Anal. Calcd. for $C_{27}H_{43}NO$: C, 81.55; H, 10.90; N, 3.52. Found: C, 81.74; H, 10.78; N, 3.43.

In a similar manner the "enamine" also was obtained from 3-ketobisnorcholanal methyl hemiacetal (X).

Pregnane-3,20-dione (XI).—A solution of 7.95 g. of 22-N-piperidylbisnor-20(22)-cholen-3-one (m.p. 98–104°, $[\alpha]_D$ +20°; N, 3.42, 3.57) in 60 ml. of benzene was added dropwise in approximately one hour to a stirring solution of 11.92 g. of sodium dichromate dihydrate in 60 ml. of benzene and 40 ml. of acetic acid. The temperature was maintained at 5–10° throughout addition of the "enamine" solution and for 2 hours thereafter. The very dark reaction mixture was diluted with 200 ml. of water, the layers were separated, the aqueous layer was extracted with 100 ml. of benzene, and the organic layers were combined. The benzene solution was washed successively with 35 ml. of water, two 35-ml. portions of 10% sodium hydroxide solution, 35 ml. of water, 35 ml. of 10% hydrochloric acid solution, and four 35-ml. portions of water. The resulting colorless solution was concentrated to dryness at 40–100° (15–20 mm.) leaving 5.02 g. (79.4% yield) of colorless oil which crystallized spontaneously on cooling. Recrystallization from ether gave pregnane-3,20-dione (XI) in two crops: (1) 2.60 g. (41% yield), m.p. 120–122°, $[\alpha]_D$ +111° (*c* 0.996); (2) 1.90 g. (30.0%), m.p. 120–122°, $[\alpha]_D$ +110° (*c* 1.048); total yield, 4.50 g. (71%). The residue (0.50 g.) was approximately 50% pregnanedione according to paper strip chromatographic assay. The above melting point agrees well with the literature values[10] which range from 120 to 123° and the infrared spectrum was identical to that for an authentic sample.

Pregnane-3,20-dione (XI), m.p. 118–121.5°, $[\alpha]_D$ +112° (*c* 2.215), also was obtained directly from aldehyde in a similar manner, without isolation of the "enamine," in a yield of 68.5%.

KALAMAZOO, MICHIGAN

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

The Synthesis of 5α-Pregnane-3β,17α,21-triol-11,20-dione (Reichstein's Substance D) and 5α-Pregnane-3β,11β,17α,21-tetrol-20-one (Reichstein's Substance V) from 5α-Pregnan-3β-ol-11,20-dione

