acetate IVb in 150 cc. of glacial acetic acid was shaken in hydrogen over 0.25 g. of a prereduced platinum catalyst at 22° and 592 mm. In 4 hours 4.1 equivalents of hydrogen had been absorbed and uptake ceased. The catalyst was removed and the filtrate was poured into water. The precipitate was collected, washed well with water and dried, when it weighed 2.95 g. and showed m.p. *ca.* 165–175°. Crystallization from chloroform–methanol furnished 1.49 g. (49%) of the saturated tetrol diacetate VIIIb with m.p. 286–292° (introduced at 280°), $[\alpha]_D$ −34°, ν_{max}^{mull} 1736 cm.$^{-1}$ and free hydroxyl band.

Anal. Calcd. for $C_{44}H_{70}O_6$: C, 76.03; H, 10.15. Found: C, 75.71; H, 10.08.

Chromatography of the mother liquors on 100 g. of neutral alumina afforded three different substances. The first (0.12 g.) showed m.p. 228–232°, the second (0.32 g.) showed m.p. 258–263° and the third (0.03 g.) showed m.p. 276–279° (depressed on admixture with VIIb). These substances have not yet been further investigated.

***sym*-Di-17α-(androstane-3β,17β-diol)-ethane (VIIa).**—A solution of 0.2 g. of the diacetate VIIb in 10 cc. of dioxane and 30 cc. of methanol was treated with 0.2 g. of potassium hydroxide in 3 cc. of water and boiled under reflux for 1 hour. Concentration to a small volume followed by addition of water gave a precipitate which was collected, washed with water and dried. Crystallization from dioxane produced 0.14 g. of the saturated tetrol VIIa with m.p. 329–335°, ν_{max}^{mull} free hydroxyl band only. The rotation could not be determined due to the compound's extreme insolubility.

Anal. Calcd. for $C_{40}H_{66}O_4$: C, 78.64; H, 10.89. Found: C, 78.70; H, 11.04.

17α-Ethinyl-Δ⁵-androstene-3β,17β-diol (IIa) from Dehydroepiandrosterone (I) and Acetylenedimagnesium Bromide.—A slow stream of purified acetylene was passed for 3 hours under anhydrous conditions through 25 cc. of a 3 *N* ethereal solution of methylmagnesium bromide (Arapahoe Chemical Co.), diluted with 100 cc. of anhydrous tetrahydrofuran. A solution of 5 g. of dehydroepiandrosterone in 50 cc. of tetrahydrofuran was then added and the mixture was boiled under reflux for 15 minutes, whereby a bulky precipitate was formed. Cooling and pouring into 1 l. of water containing 20 cc. of concentrated sulfuric acid produced the crude 17α-ethinyl-Δ⁵-androstene-3β,17β-diol (IIa) as a precipitate, which on collection, washing with water and drying weighed 5.2 g. and showed m.p. 228–232°. One crystallization from chloroform–hexane yielded 4.5 g. (83%) with m.p. 238–240°, $[\alpha]_D$ −123°, ν_{max}^{mull} free hydroxyl band only. Identity with an authentic sample was demonstrated through non-depression in m.p. on admixture and infrared comparison; reported[3] m.p. 240–242°, $[\alpha]^{25}_D$ −119°.

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.62. Found: C, 79.93; H, 9.47.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. XXXIII. Transformations in the 12-Ketosteroid Series[2]

BY EDWARD S. ROTHMAN AND MONROE E. WALL

RECEIVED SEPTEMBER 26, 1955

The behavior of steroids with C-12,20-diketonic substitution cannot be predicted from observations taken on C-11,20-diketosteroids or on C-ring unsubstituted compounds. The C-12,20-dicarbonyl interaction affects the reactivity of side chain groups markedly and affects the ease of introduction of new groups into the side chain. New series of Δ⁴-12-ketopregnenes (seven compounds) and 12-ketopregnanes (three compounds) are prepared and their properties noted. Attempts to prepare 4-pregnene-17α,21-diol-3,12,20-trione by the hecogenin route have not yet been successful.

