Stobaugh and R. S. Winniford, THIS JOURNAL, **75**, 4892 (1953).

(8) This information was kindly furnished by Drs. J. A. Moore and E. L. Wittle of Parke Davis and Co., Detroit, Mich., whom we wish to thank for their willing assistance.

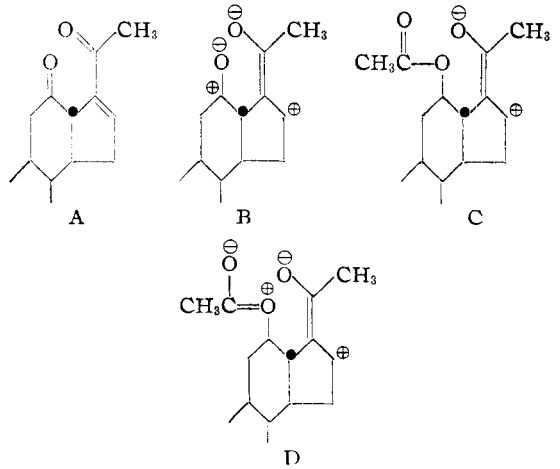
(9) *Cf.* H. Dannenberg, *Abhandl. preuss. Akad. Wiss.*, **21**, 56 (1939); A. Butenandt, L. Mamoli and A. Heusner, *Ber.*, **72B**, 1614 (1939); P. A. Plattner, H. Heusser and E. Angliker, *Helv. Chim. Acta*, **29**, 468 (1946).

(10) E. A. Braude, E. R. H. Jones, *et al.*, *J. Chem. Soc.*, 1890 (1949).

(11) R. B. Turner and D. M. Voitle, THIS JOURNAL, **73**, 1403 (1951).



ameliorated by the small resonance contribution, D, of the 12β-acetoxy group so that 3β,12β-diacetoxy-16-allopregnene-11,20-dione, ϵ_{max} 232–234 mμ,



shows a small bathochromic shift relative to the C-12 ketones.

As further evidence for this carbonyl interaction we have noted that those 16-dehydro steroids having anomalous ultraviolet spectra also display hypsochromic shifts of the C-12 carbonyl and the C-20 conjugated carbonyl groups in infrared absorption. Previously noted in several 21-acetoxy-20-ketopregnanes were similar shifts of about 22 cm.$^{-1}$ for the carbonyl function and about 15 cm.$^{-1}$ for the acetate carbonyl[12] attributed to interaction between these groups. Reference to the following data and comparison with values of 1706–1710 cm.$^{-1}$ and 1666–1670 cm.$^{-1}$ which are usual[13] for the groups in question reveal the presence of a similar type of vicinal interaction between the oxygen atoms at

(12) (a) R. N. Jones and K. Dobriner, "Infrared Spectroscopy Applied to Steroid Structure and Metabolism," "Vitamins and Hormones," Vol. VII, Academic Press, Inc., New York, N. Y., 1949, p. 328; (b) R. N. Jones, P. Humphries and K. Dobriner, THIS JOURNAL, 71, 241 (1949).

(13) Reference 12a, p. 321.

CORRELATION OF SIMILAR DATA FROM THE 16-PREGNENES

	C-12 >C=O	C-20 >C=O
3β-Acetoxy-16-allopregnene-12,20-dione	1717 cm.$^{-1}$	1678 cm.$^{-1}$
2α,3β-Diacetoxy-16-allopregnene-12,20-dione	1717	1678
3β,12β-Diacetoxy-16-allopregnene-11,20-dione	..	1685

C-12 and C-20. Finally, saturation of the double bond at C-16 releases the strain imposed and 3β-acetoxyallopregnane-12,20-dione (VIII), for example, exhibits normal carbonyl absorption at 1710 cm.$^{-1}$.

The presence of a carbonyl group at C-12 markedly affects the base-catalyzed addition of alcohol to the double bond at C-16. The C-12 ketones VII and XIII reach equilibrium with their reaction products in less than 4 minutes in 0.4 *N* methanolic potassium hydroxide, while 3β,12β-diacetoxy-16-allopregnene-11,20-dione, requiring about an hour, is more nearly like the 3β-acetoxy-5,16-pregnadien-20-one studied by Fukushima and Gallagher.[14]