BY E. M. CHAMBERLIN AND J. M. CHEMERDA

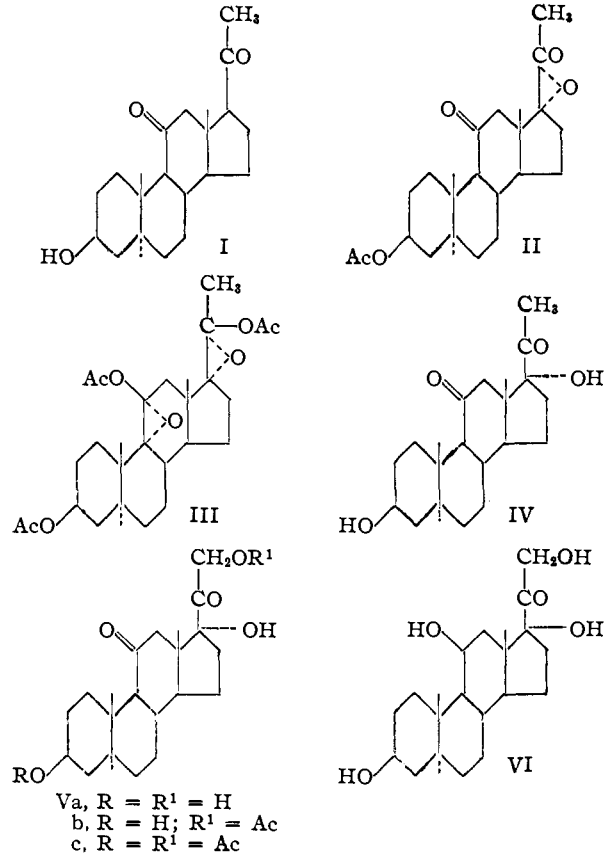
RECEIVED SEPTEMBER 25, 1954

The synthesis of 5α-pregnane-3β,17α,21-triol-11,20-dione and 5α-pregnane-3β,11β,17α,21-tetrol-20-one from 5α-pregnan-3β-ol-11,20-dione is described. The latter compound is hydroxylated at C-17 by conversion to the 17,20-enol acetate followed by peracid oxidation. Hydrolysis affords 5α-pregnane-3β,17α-diol-11,20-dione which is brominated at C-21 and then acetoxylated by reaction with potassium acetate to 5α-pregnane-3β,17α,21-triol-11,20-dione 21-acetate. The triol is transformed to 5α-pregnane-3β,11β,17α,21-tetrol-20-one by reduction of the 11-keto group with sodium borohydride after protection of the 20-keto group by formation of the semicarbazone.

The ready availability of 5α-pregnan-3β-ol-11,20-dione[1] (I) along with well developed methods for elaborating the dihydroxyacetone side chain and reduction of 11-keto groups to 11-hydroxyl makes attractive the synthesis of some of the so-called "inactive companion substances" isolated from extracts of the adrenal cortex.[2]

The present paper is concerned with the synthesis of two of these compounds, 5α-pregnane-3β,17α,-21-triol-11,20-dione (Va) (Reichstein's Substance D)[3] and 5α-pregnane-3β,11β,17α,21-tetrol-20-one (VI) (Reichstein's Substance V).[4]

The introduction of the 17α-hydroxyl group into I was accomplished by a modification of the procedure of Kritchevsky and Gallagher.[5] In the original procedure of Gallagher the enolization of the 20-keto group was brought about by distilling off acetic anhydride in the presence of *p*-toluenesulfonic acid as a catalyst. In the present instance this treatment was too drastic in that the 11-keto group also was enolized and subsequent treatment of the enol acetate with peracid afforded largely the 9(11),17,20-diepoxy compound (III) and very lit-



Va, R = R¹ = H
b, R = H; R¹ = Ac
c, R = R¹ = Ac

(1) E. M. Chamberlin, W. V. Ruyle, A. E. Erickson, J. M. Chemerda, L. M. Aliminosa, R. L. Erickson, G. E. Sita and M. Tishler, THIS JOURNAL, **73**, 2396 (1951); G. Stork, J. Romo, G. Rosenkranz and C. Djerassi, *ibid.*, **73**, 3546 (1951).

(2) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publ. Corp., New York, N. Y., 1949, 3rd Ed., p. 424 ff.

(3) T. Reichstein, *Helv. Chim. Acta*, **19**, 29 (1936).

(4) T. Reichstein and J. van Euw, *ibid.*, **25**, 988 (1942).

(5) T. H. Kritchevsky and T. F. Gallagher, THIS JOURNAL, **73**, 189 (1951).

tle of the desired monoepoxide II was obtained.[6] When the enolization was carried out at a lower temperature, *i.e.*, on the steam-bath, only the 20-keto group was transformed to the enol acetate and a satisfactory yield of 17α-hydroxy compound IV (70%) could be obtained by peroxidation and hydrolysis. Barton and his associates[7] also have experienced this difficulty with the original Gallagher procedure when applied to compounds in the 5α-series. These latter workers avoided the double enolization by carrying out the reaction at room temperature in carbon tetrachloride solution employing perchloric acid as the catalyst. It is of interest that in the 5β-series (normal series) the dienol acetate and monoenol acetate give the same product when treated with peracid and subsequently hydrolyzed, namely, the 17α-hydroxy-11-keto compound.[8] This indicates a substantial difference in reactivity toward peracid of the 9(11)- and 17(20)-double bonds in the normal series which the *allo* series does not exhibit. This difference is probably steric in nature and may be attributed to the folded A ring in the 5β-series which effectively shields the 9(11)-double bond from attack by peracid (*cf.* Barton, *et al.*, ref. 7).