In continuing our program of preparation of C-ring lactone hormone analogs[3] we desired to prepare the 12-keto derivative XIII of Reichstein's compound S as a starting material. The conversion of hecogenin to XIII has not been effected to date.[4] The following experiments record the preparation of the 21-desoxy derivative VI and the 16α,17α-epoxide derivative of 12-keto S from hecogenin.

A group in England[5] and we, independently, were able to convert hecogenin to the 4,5-dihydro*allo* compound XIV. Attempts to apply the bromination procedure of the Syntex workers for the introduction of the Δ⁴-olefinic bond[6] into this compound failed completely in spite of many experimental variations. We thought it might be possible to avoid this impassé by establishing the α–β unsaturation prior to the complete elaboration of the dihydroxyacetone side chain.

Hecogenin was converted to 16α,17α-epoxy*allo*pregnan-3β-ol-12,20-dione acetate essentially as described previously,[7] and saponification followed by mild oxidation with chromium trioxide–pyridine complex gave the 3-ketone I. Bromination with three equivalents of bromine, followed by treatment with sodium iodide and sodium bisulfite gave the new compound 16α,17α-epoxy-4-pregnene-3,12,20-trione (II). The proof of structure is based on the elementary analysis, the strong ultraviolet absorption in accord with Δ⁴-3-one structure[8] and the infrared spectrum showing ketone and α,β-unsaturated ketone bands at 1714 and 1670 cm.$^{-1}$. Hydroxyl bands were absent, indicating that the epoxide linkage was unaltered by the over-all bromination and subsequent treatments. The yield of unsaturated triketone II, 68%, was exceptionally good for this reaction. Treatment of II with hydrobromic acid diluted with acetic acid[9] gave the new bromohydrin III in 76% yield showing a strong infrared hydroxyl band at 3470 cm.$^{-1}$

(1) A Laboratory of the Eastern Utilization Research Branch, Agricultural Research Service, United States Department of Agriculture. Article not copyrighted.

(2) Paper XXXII, R. F. Mininger, M. E. Wall, R. G. Dworschack and R. W. Jackson, submitted to *Arch. Biochem. Biophys.*

(3) (a) E. S. Rothman, M. E. Wall and C. R. Eddy, THIS JOURNAL, **76**, 527 (1954); (b) E. S. Rothman and M. E. Wall, *ibid.*, **77**, 2228 (1955); (c) **77**, 2229 (1955).

(4) This compound has, however, been prepared from bile acids; W. J. Adams, D. K. Patel and V. Petrow, *J. Chem. Soc.*, 4688 (1954).

(5) W. J. Adams, D. N. Kirk, D. K. Patel, V. Petrow and I. A. Stuart-Webb, *ibid.*, 2209 (1954).

(6) G. Rosenkranz, St. Kaufmann, J. Pataki and C. Djerassi, THIS JOURNAL, **72**, 1046 (1950).

(7) G. P. Mueller, R. E. Stobaugh and R. S. Winniford, *ibid.*, **75**, 4888 (1953). See also reference 3c.

(8) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953); *cf.* p. 63.

(9) P. L. Julian, E. Meyer, W. J. Karpel and I. R. Waller, THIS JOURNAL, **72**, 5145 (1950); see also refs. 3c and 7.

and three distinct carbonyl bands (see Experimental). Reductive debromination by deactivated Raney nickel catalyst[10] gave the new 4-pregnen-17α-ol-3,12,20-trione (VI). The analyses and physical properties were in accord with the structure assigned although, anomalously, the infrared spectrum did not show the usual shift of carbonyl absorption to 1693 cm.$^{-1}$. The over-all conversion of hecogenin acetate to VI required nine steps and gave a 20% molar yield. Alternatively VI was prepared by converting the bromohydrin III to the 3-ethylene ketal[11] IV which was reductively debrominated by hydrogen–palladium-on-calcium carbonate to 5-pregnen-17α-ol-3,12,20-trione 3-ethylene ketal (V). Acid hydrolysis of V gave VI.

