was occasionally necessary to carry out a saponification step with 5% methanolic caustic. The product, m.p. 228–233°, was very soluble in hexane and ether but gave thick, hexagonal prism-like forms on recrystallization. The analytical sample thus obtained melted from 233–235° after undergoing crystal transition above 228° to whips, $[\alpha]_D^{25}$ −116° ($CHCl_3$). This compound is 11α hydroxy diosgenin.

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PHILADELPHIA 18, PA.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S.A.]

Steroids. XCVIII.[1] Synthesis of Some 10β-Hydroxy-19-norsteroids

J. PEREZ RUELAS, J. IRIARTE, F. KINCL, AND CARL DJERASSI

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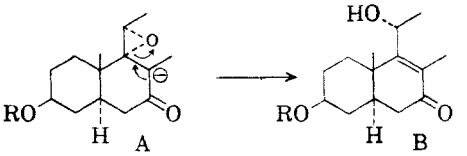
The direction and stereochemistry of the acid- and base-catalyzed opening of 5,10-epoxides of certain 19-norsteroids is discussed and the synthesis of several 10β-hydroxy-19-norsteroids is reported.

The removal of the angular methyl group at C-10 of certain steroids such as progesterone[2,3] or 17α-ethinyltestosterone[4] has led to a marked increase in biological activity. This is particularly noteworthy in the latter compound, 19-nor-17α-ethinyltestosterone (Ib)[4] whose high hormonal activity[1,4] by the oral route has led to the introduction of this compound (Norlutin) into medical practice. It was felt that it might be of interest to examine the effect of other angular substituents upon biological potency and the present paper is concerned with certain 10β-hydroxy-19-norsteroids.

Pederson and collaborators[5] reported recently that microbiological hydroxylation of 19-nortestosterone (Ia)[6] led in poor yield to a 10-hydroxy derivative, whose structure was confirmed by osmium tetroxide hydroxylation[7] of the β,γ-unsaturated precursor IIa[8] of 19-nortestosterone (Ia) followed by dehydration of the intermediate glycol. The stereochemistry of the introduced 10-hydroxyl group was not established by the Upjohn group[5] but conclusive evidence in favor of the 10β-orientation could be provided[9] by noting the coincidence of the rotatory dispersion curve of 10-hydroxy-19-nortestosterone (IVa) with that[10] of 19-nortestosterone (Ia), where the 10β-orientation is established. If the hydroxylation product had been the 10α-isomer VIa, then the rotatory dispersion curve would have been of an antipodal type.[11] Consequently, 10β-hydroxy-19-nortestosterone (IVa) can now be employed as the key reference compound for stereochemical considerations in this series.

Since we were interested in preparing 10β-hydroxy-19-norsteroids which might also bear substituents at C-5 (*vide infra*), the most attractive synthesis of 10β-hydroxy-19-norsteroids might well proceed *via* the 5,10-epoxide (*e.g.*, III) of a 5,10-unsaturated 19-nor-3-ketosteroid (II). In fact, earlier work from this laboratory[12] had demonstrated the facile conversion of the epoxy ketone A by alkaline treatment to the unsaturated hydroxy ketone B and the structural situation should be completely analogous in a 5,10-epoxy-3-ketone (III). Nevertheless, there exists a patent claim[13] that epoxidation of IIa leads to a sharp-melting epoxide (IIIa or Va) which upon exposure to alkali furnishes both C-10 epimeric hydroxy-19-nortestosterones (IVa and VIa). The mechanistic unlikeliness of such a reaction—assuming the epoxide to be homogeneous[14]—prompted us to re-examine the epoxidation of IIa and to establish



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(11) See C. Djerassi, M. Ehrenstein, and G. W. Barber, *Ann.*, **612**, 93 (1958).

(12) C. Djerassi, O. Mancera, J. Romo, and G. Rosenkranz, *J. Am. Chem. Soc.*, **75**, 3505 (1953).

(13) F. B. Colton, U.S. Patent **2,729,654**.