Acetoxylation of C-21 to give 5α-pregnane-3β,17α,21-triol-11,20-dione 21-acetate (Vb) was achieved by bromination in chloroform solution followed by replacement of the bromine by refluxing with a mixture of potassium iodide, potassium bicarbonate and acetic acid in acetone.[9] The monoacetate afforded a diacetate Vc with pyridine and acetic anhydride and a triol Va on hydrolysis with sodium methoxide in methanol. Both compounds had melting points and rotations essentially in agreement with those given by Reichstein[3] for Substance D isolated by him from the adrenal cortex.

Conversion of Va to 5α-pregnane-3β,11β,17α,21-tetrol-20-one (VI) was accomplished by formation of the 20-semicarbazone followed by reduction of the 11-keto group to 11-hydroxyl with sodium borohydride in refluxing methanol. Reversal of the reduced semicarbazone in the usual manner with pyruvic acid in acetic acid gave VI essentially the same as Reichstein's Substance V.[4]

Acknowledgment.—The authors are indebted to Messrs. R. Walker and N. Trenner for the infrared spectra, to Mr. Fred Bacher and staff for the solubility assays, and to Mr. R. N. Boos and staff for the analytical data reported.

Experimental

All m.p.'s are uncorrected.

5α-Pregnane-3β,17α-diol-11,20-dione (IV).—5α-Pregnane-3β-ol-11,20-dione acetate (3 g.) was heated on the steam-bath for 4 hours with 0.9 g. of *p*-toluenesulfonic acid monohydrate in 36 cc. of acetic anhydride. Fused sodium acetate (0.388 g.) was added and the acetic anhydride removed *in vacuo* below 40°. The residue was dissolved in 100 cc. of benzene and washed with sodium bicarbonate solution saturated with sodium chloride, with sodium chloride solution and dried over sodium sulfate. The solvent was removed *in vacuo* (bath temp. <40°), the oily residue diluted with 2 cc. of benzene and oxidized with 1.16 g. of perbenzoic acid (3 cc. of 2.8 *M*) in benzene overnight at room temperature. The reaction mixture was diluted with 25 cc. of ethyl acetate and cooled to 0–5°. The excess peracid was decomposed by the addition of 15% $NaHSO_3$ and the *p*H adjusted to ~9 by the addition of 2.5 *N* NaOH. The aqueous alkaline layer was separated, the ethyl acetate solution washed with saturated NaCl solution to *p*H ~7 and dried over Na_2SO_4. The solvent was removed *in vacuo* at room temperature, the residue dissolved in 15 cc. of methanol and hydrolyzed by the addition of 3 cc. of 10 *M* KOH added dropwise with stirring at a temperature of 20–25°. The hydrolysis was allowed to proceed for 45 minutes, the *p*H was then adjusted to ~7 with 2 *N* H_2SO_4 and the reaction mixture aged at 0–5° for 1 hour. The crude product was filtered and recrystallized from acetone–methanol 3:1, 1.4 g., m.p. 271–272°. A sample recrystallized to constant properties from acetone, had m.p. 296–299°, transition 283, phase solubility 98.6%, $[\alpha]^{24}D$ +62.9° dioxane.

Anal. Calcd. for $C_{21}H_{32}O_4$: C, 72.38; H, 9.25. Found: C, 72.18; H, 9.20.

From a larger experiment (18.6 g.), 12 g. (69%) of 17α-hydroxy compound was obtained.

