absorption spectrum ($CHCl_3$) showed maxima at 1790 cm.$^{-1}$ (5-membered lactone), 1745 cm.$^{-1}$ (acetate), 1612 and 1502 cm.$^{-1}$ (phenyl), 812 cm.$^{-1}$ (—C=C—H). No absorption was observed in the hydroxyl region.

Anal. Calcd. for $C_{25}H_{30}O_5 \cdot C_3H_6O$: C, 71.77; H, 7.74. Found: C, 71.62; H, 7.55.

Hydrogenation of VIII.—The anhydro derivative VIII (620 mg.) was dissolved in 70 ml. of methanol and stirred in an atmosphere of hydrogen with 280 mg. of platinum oxide catalyst. After the uptake of hydrogen ceased, the catalyst was removed by filtration, and the filtrate evaporated to dryness. Chromatography of the residual material (550 mg.) on silica gel followed by repeated crystallization from methanol furnished 103 mg. of a substance melting at 204–205°, $[\alpha]_{5460}$ −105° (*c* 1.3, acetone).

Anal. Calcd. for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.63; H, 7.75.

A smaller amount of a second substance, m.p. 144–147°, $[\alpha]_{5460}$ + 5.4° (*c* 1.2, acetone) also was obtained. This material was not investigated further.

Hydrolysis of the product melting at 204–205° gave material, m.p. 223–224°, that is presumed to be the free hydroxy derivative X. The amount of this substance available was, however, insufficient for analysis.

Conversion of VIII into XI.—A solution of 110 mg. of the anhydro derivative VIII in 20 ml. of methanol was treated with 10 ml. of concentrated hydrochloric acid, and the resulting mixture was refluxed for 7 hours under hydrogen. On cooling and dilution with 150 ml. of water, a white solid separated, which was purified in the following manner. The product was first dissolved in 60 ml. of methanol and stirred for 2 hours under hydrogen with 100 mg. of platinum oxide to reduce or rearrange non-aromatic unsaturation, the presence of which was suggested by a spurious absorption band in the 305–310 mμ region. The resulting material was then adsorbed from benzene solution on magnesium silicate. A crystalline compound was eluted with methylene chloride, which after recrystallization from methanol gave 30 mg. of fine needles, m.p. 185–188°, $[\alpha]_{5460}$ +48° (*c* 1.0, acetone).

Anal. Calcd. for $C_{23}H_{26}O_3$: C, 78.82; H, 7.48; $-OCH_3$, 8.85. Found: C, 78.61; H, 7.44; $-OCH_3$, 8.85.

The ultraviolet absorption data are recorded in Fig. 2.

HOUSTON, TEXAS

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

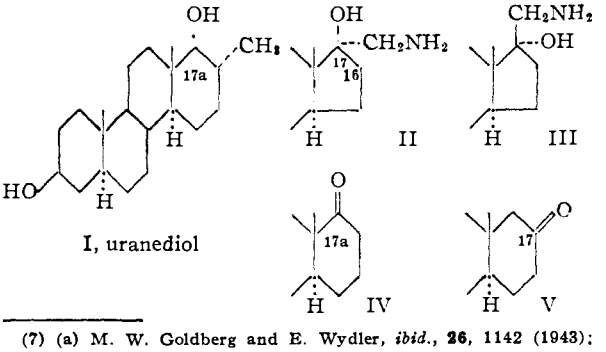
17-Keto-17a-methyl-D-homosteroids from 17α-Hydroxy-20-amino-C_{21} Steroids. Stereochemistry of D-Homoannulation

BY FAUSTO RAMIREZ AND STANLEY STAFIEJ[1]

RECEIVED JUNE 1, 1954

The action of nitrous acid on a 17α-hydroxy-20α-aminosteroid (XVa) has been studied with the view of (a) correlating the configurations at carbons 17 and 20 with the course of deamination and (b) providing a new route to C_{21}-D-homosteroids. It was found that the amino alcohol XVa rearranged exclusively to a 17-keto-17a-methyl-D-homosteroid with migration of the 13–17 bond. This result is interpreted in terms of steric strain in the transition state of the deamination, and is compared with the previously reported D-homoannulation of 17α-hydroxy-17-aminomethylsteroids, in which no steric bias is associated with carbon 20. The amino alcohol studied XVa was obtained—together with a small amount of the 20β-epimer XVIa—from the catalytic hydrogenation of a 17α-hydroxy-20-oxime (XIV). The configurations of the amino alcohols are based on the molecular rotation differences between the 20-epimeric acetamido derivatives (XVb and XVIb) by comparison with previously reported molecular rotation differences of 20-epimeric 20-acetate derivatives of 17α,20-dihydroxysteroids of analogous constitution.