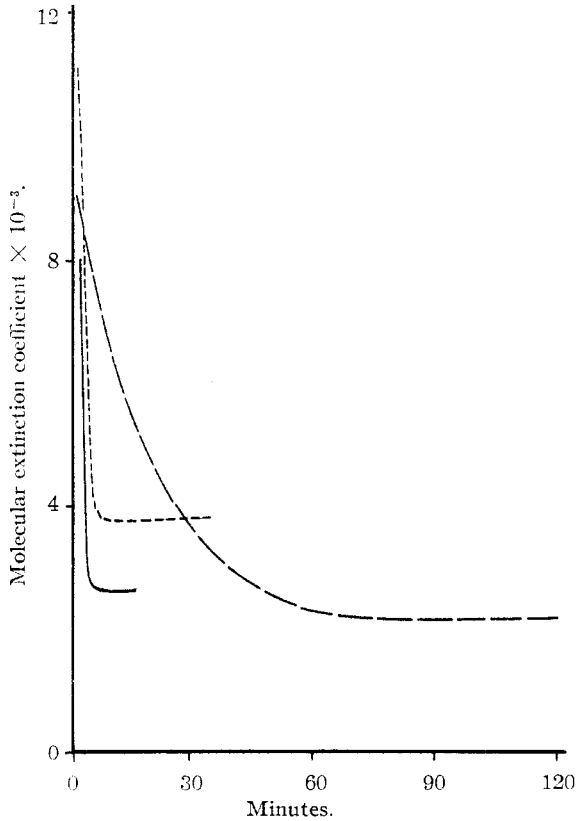


Fig. 1.—Equilibration in 0.4 *N* methanolic potassium hydroxide of 2α,3β-diacetoxy-16-allopregnene-12,20-dione (XIII), -----, observed at 229 mμ; 3β-acetoxy-16-allopregnene-12,20-dione (VII), —, observed at 229 mμ; 3β,12β-diacetoxy-16-allopregnene-11,20-dione, — —, at 235 mμ.

The 17α-hydroxy group was introduced by way of the 16α-oxide,[15] obtained by oxidation of the double bond with alkaline hydrogen peroxide. It was not possible to use perbenzoic acid as had been done successfully with similar steroids lacking the C-12 carbonyl group[16]; the product of these oxidations, m.p. 271–272°, $[\alpha]^{25}D$ +19.4°, always contained one more oxygen atom than the desired oxide. Likewise unsuccessful were repeated attempts to convert the pregnane VIII into XI through oxidation of the crude enol acetate.[17] 16α,17α - Epoxy - 3β - acetoxyallopregnane - 12,20-dione (IX) was converted to the bromohydrin X and thence with nickel and ethanol[14] or zinc and acetic acid to 3β-acetoxy-17α-hydroxyallopregnane-12,20-dione (XI).

A final point of interest is that the 17α-hydroxyl group in X and XI show complete hydrogen bonding, presumably with the C-12 carbonyl. Thus, when examined at high concentration and under high resolution with the calcium fluoride prism, these compounds did not show the strong, sharp free-hydroxyl absorption occurring regularly at 3605 cm.$^{-1}$ [18] in the steroids at our disposal. Instead, the lower, broader peak, occurring at 3470–3484 cm.$^{-1}$ in the case of hydroxy steroids, appeared as a strong, broad band of intensity comparable to the 3605 cm.$^{-1}$ band in other steroids. Absorption in this region has been attributed to bonded O–H stretching.[18,19] Such bonding between the C-12 carbonyl and C-17 hydroxyl groups appears sterically to be a highly probable phenomenon.

Acknowledgments.—We wish to express our gratitude to the Research Corporation, New York, for making this work possible and for extending their generous support throughout. Thanks are due to Fred Gibson and Bernard W. Benson of the Boyce Thompson Southwestern Arboretum; to the Chattanooga Medicine Company and Parke, Davis and Company, and to Joseph R. Meredith and William H. Tallent for invaluable assistance in the procurement and processing of raw materials. Finally, we appreciate the helpful discussions of infrared spectra with Dr. William H. Fletcher and assistance in other ways received from Drs. T. F. Gallagher, P. L. Julian and R. B. Wagner.

Experimental

All rotations, unless otherwise noted, were carried out with 10–20 mg. of substance in 1.10 ml. of purified dioxane in a 1-dm. tube. The melting points were obtained at fifty magnifications on the Kofler apparatus and are corrected.