(14) The physical constants of this epoxide are in reasonable agreement with those found in our laboratory for a homogeneous specimen.

precisely the stereochemistry of the resulting epoxide and of its transformation products.

Treatment of $\Delta^5(^{10})$-19-norandrosten-17β-ol-3-one (IIa)[8] with monoperphthalic acid at low temperature furnished in 65% yield a pure epoxide which is assigned the 5β,10β-stereochemistry (IIIa), since upon heating with methanolic potassium hydroxide solution it was transformed smoothly into the known[5,9] 10β-hydroxy-19-nortestosterone (IVa). By the same sequence of reactions, the β,γ-unsaturated isomer IIb[15] of 19-nor-17α-ethinyltestosterone (Ib)[4] was converted into the 5β,10β-epoxide IIIb and rearranged with alkali to 10β-hydroxy-19-nor-17α-ethinyltestosterone (IVb). The 10β-orientation followed from analogy to the course of this reaction sequence in the 19-nortestosterone series (Ia, IIa, IIIa, IVa) and from the fact that its rotatory dispersion curve was nearly identical with that[10] of 19-nortestosterone (Ia).

The predominant formation of the 5β,10β-epoxide (III) is noteworthy since alpha attack is usually favored among steroids and production of the α-epoxide (V) might have been expected. However in the absence of the angular methyl group at C-10, the steric factors controlling approach of the reagent are rather subtle and in particular, it should be noted that the 5α,10α-epoxide would contain the unfavorable 9,10-*syn* backbone in contrast to the 9,10-*anti* situation existing in the β-epoxide III which may well represent the controlling factor.

As has been reported earlier,[1,4] 19-nor-17α-ethinyltestosterone (Ib) is an extremely powerful, orally effective progestational agent. In a preliminary Clauberg assay in rabbits, the 10β-hydroxy analog IVb possessed[16] only about one-fourth the oral progestational activity of Ib. We can conclude tentatively, therefore, that substitution of the C-10 angular methyl group by hydroxyl does not have the biological potentiating effect of substitution by hydrogen.

Introduction of fluorine at various positions of the steroid molecule often results in interesting biological properties[17] and this applies also to progesterone.[18] It was decided, therefore, to prepare some fluorine-containing 19-norsteroids by the boron trifluoride procedure of Henbest and Wrigley,[19] although it was appreciated that fluorohydrins have generally been obtained from trialkylated epoxides while the few tetra-substituted ones[19] led to dienes. In view of the fact that the boron trifluoride–promoted opening of epoxides is very sensitive to electronic and conformational factors[19] no secure *a priori* prediction about the course of this reaction with 3-keto-5,10-epoxides IIIa and IIIb could be made. When the reaction was performed under the conditions reported in the Experimental section, there was isolated in each case in high yield a single, homogeneous fluorohydrin which on the basis of the usual *trans* diaxial opening mechanism of epoxides[20] could only possess structures VIIa and b or VIIIa and b. Of the two alternatives, VII is favored for the reason already advanced above in a discussion of the 5β,-10β-epoxide formation, namely the presence of an *anti* 9,10-backbone[21] in the fluorohydrins VIIa and VIIb. Nevertheless, it was felt that this assignment should be subjected to more secure confirmation and for that purpose, the fluorohydrins VIIa and VIIb were treated with alkali and in each instance yielded the corresponding 10β-hydroxy-Δ^4-3-ketones IVa and IVb. This result tends to support formulations VIIa and VIIb by assuming simple base-catalyzed dehydrofluorination, but it is also possible that the reaction proceeds by initial base-promoted ring closure[22] of the fluorohydrin back to the epoxide III. Since either fluorohydrin VII or VIII would yield the same epoxide III and since the latter has already been shown above to rearrange to the 10β-hydroxy-Δ^4-3-ketone IV, this alternative course weakens the structure proof of the fluorohydrin. As a result, the epoxy ketone IIIa was treated with perchloric acid in acetone solution to yield a glycol, which was not isolated but which dehydrated directly to the 10β-hydroxy unsaturated ketone IVa. The glycol had to possess structure IX or X and since dehydration in this case would not proceed *via* an epoxide, the orientation of the surviving hydroxyl group of the dehydration product must be identical with that in the glycol. Since the dehydration product was identified as the 10β-hydroxy derivative IVa, the precursor must have been the 5α,10β-glycol IX and we feel justified in assuming the identical stereochemical arrangement for the fluorohydrin (VIIa and b).