The sequence of events which resulted in the original partial syntheses of D-homosteroids[2] and in the elucidation of the structural changes taking place during these syntheses, has been extensively reviewed.[3] C_{21}-D-Homosteroids (*i.e.*, urane derivatives such as I[3d]) have been isolated from natural sources by several investigators.[4] It has been shown, furthermore,[5] that some D-homoanalogs of steroid hormones are as active or even more active than the corresponding hormones. For these reasons the partial synthesis of C_{20}- and C_{21}-D-homosteroids has received considerable attention. In a recent publication[6] the action of nitrous acid on a 17β-hydroxy-17-aminomethylsteroid (II) was described. The Swiss authors concluded that the D-homoannulation brought about by nitrous acid was stereospecific and led exclusively to a 17a-keto-D-homosteroid IV by migration of the C_{16}-C_{17} bond. It was also suggested[6] that the isomeric 17-keto-D-homosteroid V, previously isolated (together with IV) by Goldberg and co-workers[5b,7] from the action of nitrous acid on a crude mixture of 17-hydroxy-17-aminomethylsteroids,[8] resulted from the rearrangement of III with migration of the C_{13}–C_{17} bond. No satisfactory explanation has been



(1) From part of the Ph.D. Thesis of S. Stafiej.

(2) (a) W. A. Yarnall and E. S. Wallis, THIS JOURNAL, **59**, 951 (1937); (b) K. Miescher and H. Kagi, *Helv. Chim. Acta*, **22**, 184 (1939); (c) L. Ruzicka and K. Hofmann, *ibid.*, **20**, 1280 (1937); (d) H. E. Stavely, THIS JOURNAL, **61**, 79 (1939).

(3) (a) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Edition, Reinhold Publ. Corp., New York, N. Y., 1949, p. 377; (b) R. B. Turner, THIS JOURNAL, **75**, 3484 (1953); (c) R. J. W. Cremlyn, D. L. Garmaise and C. W. Shoppee, *J. Chem. Soc.*, 1847 (1953); (d) W. Klyne and C. W. Shoppee, *Chemistry and Industry*, 470 (1952).

(4) (a) W. Klyne, *Biochem. J.*, **43**, 611 (1948); (b) R. E. Marker and E. Rohrmann, THIS JOURNAL, **60**, 2719 (1938).

(5) *Cf.* (a) L. Ruzicka, N. Wahba, P. Th. Herzig and H. Heusser, *Chem. Ber.*, **85**, 491 (1952); (b) M. W. Goldberg, J. Sice, H. Robert and Pl. A. Plattner, *Helv. Chim. Acta*, **30**, 1441 (1947).

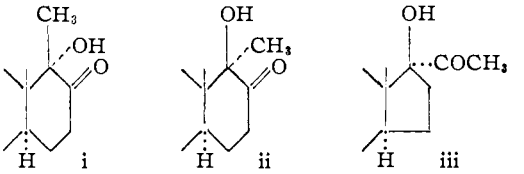
(6) H. Heusser, P. Th. Herzig, A. Furst and Pl. A. Plattner, *ibid.*, **33**, 1093 (1950).

(7) (a) M. W. Goldberg and E. Wydler, *ibid.*, **26**, 1142 (1943); (b) M. W. Goldberg and R. Monnier, *ibid.*, **28**, 376 (1940).

(8) Obtained by catalytic hydrogenation of a crude cyanohydrin mixture.

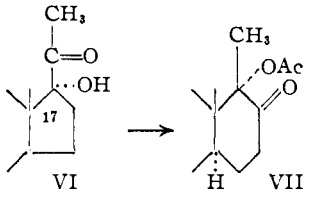
advanced to account for the observed stereospecificity of the change II → IV and for the assumed stereospecificity of the change III → V.

During a thorough investigation of the D-homoannulation of 17α-hydroxy-20-keto- and 17β-hydroxy-20-ketosteroids (VI and its 17-epimer) brought about by alkalies and by Lewis acids, Turner[3b] developed a convenient route[9] to a 17-keto-



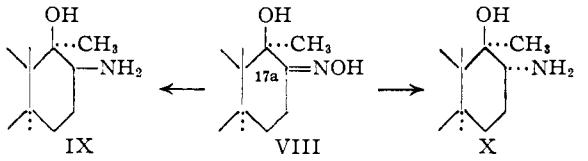
i ii iii

17aβ-methyl-17aα-acetoxy-D-homosteroid (VII) from a readily available 17α-hydroxy-20-ketosteroid (VI) and clarified the steric course of these rearrangements. Work on these reactions had been carried out previously by Ruzicka and co-workers,[10] by Shoppee and Prins[11] and by Stavely.[12]



VI VII

The action of nitrous acid on a set of stereoisomeric D-homosteroidal amino alcohols (IX, X and the corresponding 17a-epimers) has been discussed recently.[3c] These amino alcohols are available[3c,13,14] by catalytic hydrogenation of the oximes (VIII and its 17a-epimer) which gives the 17β-amino isomers (such as IX) and by the sodium–propanol reduction of the oximes, which gives the 17α-amino isomers (such as X). On treatment with nitrous acid one of these amino alcohols, namely, IX, is said to yield a 17-methyl-17a-keto-D-homosteroid (*i.e.*, uranolone)[3d,15] as a result of methyl migration; a more