Separation of Manogenin and 9(11)-Dehydromanogenin with Girard Reagent.—Four and one-tenth grams of a mixture of these sapogenins, obtained during isolation of hecogenin from plants, was refluxed 30 minutes with 8 g. of trimethylaminoacetohydrazide hydrochloride in 100 ml. of ethanol and 10 g. of glacial acetic acid. The cooled solution was treated with ice-cold sodium carbonate and extracted with ether. The ether was washed thoroughly with sodium carbonate solution and water and dried over magnesium sulfate. Evaporation gave 2.48 g. of 9(11)-dehydromanogenin, λ_{max}^{alc} 238 mμ (log ε 4.05), which was nearly pure. Acetylation with pyridine–acetic anhydride and recrystallization of the product from acetone and from ether formed the diacetate crystallizing as needles, m.p. 245–247°, $[\alpha]^{29}D$ −65.6°, λ_{max}^{alc} 237 mμ (log ε 4.01). *Anal.* Calcd. for $C_{31}H_{44}O_7$: C, 70.42; H, 8.39. Found: C, 70.51; H,

(14) D. K. Fukushima and T. F. Gallagher, THIS JOURNAL, **73**, 196 (1951).

(15) P. L. Julian, *et al.*, *ibid.*, **71**, 756, 3574 (1949); **72**, 5145 (1950).

(16) P. A. Plattner, L. Ruzicka, H. Heusser and E. Angliker, *Helv. Chim. Acta*, **30**, 385 (1947).

(17) T. H. Kritchevsky and T. F. Gallagher, *J. Biol. Chem.*, **179**, 507 (1949); THIS JOURNAL, **73**, 184 (1951).

(18) *Cf.* N. N. Coggeshall, *J. Chem. Phys.*, **18**, 978 (1950).

(19) W. Gordy, THIS JOURNAL, **60**, 605 (1938).

8.46. The pure genin was obtained as hexagonal plates by hydrolysis of the diacetate and recrystallization from ether and dioxane–water, m.p. 241.5–242.0°, $[\alpha]^{29}D$ −18.0°, λ_{max}^{alc} 238 mμ (log ε 4.08). *Anal.* Calcd. for $C_{27}H_{40}O_5$: C, 72.94; H, 9.07. Found: C, 72.70; H, 9.08.

The aqueous solution of acetohydrazones was acidified with 30 ml. of glacial acetic acid. After 30 hours the crystalline precipitate was dissolved with ether and this solution processed as usual to obtain 1.57 g. of manogenin showing only 0.7% of unsaturated material. Recrystallization from aqueous dioxane and from ethyl acetate afforded entirely saturated manogenin, m.p. 245–246°, $[\alpha]^{30}D$ −0.9°. *Anal.* Calcd. for $C_{27}H_{42}O_5$: C, 72.61; H, 9.48. Found: C, 72.60; H, 9.45. The pure diacetate was prepared by acetylation and recrystallization from acetone and from methanol, m.p. 257–259°, $[\alpha]^{29}D$ −42.4°. *Anal.* Calcd. for $C_{31}H_{46}O_7$: C, 70.16; H, 8.74. Found: C, 69.98; H, 8.92.

This separation was equally successful with mixtures of hecogenin and 9(11)-dehydrohecogenin.

Δ⁴-Hecogenone (III).—Following in general previously outlined procedures,[4] 1 g. of hecogenone in 25 ml. of glacial acetic acid was brominated at 30° with 3.85 equivalents of bromine in 18 ml. of acetic acid. Decolorization was immediate and after 30 minutes the solution was poured into cold water. The precipitate was collected, washed, and dried *in vacuo;* the yield of the unstable 2,4,23-tribromohecogenone, m.p. 160–180° dec., was 1.2 g. (77%). Its solution in 40 ml. of acetone with 1.5 g. of sodium iodide was refluxed for 12 hours; the resulting purple solution was filtered, diluted with 15 ml. of water and chilled. Crude 2-iodo-23-bromo-Δ⁴-hecogenone separated as an amorphous, light-yellow solid, m.p. 185–195° dec., weighing 0.52 g. (50%). It was treated immediately with 60 ml. of alcohol and 2 g. of zinc dust and refluxed with stirring for seven hours. The filtered, concentrated solution was chilled, giving 0.19 g. (66%) of colorless plates, m.p. 221–226°. Three recrystallizations from alcohol produced the pure Δ⁴-hecogenone as clusters of plates, m.p. 235–237°, $[\alpha]^{30}D$ +20° (alcohol), λ_{max}^{alc} 240–241 mμ (log ε 4.14). *Anal.* Calcd. for $C_{27}H_{38}O_4$: C, 76.02; H, 8.98. Found: C, 75.82; H, 8.97.