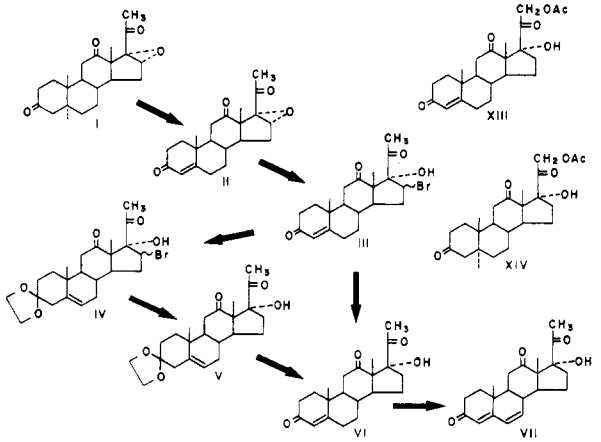

Fig. 1.

Conversion of 4-pregnen-17α-ol-3,12,20-trione to a 21-hydroxylated steroid could not be achieved. Extensive alterations occurred during bromination, and after acetoxylation only a small proportion of crystalline material[12] could be isolated. It was therefore felt that still another re-ordering of sequence was indicated which should establish first the 21-acetoxyl group, secondly the Δ^4-ene-3-one function, and last of all the 17α-ol function. For this sequence we started with 16α,17α-epoxy*allo*pregnan-3β-ol-12,20-dione (VIII), easily available from hecogenin.[7] By addition of *one* mole of bromine to VIII in carbon tetrachloride–chloroform we obtained a steroid IX containing *two* atoms of bromine. It appeared that the hydrogen bromide liberated by the initial substitutive bromination was absorbed by the epoxide to form the bromohydrin IX. Subsequent refluxing with potassium acetate in acetic acid containing catalytic amounts of potassium iodide resulted in the replacement of the C-21 bromine atom by the acetate group and *simultaneously* regenerated the epoxide ring.[13] Apparently no C-16 acetoxylation occurred, and the infrared spectrum was compatible with that expected for a diol monoacetate. Mild oxidation of the diol monoacetate X smoothly gave the triketone XI, but the introduction of the Δ^4-ene bond did not proceed to completion. A crystalline material was obtained in 74% yield which, however, proved to be a 1:1 mixture of starting material XI and the desired Δ^4-ene-3-one XII, reducing the yield to 37% for that step. The yield of pure Δ^4-ene-3-ketone XII obtained by chromatographic separation was then only 9% over-all[14] for seven reaction steps starting with hecogenin acetate.

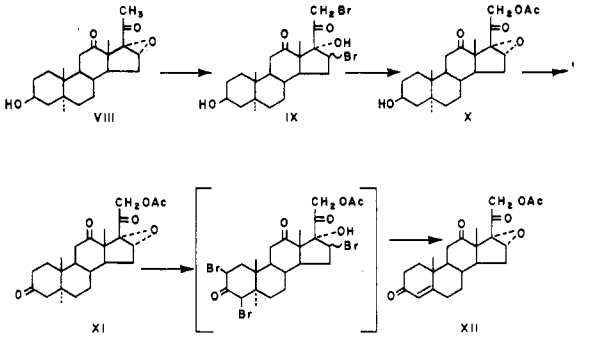

Fig. 2.

We were disappointed to observe the surprising resistance of the epoxide XII to opening under a variety of conditions. Under the usual conditions the epoxide was inert to acid (and Lewis acid) conditions and was recovered unchanged. Under more vigorous conditions glassy residues were obtained some of which showed hydroxyl absorption bands in the infrared, but we were not able to obtain crystalline 17α-ol even after careful chromatography.

These results and those previously discussed demonstrate that the behavior of steroids with C-12,20-diketonic substitution cannot be predicted from observations taken on C-11-ketosteroids or on unsubstituted C-ring compounds. The unusual shifts of ultraviolet[15] and infrared[3c] carbonyl absorption spectral band positions attributed to mutual C_{12},C_{20} interaction support this view that there is an essential difference in the general properties of C-11-oxygenated steroids as compared to C-12-oxygenated steroids.