9(11)-17(20)-Diepoxy-5α-pregnane-3,11,20-triol-3,11,20-triacetate (III).—5α-Pregnane-3β-ol-11,20-dione acetate (2 g.) was refluxed 1 hour with 1 g. of *p*-toluenesulfonic acid monohydrate in 100 cc. of acetic anhydride. Acetic anhydride then was distilled off slowly (80 cc.) over a period of 4 hours. The reaction mixture was poured into 250 cc. of ice-water and extracted with ether. The ethereal extract was washed with 1.2 *N* sodium hydroxide and finally with water to neutrality. The dried ($MgSO_4$) ethereal solution was evaporated on the steam-bath, dissolved in 6 cc. of benzene and added to 13.3 g. of perbenzoic acid suspended in 10 cc. of benzene. After 1.25 hours, the reaction mixture was diluted with benzene, washed with cold 5% potassium hydroxide and finally with water. The benzene solution was dried over magnesium sulfate and evaporated on the steam-bath. The residue was recrystallized from methanol; m.p. 213.5–215°, $[\alpha]^{25}D$ +44° ($CHCl_3$); infrared spectrum, 5.73–5.78 μ (acetate), no carbonyl.

Anal. Calcd. for $C_{27}H_{38}O_8$: C, 66.10; H, 7.46. Found: C, 66.24; H, 7.55.

21-Bromo-5α-pregnane-3β,17α-diol-11,20-dione.—5α-Pregnane-3β,17α-diol-11,20-dione (0.49 g.) was dissolved in 200 cc. of chloroform by warming to 45–50°. To the warm solution was added 0.246 g. of bromine in 25 cc. of chloroform over a period of 23 minutes. The warm solution was washed with saturated sodium bicarbonate and the solvent removed *in vacuo*. The residue was flushed with acetonitrile and then dissolved in 75 cc. of acetonitrile. The solution was concentrated to 25 cc. and the product crystallized; m.p. 242–243° dec., $[\alpha]^{24}D$ +70° (dioxane).

Anal. Calcd. for $C_{21}H_{31}O_4Br$: Br, 18.69. Found: Br, 18.38.

5α-Pregnane-3β,17α,21-triol-11,20-dione-21-acetate (Vb).—21-Bromo-5α-pregnane-3β,17α-diol-11,20-dione (0.24 g.) was dissolved in 125 ml. of acetone and the solution heated to 50–52°, 0.334 g. of powdered potassium bicarbonate was added and the mixture stirred for 2 minutes. Glacial acetic acid (0.2 g.) was then added and the mixture stirred at reflux for 5 minutes; powdered potassium iodide (0.166 g.) was then added and refluxing and stirring maintained for 4 hours. The solvent was removed *in vacuo* and the residue stirred 1 hour with 150 cc. of water. After standing overnight in the ice-box, the insoluble product was filtered off. Recrystallized from acetone–hexane (2:1), m.p. 229.5–230°, $[\alpha]^{24}D$ +68° (acetone); infrared spectrum, acetate, 5.72 μ; carbonyl, 5.79–5.90 μ and hydroxyl, 2.83–3.08 μ (lit.[10] m.p. 235–237°, $[\alpha]D$ +66° acetone).

Anal. Calcd. for $C_{23}H_{34}O_6$: C, 67.95; H, 8.43. Found: C, 67.88; H, 8.47.

(6) In the less complicated case of ergostan-3β-ol-11-one acetate the enolization of the 11-keto group by this method also has been demonstrated. A. Crawshaw, H. B. Henbest and E. R. H. Jones, *J. Chem. Soc.*, 731 (1954).

(7) D. H. R. Barton, R. M. Evans, J. C. Hamlet, P. G. Jones and T. Walker, *ibid.*, 747 (1954).

(8) H. V. Anderson, E. R. Garrett, F. H. Lincoln, Jr., A. H. Nathan and J. A. Hogg, THIS JOURNAL, **76**, 743 (1954).

(9) G. Rosenkranz, J. Pataki, S. T. Kaufmann, J. Berlin and C. Djerassi, *ibid.*, **72**, 4081 (1950).