In connection with the (perchloric) acid opening of the epoxide IIIa, there was also examined the stability of the 10β-hydroxy-Δ^4-3-keto moiety toward acidic reagents since Pederson *et al.*[5] mentioned in a preliminary communication that acid-catalyzed dehydration of 10β-hydroxy-19-nortestosterone (IVa) led to estradiol without giving any details.

(15) F. B. Colton, U.S. Patent 2,725,389.

(16) The substance exhibited anti-estrogenic activity in mice at a dose of 400γ when employing 0.4γ of estrone.

(17) See J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957) and earlier references.

(18) P. Tannhauser, R. J. Pratt, and E. V. Jensen, *J. Am. Chem. Soc.*, **78**, 2658 (1956).

(19) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4596, 4765 (1957).

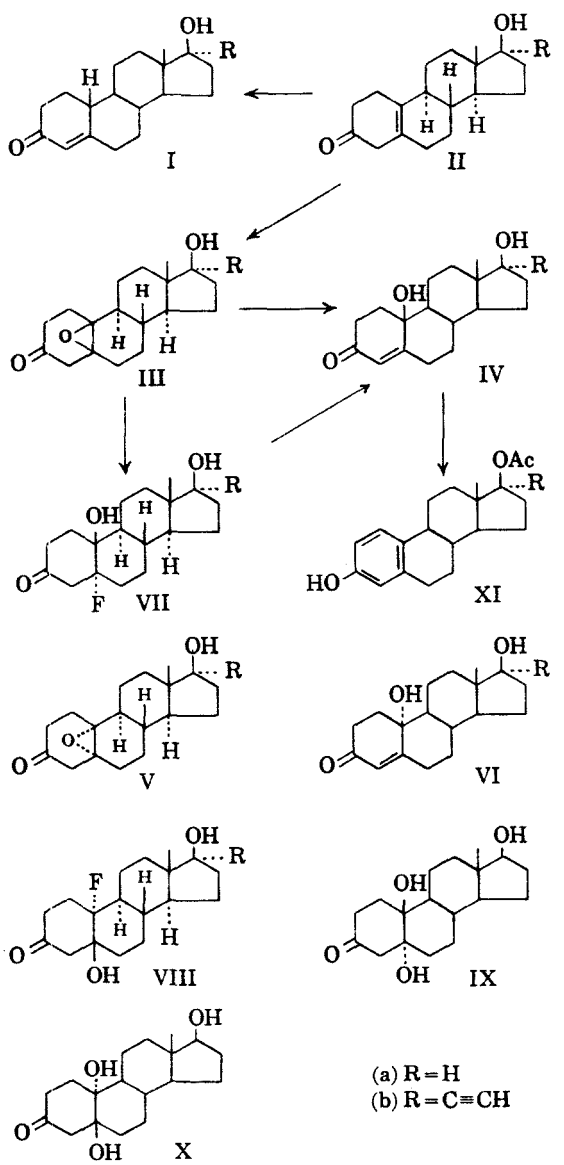
(20) A. Fürst and P. A. Plattner, 12th Internat. Congress Pure and Appl. Chem. New York, 1951, Abstracts, p. 409. For an example of abnormal epoxide opening see W. S. Knowles and Q. E. Thompson, *J. Am. Chem. Soc.*, **79**, 3212 (1957).

(21) The unfavorable *trans-syn-trans* stereochemistry (as in VIII) has already been discussed by W. S. Johnson, *Experientia*, **7**, 315 (1951).