Pseudohecogenin Derivatives IV, V.—Pseudohecogenin diacetate was prepared as previously described[20] and crystallized from acetone, methanol or aqueous methanol. The yield of crystalline product was 52%; two further recrystallizations gave a product, m.p. 92–94°, $[\alpha]^{30}D$ +69°. *Anal.* Calcd. for $C_{31}H_{46}O_6$: C, 72.34; H, 9.01. Found: C, 71.99; H, 8.92. Hydrolysis in alcoholic alkali and recrystallization from acetone and from ether yielded pseudohecogenin, m.p. 186–188°, $[\alpha]^{30}D$ +84°.

Pseudohecogenin dibutyrate was obtained in 48% yield by refluxing hecogenin with butyric anhydride. It was recrystallized from acetone or alcohol; m.p. 97–98°, $[\alpha]^{30}D$ +79°. *Anal.* Calcd. for $C_{35}H_{54}O_6$: C, 73.64; H, 9.54. Found: C, 73.77; H, 9.74.

3β-Acetoxy-16β-[δ-acetoxy-γ-methylvaleroxy]-allopregnane-12,20-dione (VI).—Oxidation of 2 g. of crystalline pseudohecogenin diacetate as described earlier[21] gave 1.81 g. (85%) of solvent-free product as a gum which defied all attempts at crystallization until seeded with another sample that had partially solidified after a year. Recrystallization from aqueous methanol yielded small needles, m.p. 78.7–81.5°, $[\alpha]^{25}D$ +49.0°. *Anal.* Calcd. for $C_{31}H_{46}O_8$: C, 68.10; H, 8.48. Found: C, 68.08; H, 8.31. This material showed no maximal absorption at 227 mμ.

3β-Acetoxy-16-allopregnene-12,20-dione (VII).—Pseudohecogenin diacetate was oxidized and hydrolyzed according to Wagner, *et al.*,[21] to give 545 mg. (39%) of product, m.p. 165–170°. Two recrystallizations from dilute methanol gave the pure pregnene, m.p. 179–181°, $[\alpha]^{25}D$ +124°, λ_{max}^{alc} 227.5 mμ (log ε 3.93), as previously characterized.

Another route, oxidation with hydrogen peroxide,[22] to the crude hecone diacetate followed by hydrolysis in *t*-butyl alcohol, gave higher yields. Thus, crystalline pseudohecogenin diacetate, m.p. 88–90°, was oxidized for six hours at room temperature in 30 ml. of glacial acetic acid containing 18 ml. of perhydrol. Dilution and extraction with ether followed by washing, drying and evaporation yielded a thick sirup. This was dissolved in 75 ml. of hot *t*-butyl alcohol and 2.5 g. of potassium carbonate in 25 ml. of hot water added. The whole was stirred at reflux 30 minutes, poured into cold water and extracted with ether. Concentration of the ether liquors in an air stream gave 1.3 g. (76%) of white needles, m.p. 158–170°. Crystallization four times from 20% hexane in alcohol gave pure 3β-acetoxy-16-allopregnene-12,20-dione, m.p. 179–181°, identical in all respects with the previous preparation.

Deacylation of the oily hecone diacetate by sublimation at 170–245° and 0.5 mm. pressure gave poorly defined products, m.p. 170–180°, showing variously, 23 to 73% of unsaturation as determined by the optical density at 227 mμ. However, when 0.93 g. of hecone diacetate was adsorbed on Merck alumina (acid washed, *p*H 4.8), 0.51 g. (81%) of product was eluted with 1:1 ether–benzene, ether and 1% methanol in ether. These fractions melted at 156–177° and on crystallization from ether–hexane mixtures yielded the pure 16-allopregnene, m.p. 178–181° (sintering at 173°), $[\alpha]^{27}D$ +128°, λ_{max}^{alc} 227–228° (log ε 3.87).

3β-Acetoxyallopregnane-12,20-dione (VIII).—A solution containing 250 mg. of 3β-acetoxy-16-allopregnene-12,20-dione in 150 ml. of absolute ether was shaken with 500 mg. of palladium oxide at 40 p.s.i. of hydrogen for four hours. After filtration and evaporation of the solution to dryness, the residue was crystallized from ether to give 184 mg. of pregnane, m.p. 181–183°. Further recrystallization resulted in a pure sample, m.p. 189–190°, $[\alpha]^{29}D$ +139°. *Anal.* Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.85; H, 9.32. This product showed no unsaturation, although the mother liquors did, and yielded an additional 100 mg. of the pregnane upon further hydrogenation.