IX VIII X

(9) This involves the use of boron trifluoride–acetic anhydride–acetic acid. The D-homoannulation of 17α-hydroxy-20-ketosteroids (VI) by potassium hydroxide leads to mixtures of 17-keto-17aβ-methyl-17aα-hydroxy- and 17-keto-17aα-methyl-17aβ-hydroxy-D-homosteroids (i and ii, respectively). From 17β-hydroxy-20-ketosteroids (iii), i or ii can be obtained using potassium hydroxide or alumina, respectively. The 17a-hydroxyl group of i has been removed by treatment with phosphorus tribromide followed by zinc (*cf.* ref. 10b). In this connection it should be noted that the polar 17aα-acetoxy of VII is presumably difficult to hydrolyze, which might interfere with the utilization of the VI → VII → i route to 17-keto-17a-methyl-D-homosteroids.)

(10) (a) L. Ruzicka and H. F. Meldahl, *Helv. Chim. Acta*, **21**, 1760 (1938); (b) L. Ruzicka and H. F. Meldahl, *ibid.*, **22**, 221 (1939); (c) L. Ruzicka, K. Gatzi and T. Reichstein, *ibid.*, **22**, 626 (1939).

(11) (a) C. W. Shoppee and D. A. Prins, *ibid.*, **26**, 185 (1943); (b) C. W. Shoppee and D. A. Prins, *ibid.*, **26**, 201 (1943); (c) C. W. Shoppee and D. A. Prins, *ibid*, **26**, 1004 (1943).

(12) H. E. Stavely, THIS JOURNAL, **63**, 3127 (1941).

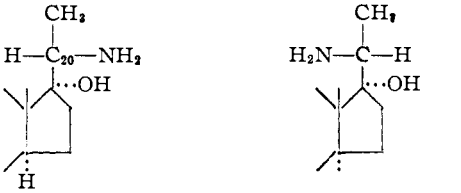
(13) D. A. Prins and C. W. Shoppee, *J. Chem. Soc.*, 494 (1946).

(14) L. Ruzicka and H. F. Meldahl, *Helv. Chim. Acta*, **24**, 1321 (1941).

(15) W. Klyne, *Nature*, **166**, 559 (1950).

direct confirmation of the structure of uranolone is, however, regarded as desirable.[3d,15]

We have undertaken a study of the action of nitrous acid on 17-hydroxy-20-amino-C_{21}-steroids (such as the pair of 17α-hydroxy-20α- and 20β-amino steroids XI and XII, respectively[16]) with the view of (a) ascertaining possible correlations between the configurations at carbon atoms 17 and 20 and the course of the deaminations, (b) comparing the course of deaminations in these systems in which carbon 20 is asymmetric with those previously reported[6] in which no steric bias is associated with carbon 20, (c) providing new routes to 17-keto-17a-methyl- and 17-methyl-17a-keto-D-homosteroids. The present paper reports our observations on an amino alcohol which we regard as having the 17α-hydroxy-20α-amino configuration XI.



17α-OH,20α-NH_2 XI 17α-OH,20β-NH_2 XII

3β,17α-Dihydroxy-20-oximidoallopregnane (XIVa) and its 3-monoacetate XIVb were prepared in nearly quantitative yields from the corresponding ketones, 3β,17α-dihydroxyallopregnane-20-one (XIIIa) and its 3-monoacetate XIIIb. The hydrogenation of the oxime-diol XIVa proceeded smoothly in acetic acid solution containing some hydrochloric acid, in the presence of a platinum catalyst. The formation of two isomeric amine-diols, 3β,17α-dihydroxy-20α-aminoallopregnane (XVa) and 3β,17α-dihydroxy-20β-aminoallopregnane (XVIa), of which one greatly predominated, was initially established by acetylation to a mixture of 3β,17α-dihydroxy-20α-acetamidoallopregnane 3-monoacetate (XVb) and 3β,17α-dihydroxy-20β-acetamidoallopregnane 3-monoacetate (XVIb). The mixture of acetate-amides (XVb and XVIb) was separated by fractional crystallization and chromatography. The amide group of XVb could not be hydrolyzed under rather vigorous conditions. In order to obtain the amine-diols, it proved convenient to hydrogenate the 3-monoacetate oxime (XIVb) and to separate the epimeric amines by fractional crystallization of their hydrochlorides with concomitant hydrolysis of the 3-acetate group. In this manner one of the amine-diols XVa could be isolated in pure form in 70% yield. On acetylation this substance gave the same acetate-amide XVb previously obtained. The isomeric amine-diol XVIa was isolated in small amounts and there is at present no satisfactory assurance of its complete purity.[17] On acetylation, XVIa gave the same lower melting, dextrorotatory acetate-amide XVIb obtained previously in pure form.

We have assigned the 20α-configuration to the

(16) Drawn according to the conventions of Fieser and Fieser (*cf.* ref. 3a, p. 412) in which the C_{18}-methyl is considered to be as far back as possible.