(22) Reformation of a fluorohydrin to the epoxide by means of potassium *t*-butoxide has already been reported by Henbest and Wrigley (ref. 19).

In our hands, exposure of the 17-acetate of 10β-hydroxy-19-nortestosterone to hydrogen chloride–acetic acid at 5–10° effected the dehydration in nearly 80% yield with formation of estradiol 17-monoacetate (XI).

The fluorohydrin VIIb or the epoxy ketone IIIb showed one-fourth or less the oral progestational[23] activity of 19-norethinyltestosterone (Ib).[1,4] 10β-Hydroxy-19-nortestosterone IVa and the fluorohydrin VIIb were examined for androgenic and anabolic activity[24] in immature male rats using testosterone as standard and were found to exhibit anabolic-androgenic ratios of 1.5 and 1.7, respectively.



(23) These assays were carried out at the Endocrine Laboratories, Madison, Wis.

(24) Assays by Dr. Ralph I. Dorfman of the Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

EXPERIMENTAL[25]

5β,10β-Oxido-19-norandrostan-17β-ol-3-one (IIIa). A solution of 400 mg. of $\Delta^{5(10)}$-19-norandrosten-17β-ol-3-one (IIa)[8] in 10 cc. of chloroform was left with 13.8 cc. of a 0.44*N* ethereal solution of monoperphthalic acid at −70° for 2 hr. and then for 18 hr. at 5–10° whereupon the consumption of reagent corresponded to 0.92 molar equivalents. Dilution with water, extraction with ether, washing with bicarbonate solution and water, followed by drying, evaporation, and recrystallization from acetone-benzene furnished 270 mg. of the epoxido ketone, m.p. 204–205°. The analytical sample was obtained from the same solvent pair and exhibited m.p. 208–210°, $[\alpha]_D$ −32, $\lambda_{max}^{CHCl_3}$ 2.74 and 5.83.

Anal. Calcd. for $C_{18}H_{26}O_2$: C, 74.44; H, 9.03; O, 16.53. Found: C, 74.32; H, 9.08; O, 16.47.

10β-Hydroxy-19-nortestosterone (IVa). The above 5β,10β-epoxide IIIa (100 mg.) was heated under reflux for 1 hr. with 15 cc. of a 5% methanolic potassium hydroxide solution, poured into water, extracted with ether and the ether solution washed well with water and dried. Evaporation and recrystallization from acetone-benzene led to 80 mg. of 10β-hydroxy-19-nortestosterone IVa, m.p. 208–210°, $[\alpha]_D$ + 80° (methanol), λ_{max}^{EtOH} 234–236 mμ, log ε 4.12, λ_{max}^{KBr} 3.0 and 6.02 μ. Except for some intensity differences[26] its rotatory dispersion curve (dioxane solution) was identical with that[9] of the microbiological specimen[5] (m.p. 199–205°, $[\alpha]_D$ +76°) and no depression in melting point was observed upon admixture.

Anal. Calcd. for $C_{18}H_{28}O_2$: C, 74.44; H, 9.03; O, 16.53. Found: C, 73.90; H, 8.87; O, 16.94.

Alternatively, 200 mg. of the epoxide IIIa in 20 cc. of acetone was left at room temperature for 16 hr. with 1.5 cc. of 1.5*N* aqueous perchloric acid and then poured into water. After processing in the usual manner followed by recrystallization from acetone-ether there was isolated 140 mg. of 10β-hydroxy-19-nortestosterone, m.p. 208–210°. Identity with the above sample was established by mixture melting point determination and infrared comparison.

5α-Fluoro-10β-hydroxy-19-norandrostan-17β-ol-3-one (VIIa). A mixture of 250 mg. of the epoxide IIIa, 30 cc. of dry benzene, 15 cc. of absolute ether, and 0.5 cc. of boron trifluoride etherate was kept at room temperature for 3 hr., washed with water, dried, and evaporated. Recrystallization of the residue from acetone-benzene furnished 230 mg. of colorless needles, m.p. 203–204°, raised to m.p. 215–217° upon repeated recrystallization, $[\alpha]_D$ −41°; no appreciable ultraviolet absorption, λ_{max}^{KBr} 2.98 and 5.85 μ.