(10) This compound has been reported briefly in a Communication to the Editor: G. Rosenkranz, J. Petaki and C. Djerassi, THIS JOURNAL, **73**, 4055 (1951); J. M. Chemerda, E. M. Chamberlin, E. H. Wilson and M. Tishler, *ibid.*, **73**, 4052 (1951).

Acetylation of Vb with pyridine–acetic anhydride afforded the diacetate (Vc) (Reichstein's Compound D diacetate), m.p. 217–220°; recrystallized from chloroform–ether, m.p. 219–222°, $[\alpha]_D$ +72° (dioxane) (lit.[6] m.p. 223–224°, $[\alpha]$ 72.3 ± 2° (dioxane)); infrared spectrum, acetate, 5.72 μ, carbonyl, 5.80–5.82 μ, and hydroxyl, 2.9 μ.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.94; H, 8.09. Found: C, 67.17; H, 8.88.

Monosemicarbazone of 5α-Pregnane-3β,17α,21-triol-11,-20-dione.—5α-Pregnane-3β,17α,21-triol-11,20-dione (2.2 g.) reacted at room temperature with 1.48 g. of semicarbazide hydrochloride and 0.84 g. of anhydrous sodium acetate in 66 cc. of purified methanol. The initial reaction mixture is a suspension which after some time dissolves and then reprecipitates. After 48 hours, 0.79 g. of anhydrous sodium acetate and 40 cc. of water were added to the cooled reaction mixture. The product was filtered and washed with water until free of chloride ion; yield 2.2 g., m.p. 302–303°; infrared spectrum, hydroxyl, amide 2.9–3.2 μ and carbonyl 5.84, 6.02 μ.

Anal. Calcd. for $C_{22}H_{35}O_5N_3$: N, 9.95. Found: N, 9.57.

Monosemicarbazone of 5α-Pregnane-3β,11β,17α,21-tetrol-20-one.—The monosemicarbazone of Va (2.2 g.) was dissolved in 500 cc. of refluxing, purified methanol. Reduction was carried out at the reflux point under an atmosphere of N_2 with 50 cc. of sodium borohydride solution (3 g. of $NaBH_4$, 0.69 g. of NaOH, 54 cc. of H_2O) added dropwise to the refluxing solution. Refluxing was continued 0.5 hour after addition of the borohydride solution was complete at which time a second 50-cc. portion of sodium borohydride solution was added dropwise and refluxing was maintained 1.5 hours after the sodium borohydride solution was complete. The cooled solution was diluted with 164 cc. of water containing 8.3 cc. of glacial acetic acid. The reaction mixture was concentrated *in vacuo* in absence of air to approximately 200 cc. The product was filtered and washed with water; yield 1.87 g., m.p. 299–301°; infrared spectrum, 2.9 μ, 3.05 μ hydroxyl and amide; 6.00 μ, 6.30 NH; no ketonic carbonyl.

5α-Pregnane-3β,11β,17α,20-tetrol-20-one (VI).—The reduced semicarbazone III (1.87 g.) was stirred as a suspension in 13.4 cc. of glacial acetic acid, 7 cc. of water and 2 cc. of pyruvic acid. After approximately 6 hours, solution was complete. Reprecipitation took place shortly thereafter. After a total reaction time of 23 hours the reaction mixture was transferred to a separatory funnel with 250 cc. of ethyl acetate. Sodium bicarbonate (21 g.) and 25 cc. of water was added and the mixture shaken; an additional 25 cc. of water was added and, after shaking, the aqueous layer was removed. The ethyl acetate was then washed with 50 cc. of saturated sodium bicarbonate solution followed by 75 cc. of saturated sodium chloride solution. The combined washes were extracted three times with 50 cc. of ethyl acetate. The combined ethyl acetate solutions were dried by shaking with granular drierite and the solvent removed in the absence of air on the oil-pump. The residue was taken up in 80% methanol and concentrated again to the point of crystallization. After standing overnight in the ice-box the product was filtered; yield 0.88 g., m.p. 218–223°, $[\alpha]^{24}_D$ +52° (dioxane).