Experimental

All melting points were taken on the Kofler hot-stage but are otherwise not corrected. Rotations were determined

(10) L. B. Barkley, M. W. Farrar, W. S. Knowles and H. Raffelson, THIS JOURNAL, **76**, 5019 (1954).

(11) R. Antonucci, S. Bernstein, R. Littell, K. J. Sax and J. H. Williams, *J. Org. Chem.*, **17**, 1341 (1952).

(12) This substance was assigned the $\Delta^{4,6}$-diene-3-one structure on the basis of its *single* ultraviolet absorption maximum at 281.5 mμ. Dorfman[8] lists 280 mμ as the calculated value and 284 mμ as the average observed value for the $\Delta^{4,6}$-diene-3-ketone system. Alternative possibilities that the system might be $\Delta^{1,4}$-diene-3-ketone, $\Delta^{1,4,6}$-triene-3 ketone or $\Delta^{7,9}$-diene-12-ketone of average observed values of 244; 223, 256, 298; 239, 292 mμ, respectively, were excluded by the evidence of both band position and the observed intensity of the absorption.

(13) It is probable that similar intermediates formed in the reaction sequence I → II but these were not isolated.

(14) No allowance was made for an equal amount of recovered saturated triketone which could be recycled to improve the yield. The brominative and debrominative sequence[6] to insert the double bond are here treated as one "step."

(15) R. B. Wagner, J. A. Moore and R. F. Forker, THIS JOURNAL, **72**, 1856 (1950); G. P. Mueller, R. E. Stobaugh and R. S. Winniford, *ibid.*, **75**, 4888 (1953). An anomaly in the infrared spectrum of 21-acetoxy-16-allopregnen-3,12,20-trione (m.p. 220–221.5°, $[\alpha]^{22}D$ +143°, λ_{max}^{MeOH} 288 mμ, log ϵ 3.89. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.56; H, 7.86) is the absence of α,β-unsaturated ketone bands between 1650–1700 cm.$^{-1}$ although the olefin band at 1598 cm.$^{-1}$ is present as usual. Compare with the maxima reported by W. S. Allen and S. Bernstein, THIS JOURNAL, **77**, 1028 (1955).

in chloroform at a concentration of 16 mg. per ml. in a 2-dm. tube.

16α,17α-Epoxy-4-pregnene-3,12,20-trione (II).—16α,17α-Epoxy*allo*pregnane-3,12,20-trione (I) was prepared from 16-*allo*pregnen-3β-ol-12,20-dione acetate[16] in 62% over-all yield by hydrogen peroxide oxidation in alkaline methanol, saponification and pyridine–chromium trioxide oxidation overnight at room temperature. The product I exhibited the same melting point behavior reported by Mueller and Norton. A solution of I (15.4 g.) in 400 ml. of chloroform and 200 ml. of carbon tetrachloride was treated with three equivalents of bromine in 530 ml. of carbon tetrachloride during a 5.5-hr. addition period followed by 0.5 hr. additional stirring. After evaporation of the solvent *in vacuo*, the residue was refluxed 16 hr. with 400 g. of acetone and 50 g. of dry sodium iodide. Solids were filtered off without cooling, and the mixture was evaporated to dryness *in vacuo*. The greenish-black crystalline residue was brought into solution with a two-phase mixture of aqueous 10% sodium bisulfite–ether–benzene and the mixture was shaken 20 min. although the iodine color discharged almost immediately. The organic layer was washed briefly with water, dried with sodium sulfate and evaporated *in vacuo* to a white frothy solid residue of II. The product was low in halogen, but crystallizability was greatly improved by overnight stirring with zinc dust in hot ethanol. The white crystalline crude product isolated from ethyl acetate in 68% yield had a melting range of 237–255° after transition to stellated clusters. Its infrared spectrum was essentially the same as that of a pure sample, recrystallized from acetone to give cigar-like shapes which melted, after transition to long blades, from 275.5–277° with characteristic reddening of the melt, $[\alpha]^{25}D$ +199°, λ_{max}^{MeOH} 238.5 mμ, ε 16,190; $\bar{\nu}_{max}^{CHCl_3}$ 1620(m), 1670(s), 1714(s) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.66. Found: C, 73.35; H, 7.56.