Anal. Calcd. for $C_{18}H_{27}FO_2$: C, 69.65; H, 8.77; F, 6.12. Found: C, 70.01; H, 8.59; F, 5.58.

When 140 mg. of the fluorohydrin was heated under reflux with 5% methanolic potassium hydroxide solution for 1 hr., there was isolated 90 mg. of 10β-hydroxy-19-nortestosterone (IVa).

5β,10β-Oxido-17α-ethinyl-19-norandrostan-17β-ol-3-one (IIIb). The epoxidation of 400 mg. of 17α-ethinyl-$\Delta^{5(10)}$-19-norandrosten-17β-ol-3-one (IIb)[15] was performed exactly as described above for IIa and yielded 350 mg. of the epoxide IIIb, m.p. 168–170°. Further recrystallization from hexane-acetone provided the analytical sample, m.p. 185–187°, $[\alpha]_D$ −75° (methanol), λ_{max}^{KBr} 2.85, 3.05, and 5.85 μ.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 76.40; H, 8.34; O, 15.26. Found: C, 76.63; H, 8.36; O, 15.24.

(25) Melting points are uncorrected. Unless noted otherwise rotations were measured in chloroform solution. All rotation, rotatory dispersion, ultraviolet and infrared measurements were carried out by Dr. L. Throop and staff. The microanalyses are largely due to Mr. Joseph F. Alicino, Metuchen, N. J.

(26) This is probably due to the fact that the product obtained by microbiological hydroxylation[5] was not completely pure as judged also by the melting point.

5α-Fluoro-17α-ethinyl-19-norandrostane-10β,17β-diol-3-one (VIIb). The boron trifluoride reaction of 200 mg. of the epoxide IIIb was carried out as described above for IIIa and after recrystallization from methanol-benzene there was obtained 160 mg. of the fluorohydrin VIIb, m.p. 247–249°, $[\alpha]_D$ −39° (methanol).

Anal. Calcd. for $C_{20}H_{27}FO_2$: C, 71.83; H, 8.14; F, 5.68. Found: C, 71.71; H, 7.99; F, 5.47.

10β-Hydroxy-17α-ethinyl-19-nortestosterone (IVb). This substance was obtained in about 80% yield when the epoxide IIIb or the fluorohydrin VIIb was heated under reflux for 1 hr. with 5% methanolic potassium hydroxide solution. The analytical sample crystallized from acetone or ethyl acetate and exhibited m.p. 263–264°, $[\alpha]_D$ + 4.5° (methanol), λ_{max}^{EtOH} 236 mμ, log ε 4.16, λ_{max}^{KBr} 2.95, 3.05, and 6.04 μ. The rotatory dispersion curve measured in dioxane solution (*c*, 0.059) was typical[27] of a Δ^4-3-ketosteroid with troughs[27] at $[\alpha]_{378}$ −556° and $[\alpha]_{355}$ −665° and a peak at $[\alpha]_{309}$ −604°.

Anal. Calcd. for $C_{20}H_{28}O_2$: C, 76.40; H, 8.34; O, 15.26. Found: C, 76.22; H, 8.35; O, 15.06.

Dehydration of 10β-hydroxy-19-nortestosterone acetate to estradiol 17-acetate (XI). A current of dry hydrogen chloride was passed for 2 hr. at 5–10° through a solution of 200 mg. of 10β-hydroxy-19-nortestosterone 17-acetate[5] (m.p. 182–183°, $[\alpha]_D$ +70°) in 10 cc. of glacial acetic acid. After diluting with water, extracting with ether, washing until neutral, drying, and evaporating there was left a solid residue which was recrystallized from acetone-hexane to give 145 mg. of estradiol 17-acetate (XI), m.p. 217–218.5°. Identity with an authentic specimen[28] was established by mixture melting point determination and infrared comparison.