16α,17α-Epoxy-3β-acetoxyallopregnane-12,20-dione (IX).—Residues from recrystallization of 3β-acetoxy-16-allopregnene-12,20-dione containing a major proportion of unsaturated material were generally suitable for oxidation. Thus, 1.66 g. of the pregnene, m.p. 158–164°, in 50 ml. of methanol was cooled in ice, treated with 13 ml. of perhydrol and 6 ml. of 4 *N* sodium hydroxide and allowed to stand overnight at 10°. The crystalline material was collected, the liquors diluted with water and a second crop obtained. Recrystallization from ether gave 0.89 g. (51%) of product, m.p. 228–230°. Further crystallization from ether and from methanol resulted in the pure oxide, crystallizing as rectangular rods or prisms, m.p. 234–235°, $[\alpha]^{32}D$ +103°. *Anal.* Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.31. Found: C, 70.90; H, 8.19.

16β-Bromo-3β-acetoxy-17α-hydroxyallopregnane-12,20-dione (X).—A solution of 100 mg. of the oxide, m.p. 228–230°, in 3 ml. of glacial acetic acid was cooled to 15° and 1 ml. of a solution of 1 ml. of 48% hydrobromic acid in 12 ml. of acetic acid added.[23] The mixture became yellow and the temperature rose to 23° immediately. After standing 35 minutes at 30°, the solution was poured into cold water, extracted with ether and the latter solution washed with sodium bicarbonate and water. It was dried and allowed to evaporate slowly, the initial crop of crystals being unreacted oxide, 22 mg., m.p. 229–231°. Further concentration left 67 mg. (71% of the 78 mg. of oxide not recovered) of pale-yellow clusters of rods, m.p. 151–155°. This material crystallized slowly but was nevertheless recrystallized five times from 1:1 ether–petroleum ether, appearing finally as rhombs, m.p. 176–178°, $[\alpha]^{30}D$ +39° (alc.). *Anal.* Calcd. for $C_{23}H_{33}O_5Br$: C, 58.85; H, 7.09; Br, 17.04. Found: C, 58.95; H, 7.12; Br, 16.88.

3β-Acetoxy-17α-hydroxyallopregnane-12,20-dione (XI).—Three grams of Raney nickel under ethanol was added to 550 mg. of the bromohydrin, m.p. 150–160°, in 25 ml. of ethanol. The solution was refluxed four hours with stirring, filtered through Celite and concentrated to dryness. The product, 340 mg. (74%), m.p. 133–137°, appeared as colorless needles, which after recrystallization once from alcohol and three times from 1:1 ether–petroleum ether came down as fern-like crystals, m.p. 175–176°, $[\alpha]^{30}D$ +117°. *Anal.* Calcd. for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.94; H, 8.63.

Zinc dust gave consistently a product of slightly better

(20) R. E. Marker and E. Rohrmann, THIS JOURNAL, **62**, 518 (1940).

(21) R. B. Wagner, J. A. Moore and R. F. Forker, *ibid.*, **72**, 1856 (1950).

(22) R. E. Marker, E. M. Jones and J. Krueger, *ibid.*, **62**, 2532 (1940); R. E. Marker, E. M. Jones and E. L. Wittbecker, *ibid.*, **64**, 468 (1942).

(23) P. L. Julian, E. W. Meyer, W. J. Karpel and I. R. Waller, *ibid.*, **72**, 5145 (1950).

quality in about 70% yields. Thus 600 mg. of the bromohydrin in 40 ml. of glacial acetic acid with 1 g. of zinc dust, stirring at 100° for four hours, gave 350 mg. (70%) of product, m.p. 160–170°. Two recrystallizations from alcohol gave a product of high purity, m.p. 174–176°.

2α,3β-Diacetoxy-16-allopregnene-12,20-dione (XIII).—Pseudomanogenin triacetate, m.p. 159–161°, was prepared in 55% yield by the published procedure.[24] In order to record its rotation the material was recrystallized to a constant melting point, 164–165°, $[\alpha]^{24}D$ +26°.

Oxidation of 2.0 g. of the triacetate at 15° for six hours in 50 ml. of glacial acetic acid with 20 ml. of perhydrol yielded 1.9 g. (90%) of colorless, sirupy manone triacetate, isolated by extraction with ether. This was deacylated with potassium carbonate in *t*-butyl alcohol, as described for hecone diacetate, and the glassy residue crystallized from 1:1 ether–petroleum ether; then from 20% methanol in ether. The yield was 0.98 g. (72%) of platelets, m.p. 223–227°. The analytical sample was prepared by further recrystallization from ether; m.p. 240.0–240.5°, $[\alpha]^{25}D$ +68° (chloroform), λ_{max}^{alc} 227.5 mμ (log ε 4.07). *Anal.* Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96. Found: C, 69.76; H, 7.94.