16-Bromo-4-pregnen-17α-ol-3,12,20-trione (III).—The product II (7.1 g.) in 140 ml. of acetic acid at 15° was treated with 12.8 ml. of aqueous 48% hydrogen bromide dissolved in 35.5 ml. of acetic acid and let stand 20 hr. at 10°. The solvents were removed by distillation, 40° (10 mm.), and crystallized by trituration with ether to give a product, m.p. 211–219° dec., yield 76%. Recrystallization of an analytical sample from ethanol gave small needles, m.p. 217–219°, $[\alpha]^{25}D$ +64°, λ_{max}^{MeOH} 238.3 mμ, ε 18,000; $\bar{\nu}_{max}^{CHCl_3}$ 3470(s), 1621(m), 1672(s), 1695(s), 1721(s) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{27}O_4Br$: C, 59.57; H, 6.43; Br, 18.88. Found: C, 59.96; H, 6.68; Br, 19.03.

16-Bromo-5-pregnen-17α-ol-3,12,20-trione 3-Ethylene Ketal (IV).—The bromohydrin III (2.0 g.) in 10 ml. of ethylene glycol, 40 mg. of *p*-toluenesulfonic acid monohydrate and 100 ml. of benzene dried by distilling 10 ml. from the system[11] was refluxed gently 16 hr. under the usual water-removal conditions. The 3-ethylene ketal of the bromohydrin, obtained as a foam after isolation with ether and evaporation of solvent *in vacuo*, crystallized on the addition of 10 ml. of methanol. The product, m.p. 175–180°, 2 g., recrystallized from boiling methanol as rectangular plates melting without decomposition from 179–181°, $[\alpha]^{25}D$ +50°.

Anal. Calcd. for $C_{23}H_{31}O_4Br$: C, 59.10; H, 6.69; Br, 17.10. Found: C, 58.75; H, 7.12; Br, 16.55.

5-Pregnen-17α-ol-3,12,20-trione 3-Ethylene Ketal (V).—The bromohydrin IV (2.0 g.) in 90 ml. of methanol and 10 ml. of water was shaken for 5 hr. with hydrogen in the presence of 1 g. of 10% palladium-on-calcium carbonate.[3c,17] The catalyst was filtered off and the solvents evaporated. The resulting froth on crystallization from ethanol gave 0.4 g. of needles, m.p. 177–184°. The analytical sample melted from 181–184°, $[\alpha]^{25}D$ +3.3°; $\bar{\nu}_{max}^{CHCl_3}$ 3490, 1693, 1704 (shoulder), 1100, 1045, 1025, 1000 cm.$^{-1}$. The mother liquors were suitable for conversion to VI, *vide infra*.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.20; H, 8.65.

4-Pregnen-17α-ol-3,12,20-trione (VI).—(a) Preferred method: Debromination of III (8.1 g.) using 80 g. of acetone deactivated Raney nickel[10] in 500 ml. of acetone acidified with 1.6 ml. of acetic acid occurred during a 4-hr. reflux period. The product, eluted from a silicic acid column with chloroform, melted from 209–219°. The analytical sample recrystallized from ethanol melted from 214–218° without decomposition, but occasionally undried samples from aqueous acetone melted from 230–231° after incomplete sublimation, $[\alpha]^{25}D$ +124°, λ_{max}^{MeOH} 238.5 mμ, ε 16,190; $\bar{\nu}_{max}^{CHCl_3}$ 3520, 1624(m), 1670(s), 1705(s) cm.$^{-1}$.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19. Found: C, 72.94; H, 8.48.