(17) The somewhat large melting range of XVIa (8° in the Kofler block) remained constant throughout several recrystallizations.

higher melting, levorotatory acetate-amide XVb and to the corresponding amine-diol XVa, which greatly predominated in the catalytic hydrogenation, on the basis of the following considerations:

(a) It has been pointed out[18] that a 20β-hydroxy steroid in an acetylated condition is significantly more dextrorotatory than the 20α-epimer. Table I brings out this relationship. It will be noted that the lower melting acetate-amide XVIb is likewise considerably more dextrorotatory than the higher melting epimer XVb. Table I also shows the correspondence in the sign of the molecular rotation differences resulting from acetylation in both the 20-hydroxy and 20-amino series.[19]

TABLE I

MOLECULAR ROTATIONS. M_D = [α]D × MOL. WT./100

Compound	Stanol	M_D 3,20-diAc	$(M_D)_{diAc}-(M_D)_{stanol}$	$(M_D)_{diAc}-(M_D^{20\beta})_{diAc}$
3β,17α,20α-Trihydroxyallopregnane[a] (O)	−44[c]	−126[f]	− 82	...
3β,17α-20β-Trihydroxyallopregnane[a] (J)	−27[e]	+105[f]	+132	+231
3β,17α-Dihydroxy-20α-aminoallopregnane (XVa)	−67[d]	−126[d]	− 59	...
3β,17α-Dihydroxy-20β-aminoallopregnane (XVIa)	(+ 3?)[d]	+146[d]	+143	+272

	Stanol	3-Ac	$(M_D)_{Ac}-(M_D)_{stanol}$
3β-Hydroxy-D-homoandrostan-17-one[b]	+70[e]	− 14[e]	− 84
3β-Hydroxy-17aβ-methyl-D-homoandrostan-17-one	− 85[d]	−164[d]	− 79
3β,17α-Dihydroxy-20-oximidoallopregnane (XIVa)	− 8[e]	− 52[e]	− 44

[a] M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **21**, 546 (1938). [b] M. W. Goldberg and E. Wydler, *ibid.*, **26**, 1192 (1943). [c] In MeOH. [d] In chloroform. [e] In EtOH. [f] In acetone.

The action of nitrous acid on the amine-diol XVa gave only one isolable product, 3β-hydroxy-17a-methyl-D-homoandrostan-17-one (XVIIa)[20] in 81% yield.[21] Acetylation of XVIIa gave XVIIb, and oxidation gave the diketone XVIII. The infrared spectra of the D-homosteroids (see Experimental) are in agreement with the structures assigned. The hydroxy ketone XVIIa and its oxidation product XVIII, of melting points similar to ours, have been reported by Ruzicka and Meldahl.[22]

(18) (a) Reference 3a, p. 415; (b) W. Klyne and D. H. R. Barton, THIS JOURNAL, **71**, 1500 (1949); (c) W. Klyne, *Chemistry and Industry*, 426 (1951).

(19) *Cf.* K. Freudenberg, "Stereochemie," Franz Deuticke, Leipzig, 1933, p. 699.

(20) The D-homosteroid XVIIa was stable to bases, therefore it is written as having the presumably more stable (equatorial) 17aβ-methyl configuration (*cf.*, ref. 15 for the related case of a 17α-methyl configuration).

(21) As described in the Experimental a small amount of amine-diol escapes deamination, presumably through formation of a sparingly soluble nitrate, also isolated.

(22) L. Ruzicka and H. F. Meldahl, *Helv. Chim. Acta*, **23**, 364 (1940). For the 3β-hydroxy-17a-methyl-D-homoandrostan-17-one acetate (XVIIb) the Swiss authors reported a m.p. of 174–175°, at variance with ours. The method of preparation of XVIIb described by Ruzicka and Meldahl is not inconsistent with the view that the difference in m.p. may be due to isomerism at C-17a.

The observed stereospecificity of the deamination XVa → XVIIa may be interpreted in terms of steric strain in the transition state with reference to Fig. 1.[23] Thus, a 17-keto-17a-methyl-D-homosteroid (such as XVIIa) would result from a 17α-hydroxy-20α-aminosteroid by migration of the C_{13}–C_{17} bond