2α,3β-Diacetoxyallopregnane-12,20-dione (XIV).—One-tenth gram of the pregnene was hydrogenated in 100 ml. of dry ether over 200 mg. of palladium-black catalyst for three hours at 40 p.s.i. Filtration and concentration gave 90 mg. (89%) of small plates, m.p. 252–256°. Three recrystallizations from ether gave small plates which sublimed as long needles at 215° and melted at 258–260°, $[\alpha]^{29}D$ +51°, λ_{max}^{alc} 288 mμ (log ε 2.14). *Anal.* Calcd. for $C_{25}H_{36}O_6$: C, 69.42; H, 8.39. Found: C, 69.47; H, 8.22.

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(24) *Cf.* ref. 1, p. 2183. The preparation of pseudomanogenin triacetate herein described is erroneously entitled "pseudomanogenin."

[CONTRIBUTION NO. 122 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

Ring C Ketols in the Hecogenin and Allopregnane Series

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The 11α,23- and 11β,23-dibromohecogenin acetates have been characterized, dehydrobrominated and hydrolyzed under varying conditions; derivatives of three of the four possible isomeric ketols have been obtained. 3β,12β-Dihydroxy-5α,22a-spirostan-11-one (11-ketorockogenin) has resisted many attempts to remove the hydroxyl group at C-12 but has been degraded to 3β,12β-diacetoxy-16-allopregnene-11,20-dione and related compounds. Two rockogenin derivatives and 23-bromomanogenin diacetate are reported.

The dibromination of hecogenin acetate[1,2] proceeds readily in either acetic acid or chloroform and the yield of crude product is nearly quantitative. Even so, the reaction is erratic, going sometimes with little color development but more often with formation of green, blue or purple side products. Material contaminated with these colored products decomposes on standing, even in the dry state. In addition to the compound already reported, which we regarded as 11β,23-dibromohecogenin acetate IV, we now have obtained the α-isomer III, which is higher melting and more stable. The 11β-bromide was readily dehydrobrominated by treatment with ordinary solvents and by adsorption on alumina. Chromatography or collidine treatment of the dibromo mixture furnished 9(11)-dehydro-23-bromohecogenin acetate[1] which was debrominated to the known 9(11)-dehydrohecogenin acetate.[3] Attempts to extend the conjugation in these unsaturated ketones with the formation of 3β-acetoxy-5α,22a-spirosta-7,9(11)-dien-12-one were made using selenium dioxide and the 23-bromo compound and by treating 9(11)-dehydrohecogenin acetate itself with mercuric acetate under a variety of conditions. These were not successful.

The 11,23-dibromohecogenin acetates are similar to the 3α-hydroxy-11-bromoetiocholane-17β-carboxylic acids[4] in that they are formed in less than two hours by bromination at room temperature, and are almost completely hydrolyzed in six minutes at room temperature in 0.25 *N* alkali. Likewise, hydrolysis and rearrangement to the more stable 12β-hydroxy-11-keto structure may be carried out at room temperature. As Gallagher has indicated, this behavior stands in marked contrast to that of the two 11-bromo-12-ketocholanates,[5] which are far more resistant both to formation and to hydrolysis and rearrangement. Although he has suggested that increased activity in the etianic acids lies with some sort of activation by the carboxyl group at C-17, it appears here as with the sapogenins that this activity must be ascribed rather to the absence of hindering groups in the vicinity of ring C. Thus, the configuration of rings C, D and E[6] is such that the bulky spiroketal side chain is rigidly held away from ring C and even the carbonyl group is not seriously hindered. However, free rotation of the cholanic acid side chain about the C-17,C-20 axis not only permits greater interference between the C-12 carbonyl and C-21 methyl groups but the carboxyl group and remainder of the side chain are capable of shielding large areas near C-11 and C-12 *on either the α- or β-side of the molecule.* Thus bromination, if by Newman's mechanism,[7] may receive interference at both the oxygen and α-carbon atoms, while hydrolysis of 11β-, and more so, 11α-bromine atoms will be similarly hindered. We have not yet studied the pure 11-bromosapogenin isomers sufficiently to be able to assess the relative magnitudes of these effects.

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