(b) Alternative method: A sample of V (0.4 g.) was hydrolyzed with dilute (aqueous) ethanol using sulfuric acid catalyst and the general conditions of Antonucci, Bernstein, *et al.*, ref. 11, p. 1347, to yield 0.3 g. of VI, m.p. 214–218°. The mother liquors from the preceding preparation of V were separately hydrolyzed to give 1.3 g. of a mixture of II and VI separable by chromatography.

4,6-Pregnadien-17α-ol-3,12,20-trione (VII).—A sample of VI (1.0 g.) in 30 ml. of chloroform and 30 ml. of carbon tetrachloride was treated at 3° with two molar equivalents of bromine in 23.60 ml. of carbon tetrachloride. During the bromination an emulsion formed and it was necessary to add 15 ml. of chloroform to maintain solution. The solvents were evaporated *in vacuo*, 75 ml. of acetone and 4 g. of sodium iodide were added and the mixture refluxed for 8 hr. The solids were filtered off, the solvents removed, water added and the product isolated with ether. The residue obtained on evaporation was refluxed and stirred 20 hr. with 4 g. of dry potassium acetate, 44 mg. of potassium iodide, 0.63 ml. of acetic acid and 63 ml. of acetone, and the mixture was evaporated *in vacuo* to a dark brown tar. The tar was dissolved in methylene chloride, washed with water, dried and chromatographed on Florisil.[18] Chloroform elution gave 200 mg. of a clean crystalline fraction while resinous material was retained on the column. The product, prisms from ethanol, melted from 200–205°, $[\alpha]^{25}D$ +59.5°, λ_{max}^{MeOH} 281.5 mμ, ε 19,940, log ε 4.3; $\bar{\nu}_{max}^{CHCl_3}$ 3520, 1587, 1619, 1660, 1699 cm.$^{-1}$. When acetic acid was used as the bromination medium, equally small amounts of crystalline material were isolated. These materials are characterized mainly by a strong absorption band at 1805 cm.$^{-1}$.

16,21-Dibromo*allo*pregnane-3β,17α-diol (IX).—16α,17α-Epoxy*allo*pregnan-3β-ol-12,20-dione (VIII) (12 g., prepared in 65% yield from hecogenin acetate) in 250 ml. of commercial C.P. chloroform ("0.75% EtOH") was brominated at 28° with 140 ml. of a carbon tetrachloride solution containing one equivalent of bromine, added during 4 hr. time. Hydrogen bromide was not evolved. The solid foam obtained on evaporation *in vacuo* was dissolved in methanol and let stand two days to deposit 2.5 g. of rectangular blades, m.p. 164–170°. Recrystallization from absolute ethanol raised the m.p. to 170–170.3° (dried sample), $[\alpha]^{25}D$ +68°; $\bar{\nu}_{max}^{CHCl_3}$ 3640, 1714 cm.$^{-1}$. This material in spite of the sharp melting point and regularity of crystal form did not give an analysis agreeing with the theoretical, but the results showed that nearly two atoms of bromine were present. *Anal.* Calcd. for $C_{21}H_{31}O_4Br$: Br, 18.64. Calcd. for $C_{21}H_{30}O_4Br_2$: Br, 31.57. Found: Br, 29.50. The mother liquors from this preparation were usable for the preparation of the following compound.

16α,17α-Expoxy-21-acetoxy*allo*pregnan-3β-ol-12,20-dione (X).—The evaporated mother liquor residues from the preceding preparation in 500 ml. of acetone were treated with potassium iodide (150 mg.), potassium acetate (40 g.), acetic acid (6.3 ml.) and were stirred with refluxing for 16 hr. The solids were filtered and the filtrate evaporated *in vacuo*. The residue was taken up in water and methylene chloride, and the organic layer was washed with water, separated, dried and rapidly chromatographed on a short, broad Florisil column to remove highly colored, tenaciously adsorbed matter. The product separated from benzene,

(16) G. P. Mueller and L. L. Norton, THIS JOURNAL, **77**, 143 (1955), reported a 40% yield *via* dichromate oxidation in acetic acid. Caution should be used to get complete extraction of the product during the work-up since with the usual organic extractants the partition coefficient is unfavorable.