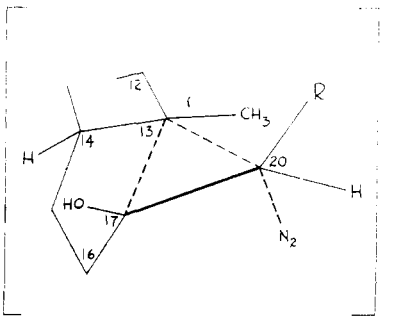
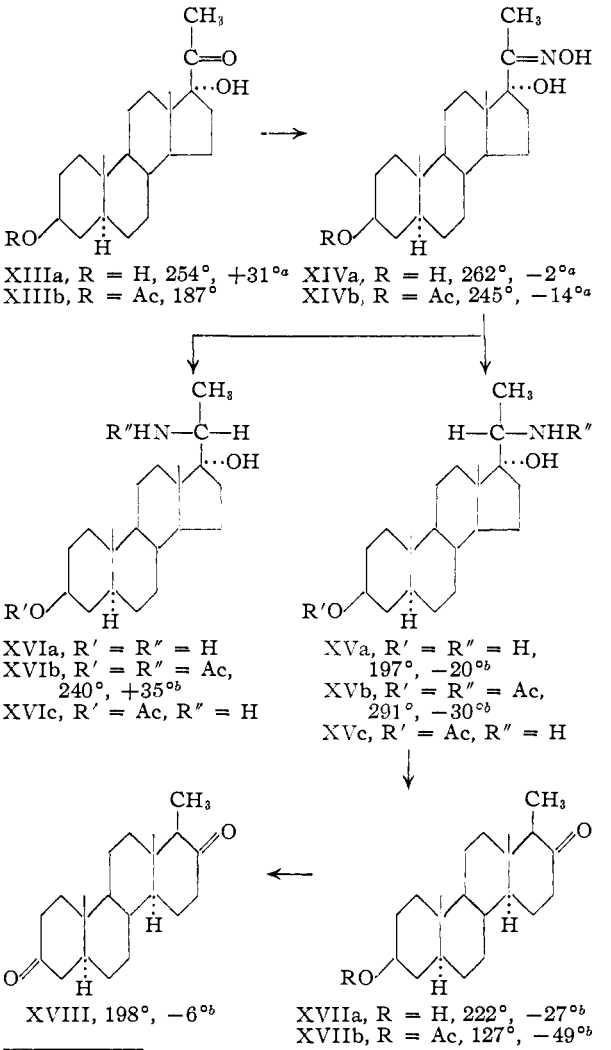


Fig. 1.

CHART I

CONSTANTS REPORTED: M.P. (KOFLER), [α]^{25}D; [a] EtOH, [b] chf.



(23) For a discussion of the mechanism of nitrosation of amino alcohols, see (a) M. C. Crew, Ph.D. dissertation, Columbia University, New York, 1954; (b) P. I. Pollak and D. Y. Curtin, THIS JOURNAL, **72**, 961 (1950); (c) D. Y. Curtin and P. I. Pollak, *ibid.*, **73**, 992 (1951).

via a transition state in which the groups in direct opposition are R–OH and H–C_{16}.[24,25]

Experimental[26]

Preparation of 3β,17α-Dihydroxyallopregnan-20-one (XIIIa) and of its 3-Monoacetate (XIIIb) from Δ⁵-Pregnene-3β-ol-20-one Acetate (Pregnenolone Acetate).—The conversion of pregnenolone acetate into pregnanolone acetate by means of a platinum catalyst and involving partial reduction of the 20-keto group followed by reoxidation has been recorded.[27] The following direct procedure using a palladium catalyst proved quite satisfactory.

A mixture of 25 g. of pregnenolone acetate, 750 ml. of anhydrous ethanol and 2.4 g. of 10% palladium-on-charcoal (Baker) was shaken in a hydrogen atmosphere (30 pounds per square inch) for 6.5 hr. The catalyst was filtered, the solvent was removed from the filtrate and the residue was recrystallized from ethanol; yield of 3β-hydroxy-allopregnan-20-one acetate (identified by infrared spectra and mixture m.p. with authentic material): 17.36 g., m.p. 141–144°; 4.32 g., m.p. 135–141°.

From 3β-hydroxyallopregnan-20-one acetate (21.68 g.), 3β,17α-dihydroxyallopregnan-20-one (XIIIa) (yield 14.6 g., m.p. 254–258°, $[\alpha]^{25}D$ +31° EtOH) was obtained by the method of Kritchevsky and Gallagher.[28] 3β,17α-Dihydroxyallopregnan-20-one 3-monoacetate (XIIIb) (m.p. 187–189°) was obtained in quantitative yield from XIIIa as described.[28] Both XIIIa and XIIIb were identified by comparison with authentic samples.

3β,17α-Dihydroxy-20-oximidoallopregnane (XIVa).—To a solution of 1.00 g. of XIIIa in 30 ml. of ethanol was added a solution of 2.0 g. of hydroxylamine hydrochloride and 2.1 g. of sodium acetate in 10 ml. of water. The mixture was diluted with 80 ml. of ethanol and refluxed for 6 hours. The oxime which precipitated on cooling (0.570 g.) had m.p. 262–264°. Addition of water to the filtrate gave 0.468 g. of additional oxime of the same m.p.; total yield 98%. After recrystallization from ethanol–water and drying at 130° *in vacuo*, the oxime XIVa had m.p. 262–264°, $[\alpha]^{25}D$ −2 ± 1° EtOH (*c* 0.585).

Anal. Calcd. for $C_{21}H_{35}O_3N$: C, 72.2; H, 10.1. Found: C, 72.2; H, 10.0.