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(27) For nomenclature see C. Djerassi and W. Klyne, *Proc. Chem. Soc.*, 55 (1957).

(28) C. Djerassi, G. Rosenkranz, J. Romo, S. Kaufmann, and J. Pataki, *J. Am. Chem. Soc.*, 72, 4534 (1950).

[CONTRIBUTION FROM THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, UNIVERSITY OF KANSAS MEDICAL CENTER]

Synthesis of Some 17-Methyl Phenolic Steroids

HAROLD J. NICHOLAS

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17α-Methylestradiol was dehydrated with acid to give a product to which the structure 17-methyl-1,3,5(10),16-estratetraen-3-ol was assigned. The position of the double bond was not established unequivocally. Pd-on-charcoal reduction of the tetraene gave two 17-methyl-1,3,5(10)-estratriene isomers. Neither of the three new compounds was estrogenically active at 5-micrograms in preliminary testing.

Myers *et al.*[1] have stated that "it would be of practical as well as theoretical interest if compounds could be discovered which possess little or no primary hormonal activity, but which still have the ability to modify or regulate endocrine balance." With this general objective in mind several 17-methyl phenolic steroids of the estrane series were prepared; in preliminary testing the substances were estrogenically inactive at a 5 microgram level. One of the compounds has been mentioned in the early literature, but was never properly characterized.

The starting material for their preparation was 17α-methyl estradiol, which has been adequately characterized and tested;[2-4] it is about equal in estrogenic activity to 17β-estradiol. It has been reported[5] that dehydration of 17α-methylestradiol in boiling acetic acid, followed by high vacuum sublimation gives rise to a substance, m.p. 157–159°, having the structure shown in either IIa or III. In our hands treatment of 17α-methylestradiol (I) with either hot acetic acid or hydrochloric acid gave a crystalline mixture which could not be resolved by fractional crystallization. Chromatography on Celite–Mg trisilicate afforded a quantitative separation of unreacted I and a second crystalline substance. The latter when purified melted at 162–162.5°. Julia and Heusser[6] in a somewhat analogous procedure in the androstane series, dehydrated 17-methyl-5-androstene-3β, 17β-diol-3-acetate by mild treatment with phosphorus oxychloride–pyridine and (as the diacetate) by treatment with acetic anhydride–pyridine. In both cases a mixture of 17-methyl and 17-methylene dehydration products were obtained, the latter identified by its characteristic methylene absorption in the infrared at 11.36μ and 6.03μ. Only one product (besides a small amount of unreacted starting material) was found on dehydrating 17α-

(1) T. C. Myers, R. J. Pratt, R. L. Morgan, J. O'Donnell, and E. V. Jensen, *J. Am. Chem. Soc.*, 77, 5655 (1955).

(2) Elsevier's *Encyclopedia of Organic Chemistry*, Series III, Vol. 14, Supplement, Elsevier Publishing Company, New York, N. Y., 1956, p. 1988s. Several foreign patents are mentioned in this reference. Only the melting point of the free compound is given for characterization.

(3) H. H. Inhoffen and G. Zuhlsdorff, *Ber.*, 74, 604 (1941).

(4) B. C. Bocklage, H. J. Nicholas, E. A. Doisy, Jr., W. H. Elliott, S. A. Thayer, and E. A. Doisy, *J. Biol. Chem.*, 202, 27 (1953).

(5) Elsevier's *Encyclopedia of Organic Chemistry*, Series III, Vol. 14, Supplement, Elsevier Publishing Company, New York, N. Y., 1954, p. 1514s. Several foreign patents herein cited give only the m.p. of the free compound. Possible preparation of the compound is mentioned in Ref. 4.

(6) S. A. Julia and H. Heusser, *Helv. Chim. Acta*, 35, 2080 (1952).