(17) W. J. Adams, D. K. Patel, V. Petrow and I. A. Stuart-Webb, *J. Chem. Soc.*, 1825 (1954).

(18) Mention of a trade name does not imply recommendation or endorsement by the United States Department of Agriculture of this brand over others not mentioned.

chloroform, and 1:19 ethanol–chloroform cuts as a glass crystallizable by trituration with ether. The product (2 g., m.p. 193 to 198°) was recrystallized from ethanol and melted from 202–204°, $[\alpha]^{25}D$ +127.5°; $\bar{\nu}_{max}^{CHCl_3}$ 3630(m), 3450(w) (broad), 1710(s), 1725(s), 1745 (shoulder) cm.$^{-1}$. *Anal.* Calcd. for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 68.15; H, 8.17. The yield from *crystalline* IX was 80%.

16α,17α-Epoxy-21-acetoxy-*allo*pregnane-3,12,20-trione (XI).—Compound X (3 g.) in 30 ml. of pyridine was treated with a suspension of chromium trioxide prepared by sifting 3 g. of chromium trioxide slowly into 30 ml. of pyridine at 5°. The mixture was let stand overnight at 28°, was transferred to a separatory funnel with ether and water, and shaken with dilute hydrochloric acid and dilute sodium bisulfite until the chromium was reduced to a trivalent condition. The ether layer then de-emulsified and could be separated cleanly. If an insufficient volume of ether was used crystals of the steroid collected at the interface. The ether on concentration deposited 2.8 g. of the desired product in a high state of purity. The analytical sample, four-sided scales, melted from 270–272° with characteristic reddening of the melt, $[\alpha]^{25}D$ +144°, broad infrared band 1700 to 1745 cm.$^{-1}$. *Anal.* Calcd. for $C_{23}H_{30}O_6$: C, 68.83; H, 7.51. Found: C, 68.40; H, 7.61.

21-Acetoxy-16α,17α-epoxy-4-pregnene-3,12,20-trione (XII).—A sample of XI (12.8 g.) dissolved in 167 ml. of carbon tetrachloride and 167 ml. of chloroform was brominated at 25° for 1.25 hr.[19] with 238.9 ml. of a carbon tetrachloride solution containing two molar equivalents of bromine. The solvents were then evaporated *in vacuo* and the resulting frothy solid stirred and refluxed overnight with 42 g. of sodium iodide in 0.5 l. of dry acetone. Insolubles were filtered off and the filtrate was evaporated, taken up in ether–benzene–10% sodium bisulfite mixture and shaken for 20 min. The organic layer was separated, evaporated to dryness and taken up in 300 ml. of absolute ethanol. The solution was stirred 8 hr. with 20 g. of zinc dust, filtered, and again evaporated *in vacuo*. The crystalline residue was triturated with ether to give 9.5 g. of a light tan powder, m.p. 230–242°, $[\alpha]^{25}D$ +169, λ_{max}^{MeOH} 237 mμ, ε 9,250, log ε 3.9, that proved to be a mixture of about equal parts of XI and XII. The mixture was separated by chromatography on 130 g. of 100-mesh silicic acid in a short, thick column.

The column was packed and the steroid placed on the adsorbent in benzene; however, methylene chloride was used immediately thereafter. Washing with methylene chloride containing 0.5 ethanol eluted the saturated steroid, and methylene chloride containing 2% ethanol eluted the α,β-unsaturated ketone XII, m.p. 256–260°, $[\alpha]^{25}D$ +192°, λ_{max}^{MeOH} 237 mμ, ε 17,200, log ε 4.24; $\bar{\nu}_{max}^{CHCl_3}$ 1622, 1675, 1713, 1727, 1745 (shoulder) cm.$^{-1}$.