A sample recrystallized from methanol–water, m.p. 221–224°; from dioxane–water, m.p. 233–235°, $[\alpha]^{24}_D$ +55° (dioxane), lit., m.p. 220–225°, $[\alpha]_D$ +52° (dioxane); infrared spectrum, 2.94–3.0 μ hydroxyl, 5.85 μ carbonyl; sulfuric acid chromogen spectrum λ_{max} 333, 417, 510 mμ; lit.[11] λ_{max} 285, 330, 415 mμ; 510 mμ.

Anal. The compound crystallizes from dioxane–water with 1 mole of dioxane of crystallization which is lost only on prolonged drying (24 hours) at a temperature of 103°.

Anal. Calcd. for $C_{21}H_{34}O_5 \cdot C_4H_8O_2$: C, 66.04; H, 9.31. Found: C, 66.50; H, 8.82. Calcd. for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 69.14; H, 9.05.

(11) A. Zaffaroni and R. B. Burton, *J. Biol. Chem.*, **193**, 749 (1951).

RAHWAY, N. J.

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

The Stereochemistry of Steroidal Sapogenins. II[1]

BY J. B. ZIEGLER, W. E. ROSEN AND A. C. SHABICA

RECEIVED JULY 30, 1954

The complexity of the stereochemistry of the E and F rings of the steroidal sapogenins is considerably greater than was originally realized. Assuming identical configurations at C-16 and C-17, the asymmetric centers at C-20, C-22 and C-25 permit the existence of eight diastereoisomers for each nuclear type; four of these are now known. Studies of the reactions of these isomers, together with assumptions of mechanisms for their formation and interconversion, have permitted assignment of absolute configurations which appear to be consistent with all established experimental facts.

The stereochemistry of the nucleus in the various steroidal sapogenins[2] has for the most part been well delineated.[3] However, the stereochemistry of the E and F rings is much less well known. The asymmetric centers at C-20, C-22 and C-25 permit the existence of a maximum of eight side-chain diastereoisomers, even assuming that all sapogenins have the same configurations at C-16 and C-17.

It has been recognized that certain naturally occurring pairs of sapogenins exist, one member ("normal" series) of each pair being convertible to the other member ("iso" series) by vigorous treatment with mineral acid.[4–7] Evidence derived from degradative studies indicated that the seat of this isomerism lay in the side chain, and the assumption was made that the actual locus was the C-22 or spiro position; reports[5a,8] of the identity of the pseudo and dihydro derivatives of, for example, sarsasapogenin ("normal" series) and smilagenin ("iso" series) were consistent with this hypothesis. It would appear that for some time the other asym-

(1) Paper I is a Communication to the Editor of THIS JOURNAL, **76**, 3865 (1954).

(2) The term "sapogenin" will hereafter be used to mean "steroidal sapogenin."

(3) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publ. Corp., New York, N. Y., 1949, Chapt. VIII.

(4) Early evidence for these transformations was not convincing. Only recently have they been established by infrared spectroscopy[7,13,21] and by degradation.[14]

(5) (a) R. E. Marker and E. Rohrmann, THIS JOURNAL, **61**, 846 (1939); (b) G. A. R. Kon, H. R. Soper and A. M. Woolman, *J. Chem. Soc.*, 1201 (1939).

(6) R. E. Marker, R. B. Wagner, P. R. Ulshafer, E. L. Wittbecker, D. P. J. Goldsmith, and C. H. Ruof, THIS JOURNAL, **69**, 2185 (1947).

(7) M. E. Wall, C. R. Eddy, S. Serota and R. F. Mininger, *ibid.*, **75**, 4437 (1953).

(8) R. E. Marker, E. Rohrmann and E. M. Jones, *ibid.*, **62**, 648 (1940).