The dihydroxy oxime XIVa forms tenacious hydrates. Thus a sample dried *in vacuo* at 68° gave: *Anal.* Calcd. for $C_{21}H_{35}O_3N \cdot {}^1/_2H_2O$: C, 70.8; H, 10.2; N, 3.9. Found: C, 70.9; H, 10.4; N, 4.1.

3β,17α-Dihydroxy-20-oximidoallopregnane 3-Monoacetate (XIVb).—A mixture of 1.315 g. of XIIIb, 60 ml. of ethanol, 2.64 g. of hydroxylamine hydrochloride, 2.76 g. of sodium acetate and *ca.* 15 ml. of water was refluxed for 6.5 hours. Upon evaporation of some solvent, crystallization ensued; yield of XIVb 1.235 g., m.p. 243–246°, and 98 mg., m.p. 240–244° (98%). After recrystallization from ethanol–water and drying at 68° *in vacuo*, the oxime XIVb had m.p. 245–246°, $[\alpha]^{25}D$ −14 ± 1° EtOH (*c* 0.72).

Anal. Calcd. for $C_{23}H_{37}O_4N$: C, 70.6; H, 9.5; N, 3.6. Found: C, 70.6; H, 9.5; N, 3.6.

3β,17α-Dihydroxy-20α-acetamidoallopregnane 3-Monoacetate (XVb) and 3β,17α-Dihydroxy-20β-acetamidoallopregnane 3-Monoacetate (XVIb).—The dihydroxy oxime XIVa (0.609 g.) in acetic acid solution (60 ml.) containing one drop of concentrated hydrochloric acid was hydrogenated at atmospheric pressure in the presence of platinum oxide catalyst (0.120 g.). The catalyst was filtered and the acetic acid was removed from the filtrate under vacuum. The residue was allowed to stand overnight with acetic anhydride (6 ml.) and pyridine (16 ml.). The mixture was poured into ice-water containing some sulfuric acid and the product which precipitated was extracted with ether and chloroform. The organic layer was washed, dried over magnesium sulfate and evaporated. The residue was recrystallized from benzene and yielded 0.271 g. of product, m.p. 289–290°. The analytical sample of XVb, recrystallized from benzene and dried at 67° *in vacuo*, had m.p. 291–292°, $[\alpha]^{25}D$ −30 ± 1° chf. (*c* 1.02), $\lambda_{max.}^{chf.}$ 2.90, 5.83, 6.05 μ.

Anal. Calcd. for $C_{25}H_{41}O_4N$: C, 71.6; H, 9.8; N, 3.3. Found: C, 71.8; H, 9.8; N, 3.2.

Concentration of the mother liquid from which XVb had been obtained gave a second crop which was dissolved in benzene and placed in a column of acid-washed alumina (12 g.). The column was eluted successively with benzene, with mixtures of benzene–ether, with ether and with mixtures of ether–chloroform (a total of 19 fractions). Fraction no. 16 consisting of 1:1 ether–chloroform gave colorless crystals, m.p. 231–236°. One recrystallization of this product from benzene–hexane gave 56 mg. of acetate-amide XVIb, m.p. 240–240.5°, $[\alpha]^{25}D$ +35 ± 1° chf. (*c* 1.03), $\lambda_{max.}^{chf.}$ 2.90, 5.83, 6.05 μ.

Anal. Calcd. for $C_{25}H_{41}O_4N$: C, 71.6; H, 9.8; N, 3.3. Found: C, 71.9; H, 10.0; N, 3.5.

A mixture melting point of the two acetate-amides XVb and XVIb was 218–223°.

All attempts to effect the hydrolysis of the acetate-amide XVb to the amino alcohol XVa failed; the infrared spectra of the products indicated that the amide group was not hydrolyzed.

3β,17α-Dihydroxy-20α-aminoallopregnane (XVa) and 3β,17α-Dihydroxy-20β-aminoallopregnane (XVIa).—A mixture of 3β,17α-dihydroxy-20-oximidoallopregnane 3-monoacetate (XIVb) (0.935 g.), acetic acid (93 ml.), concentrated hydrochloric acid (one drop) and platinum oxide catalyst (0.190 g.) was shaken in a hydrogen atmosphere (atmospheric pressure) for 14 hr. At the end of this time the theoretical amount of hydrogen had been taken up. The catalyst was filtered and the solvent removed by distillation under vacuum. The crystalline residue, still containing some acetic acid, was dissolved in methanol (25 ml.) and the solution cooled in ice-water while anhydrous hydrogen chloride was being bubbled through it. The hydrochloride which precipitated (crop 1) was filtered. The filtrate was concentrated until more hydrochloride began to crystallize out (crop 2). In this manner two more crops of hydrochloride (3 and 4) were obtained. Each one of these crops was treated with methanolic potassium hydroxide with the following results: from crop 1: 0.536 g., m.p. 194–196°; from crop 2: 51 mg., m.p. 194–196° (yield of amino-diol XVa 70%); from crop 3: 0.140 g., m.p. 199–207°; from crop 4: 30 mg., m.p. 186–207°. Crops 3 and 4 represent somewhat impure amino-diol XVIa (*vide infra*).