Acknowledgment.—The authors wish to express their thanks to H. C. Amsterdam for technical assistance, to C. R. Eddy and C. S. Fenske for infrared curves, to C. L. Ogg and K. Zbinden for microanalyses, to A. Smith for ultraviolet spectra, and to R. F. Mininger for optical rotation determinations.

PHILADELPHIA 18, PA.

(19) There is reason to believe that a longer bromination time of *ca.* five hours is preferable and leads to a single product instead of the mixture obtained in this experiment.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. XXXIV. Preparation of 3-Desoxysapogenins (20α- and 20β-Series)[2,3]

BY MONROE E. WALL AND SAMUEL SEROTA

RECEIVED NOVEMBER 11, 1955

Desoxysarsasapogenin (I), desoxysmilagenin (II) and desoxytigogenin (III) were prepared by Wolff–Kishner reduction of the corresponding 3-ketones. Desoxyhecogenin (IV) was made by mild Clemmensen reduction of hecogenone. A preferable procedure applicable to all saturated members of the 20α-series involved $LiAlH_4$ reduction of the corresponding 3-tosylates. The unsaturated 20α-sapogenins, desoxydiosgenin (V) and desoxyyamogenin (VI), were prepared by converting the corresponding 3-tosylates to iodo derivatives which in turn were reduced with zinc–acetic acid.

Some of the saturated members of the 20β(20-iso)-series could be prepared by Wolff–Kishner reduction of the corresponding 3-ketones. A more general procedure applicable to saturated and unsaturated 20β-desoxysapogenins involved formation of the desoxypseudosapogenin from the corresponding 20α-series, followed by isomerization in methanol–acetic acid.

In continuation of our previous studies of the steroidal sapogenin side chain,[4a,b,c,d] it was necessary that we prepare and determine the physical properties of the various 20α,25D- or 25L-3-desoxysapogenins and their 20β-analogs. Some of the compounds in the 20α-series were previously prepared by Marker and his co-workers.[5a,b,c] Their yields were low and the physical properties incompletely presented.

The primary intermediates for the preparation of 3-desoxysapogenins were the corresponding 3-hydroxy analogs. Figure 1 outlines the methods used. Initially attempts were made to prepare 3-halogen derivatives using phosphorus tri- and pentahalides or thionyl chloride prior to reduction. This route was unsuccessful because of the attack of the reagents on the sapogenin side chain.[6] Desoxysarsasapogenin (I), desoxysmilagenin (II) and desoxytigogenin (III), were prepared by CrO_3–acetic acid oxidation of the corresponding 3β-hydroxy analogs to give the 3-ketones. These were then reduced to the hydrocarbons by the Huang-Minlon[7] modification of the Wolff–Kishner reduction. A preferable procedure involved preparation

(1) A laboratory of the Eastern Utilization Research Branch, Agricultural Research Service, United States Department of Agriculture. Article not copyrighted.

(2) Paper XXXIII, E. S. Rothman and M. E. Wall, THIS JOURNAL, **78**, 1744 (1956).

(3) Presented in part at Fifth Meeting-in-miniature, Philadelphia Section, American Chemical Society, January 29, 1953.

(4) (a) M. E. Wall, C. R. Eddy and S. Serota, THIS JOURNAL, **76**, 2849 (1954); (b) M. E. Wall and S. Serota, *ibid.*, **76**, 2850 (1954); (c) M. E. Wall, S. Serota and C. R. Eddy, *ibid.*, **77**, 1230 (1955); (d) M. E. Wall, S. Serota and L. P. Witnauer, *ibid.*, **77**, 3086 (1955).

(5) (a) R. E. Marker and E. Rohrmann, *ibid.*, **61**, 846, 1284 (1939); (b) R. E. Marker and D. L. Turner, *ibid.*, **63**, 767 (1941); (c) R. E. Marker, *et al.*, *ibid.*, **69**, 2167 (1947); *cf.* p. 2180.

(6) For a similar example *cf.* C. Djerassi, H. J. Ringold and G. Rosenkranz, *ibid.*, **73**, 5513 (1951).

(7) Huang-Minlon, *ibid.*, **71**, 3301 (1949).