After recrystallization from methanol–water and drying at 110° *in vacuo*, the amino-diol XVa had m.p. 197–199°, $[\alpha]^{25}D$ −20 ± 2° chf. (*c* 1), $\lambda_{max.}^{chf.}$ 2.9 μ (wide), no bands in the 5–6,3 μ region,

Anal. Calcd. for $C_{21}H_{37}O_2N$: C, 75.2; H, 11.1, Found: C, 75.1; H, 11.1.

The amine-diol XVa forms hydrates and is furthermore quite hygroscopic when thoroughly dry. Thus, a sample analyzed without precautions against moisture had: *Anal.* Calcd. for $C_{21}H_{37}O_2N \cdot H_2O$: C, 71.3; H, 11.1; N, 4.0. Found: C, 71.7; H, 10.9; N, 3.7.

Acetylation of the amine-diol XVa (60 mg., m.p. 194–196°) with acetic anhydride (15 drops) in pyridine (1.0 ml.) gave the 20-acetamido-3-monoacetate (XVb) (42 mg., m.p. 283–286°), which after one recrystallization from benzene, did not depress the m.p. of XVb previously obtained.

The material (0.140 g., m.p. 199–207°) obtained above from crop 3 was recrystallized further from methanol–water (3 times) without any change in the melting range. The analytical sample was dried at 110° *in vacuo* and had m.p. 199–207°, $[\alpha]^{25}D$ +1 ± 1° chf. (*c* 1).

Anal. Calcd. for $C_{21}H_{37}O_2N$: C, 75.2; H, 11.1. Found: C, 75.1; H, 11.0.

(24) Formation of a 17-methyl-17a-keto-D-homosteroid from the same amino alcohol would involve the opposition of R–C_{13} and H–OH in the transition state, a less favorable situation.

(25) An analogous explanation could be offered for the stereospecificity in the C_{20}-amino alcohol, (III → V). The favorable transition state here involves C_{16}–H in opposition (Fig. 1, R = H); the unfavorable transition state involves C_{16}–H in opposition, with the angular methyl group (C_{18}) at C_{13} *facing* the H at C_{20}. A consideration of the previously reported[6] D-homoannulation II → IV, in which the C_{16}–C_{17} bond appears to have migrated, would suggest that the nature of the migrating group does not exert a dominant role in directing the course of D-homoannulation. In this case (II → IV)[6] the favored transition state seems to involve C_{13}–H opposition, but with the angular methyl group (C_{18}) at C_{13} *pointing away* from the H at C_{20}.

(26) Microanalyses by Micro-Tech Laboratories, Skokie, Ill. The melting points were taken in a Kofler hot-stage microscope.

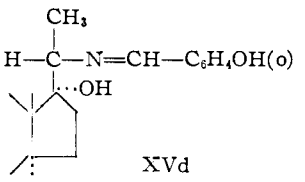
(27) A. Ruff and T. Reichstein, *Helv. Chim. Acta*, **34**, 70 (1951).

(28) T. H. Kritchevsky and T. F. Gallagher, THIS JOURNAL, **73**, 184 (1951).

Acetylation of this substance, m.p. 199–207°, with acetic anhydride–pyridine gave, after four recrystallizations from benzene–hexane, the 20-acetamido-3-monoacetate (XVIb), m.p. 235–239°, alone and mixed with XVIb previously obtained.

Characterization of 3β,17α-Dihydroxy-20α-aminoallopregnane 3-Monoacetate (XVc) as the 2-Hydroxybenzal Derivative.—The crude mixture of epimeric 3-acetate-amino alcohols (XVc and XVIc) obtained by catalytic hydrogenation of the oxime acetate XIVb as described above, was dissolved in chloroform and washed with 10% aqueous sodium carbonate to remove the acetic acid held by the amino acetates. The residue obtained after removal of the chloroform (0.105 g.) was dissolved in benzene (50 ml.) containing two drops of freshly distilled salicylaldehyde. The mixture was distilled slowly in order to remove the water formed. After two hours, the solvent was evaporated and the residue was recrystallized from benzene–hexane. The yield of yellow imide XVd was 60 mg., m.p. 206–211°. The analytical sample, recrystallized from benzene–hexane and dried at 68° *in vacuo*, melted at 214–218°.

Anal. Calcd. for $C_{30}H_{43}O_4N$: C, 74.8; H, 9.0; N, 2.9. Found: C, 74.8; H, 9.1; N, 2.9.



XVd

3β-Hydroxy-17aβ-methyl-D-homoandrostan-17-one (XVIIa).—To a solution of amine-diol XVa (0.400 g., m.p. 196–198°) in 5 ml. of acetic acid and 10 ml. of water, kept at 0°, was added dropwise, with stirring, a solution of 0.640 g. of sodium nitrite in 10 ml. of water. The addition lasted 2.5 hours and after the first 20 minutes a white solid began to separate. The mixture was allowed to stand at room temperature for 15 hr., poured onto water and extracted once with ether and once with chloroform. An insoluble crystalline material which separated during this operation (47 mg.) was filtered off. As shown below, this material appears to be the nitrate of the original amine-diol (XVa). The aqueous layer was neutralized with sodium carbonate and yielded 8 mg. of original amine-diol XVa (m.p. 197–198°). The combined ether–chloroform extracts were washed with aqueous sodium carbonate and water, dried over sodium sulfate and evaporated. The residue (*ca.* 0.36 g.) was recrystallized from methanol and yielded 0.266 g. of keto alcohol XVIIa, m.p. 222–225°. The yield of XVIIa, based on recovered starting material was 81%; no other product could be isolated. The analytical sample of XVIIa, obtained from methanol and dried at 110° *in vacuo*, had m.p. 222–225°, $[\alpha]^{25}D$ −27 ± 1° chf. (*c* 1), $\lambda_{max.}^{chf.}$ 2.7 (very weak), 5.90 μ; reported[25] for XVIIa, m.p. 222–224°, no rotation given.

Anal. Calcd. for $C_{21}H_{34}O_2$: C, 79.2; H, 10.8. Found: C, 79.1; H, 10.7.

The water-insoluble, ether-insoluble material described above (47 mg.) was recrystallized from methanol–benzene to give a product whose properties (decomposition point *ca.* 292°, infrared spectrum) are consistent with those of a nitrate salt of the amine-diol XVa. Several experiments gave comparable results.

Anal. Calcd. for $C_{21}H_{37}O_2N \cdot HNO_3$: C, 63.3; H, 9.6; N, 7.0. Found: C, 63.2; H, 9.6; N, 6.9.

A solution of XVIIa in methanol was treated with methanolic potassium hydroxide at room temperature for *ca.* 30 hours. The crude material recovered had m.p. 195–218°; recrystallization from methanol (1st, m.p. 206–218°; 2nd, m.p. 213–218°; 3rd, m.p. 218–221°) gave XVIIa.

3β-Hydroxy-17aβ-methyl-D-homoandrostan-17-one Acetate (XVIIb).—A mixture of the hydroxy ketone XVIIa (0.100 g.), acetic anhydride (1 ml.) and pyridine (2 ml.) was kept overnight at room temperature. The resulting solution was poured onto ice-cold 1 *N* sulfuric acid. The mixture was extracted with ether and the ether extract was washed with dilute acid and dried. The material obtained on removal of the ether was recrystallized from methanol–water to yield 0.103 g. of XVIIb, m.p. 127–129°. The analytical sample, obtained from methanol–water, was dried at room temperature *in vacuo* and had m.p. 127–129°, $[\alpha]^{25}D$ −49 ± 1° chf. (*c* 1).

Anal. Calcd. for $C_{23}H_{36}O_3$: C, 76.6; H, 10.1. Found: C, 76.4; H, 10.0.

Hydrolysis of XVIIb with alcoholic potassium hydroxide gave XVIIa.

17aβ-Methyl-D-homoandrostan-3,17-dione (XVIII).—The hydroxy ketone XVIIa (0.100 g.) was mixed with CrO_3 (32 mg.), acetic acid (2 ml.) and water (two drops) and allowed to stand at room temperature for 18 hours. Some sodium bisulfite solution was added followed by water. The mixture was extracted with ether, the ether was washed with sodium carbonate solution and dried. The material which remained after removal of the ether was recrystallized from methanol to yield 57 mg. of XVIII of m.p. 192–200° and 12 mg. of m.p. 187–198°. The two crops were combined and sublimed at 120° and 0.001 mm. to yield material which after three recrystallizations from methanol furnished the analytical sample of XVIII, m.p. 198–200°, $[\alpha]^{25}D$ −6 ± 1° chf. (*c* 1, chf.).

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.7; H, 10.2. Found: C, 79.9; H, 10.2.

Infrared Spectra of D-Homosteroids.—The infrared spectra of the D-homosteroids were kindly determined and interpreted by Miss F. Herling of the Sloan–Kettering Institute: compound XVIIa (in CS_2) 1713 cm.$^{-1}$ (17-keto), (in chf.) 3640 cm.$^{-1}$ (OH), 1702 cm.$^{-1}$ (17-keto); compound XVIIb, (in CS_2) 1735 cm.$^{-1}$ (acetate), 1713 cm.$^{-1}$ (17-keto); compound XVIII, (in CS_2) 1717–1714 cm.$^{-1}$.

Quantitative 17-Ketosteroid Determination of D-Homosteroids.—These were carried out at the Sloan–Kettering Institute, through the courtesy of Dr. T. F. Gallagher. The colorimetric determination agrees with structures XVIIa, XVIIb and XVIII. 17-Methyl-17a-keto-D-homosteroids do not give any color in this reaction.

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