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STEROIDS CCLXVIII.(1) STEROIDS OF UNNATURAL CONFIGURATION: A NEW ROUTE TO 9β,10α-19-NORSTEROIDS

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Except for totally synthetic methods,(2) the preparation of 9β,10α-19-norsteroids (19-nor-retrosteroids) from natural steroid precursors has been recorded in only one instance.(3) We wish to describe a new route to this interesting class of 19-nor-steroids which is exemplified by the synthesis of 17β-hydroxy-9β,10α-estr-4-en-3-one (19-nor-retrotestosterone) (I).(2)

The success of the synthesis was dependent upon the realization of two predictions: first, that the strong steric interactions on the β-face of a 3β-substituted 5α,10α-19-nor-steroid-11-ketone could find relief in epimerization at C-9, in spite of the α-face proton-proton interactions which develop; second, that the resultant 5α,9β,10α-19-norsteroid-11-ketone would brominate preferentially and axially at C-12.**

Hydrogenation of 11α-hydroxyestradiol(5) over ruthenium

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**These predictions were based on standard principles of conformational analysis(4) and on a consideration of the likely mechanism of bromination. The lines of reasoning will be presented in our full paper.

oxide$^{(6)}$ furnished 5α,10α-estrane-3β,11α,17β-triol (IIa) (m.p 250-251°; $(\alpha)_D$ -44° (pyridine). Found: C, 73.39; H, 10.45; O, 16.50) which was oxidized with 8N chromium trioxide to the 3,11,17-trione (IIb) (m.p. 183-184°; $(\alpha)_D$ -1° ($CHCl_3$); ν_{max}^{KBr} 1750, 1725 and 1700 cm^{-1}. Found: C, 75.19; H, 8.50; O, 16.58). Brief exposure (15 min.) of the trione to an excess of lithium tritertiarybutoxy aluminum hydride in boiling tetrahydrofuran gave 3β, 17β-dihydroxy-5α,10α-estran-11-one (IIc) (m.p. 235-237°; $(\alpha)_D$ -70° (pyridine); ν_{max}^{KBr} 3300 and 1700 cm^{-1}. Found: C, 74.17; H, 9.79; O, 16.65) also characterized as the 3,17-diacetate (IId) (m.p. 190-192°; $(\alpha)_D$ -60° ($CHCl_3$); ν_{max}^{KBr} 1740, 1700 and 1250 cm^{-1}. Found: C, 70.02; H, 8.68; O, 21.48).

Treatment of the dihydroxy ketone (IIc) with boiling 2% methanolic sodium hydroxide (72 hr.) afforded a 2:1 mixture of starting material and the key intermediate 3β,17β-dihydroxy-5α,9β,10α-estran-11-one (IIe)* (m.p. 230-232°; $(\alpha)_D$ +42° (pyridine); ν_{max}^{KBr} 3350 and 1700 cm^{-1}. Found: C, 73.99; H, 9.73; O, 16.62) which was further characterized as the 3,17-diacetate (IIf) (m.p. 158-159°; $(\alpha)_D$ +39° ($CHCl_3$); ν_{max}^{KBr} 1740, 1700 and 1250 cm^{-1}. Found: C, 69.81; H, 8.69; O, 21.58). The 9β stereochemistry in IIe follows from the optical rotatory dispersion curve of its diacetate,** its reconversion in part to the 9α-ketone on treatment with base and from subsequent

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*In a single equilibration the 9β isomer was isolated in ca. 25% yield. However by recycling the recovered starting material once the yield of IIe could be raised to 40%.

**The 3β,17β-diacetoxy-5α,9α,10α-estran-11-one (IId) was characterized by a weakly negative rotatory dispersion curve. In contrast, the 9β-keto diacetate (IIf) showed, as expected, a strongly positive Cotton effect curve (at the peak, $(\Phi)_{325}$ +5900°) since in this isomer the C_9-C_{10} (axial) bond now occupies a positive octant.

reactions. Thus the predicted epimerization had taken place.

Conversion of the 9β,11-keto diacetate (IIf) to 19-nor-retrotestosterone was achieved by treatment with bromine in acetic acid and reduction of the resulting 12α-bromo compound (IIIa)* (m.p. 172-173°; $(\alpha)_D$ -52° ($CHCl_3$); ν_{max}^{KBr} 1740, 1710 and 1250 cm^{-1}. Found: C, 58.03; H, 6.94; Br, 17.77; O, 17.48) with lithium borohydride(7) in tetrahydrofuran to 12α-bromo-5α,9β,10α-estrane-3β,11ξ,17β-triol 3,17-diacetate (IIIb) (m.p. 190-191°; $(\alpha)_D$ ±0° ($CHCl_3$); ν_{max}^{KBr} 3450, 1740-1720 and 1260- 1230 cm^{-1}. Found: C, 57.95; H, 7.38; Br, 18.41). Treatment of the bromohydrin with zinc in acetic acid furnished the 9β-Δ^{11}-olefin (IVa) (m.p. 111-112°; $(\alpha)_D$ -95° ($CHCl_3$); ν_{max}^{KBr} 1740, 1250 and 750 cm^{-1}. Found: C, 73.01; H, 9.11; O, 17.71) with resonances in the n.m.r. corresponding to two <u>cis</u> olefinic protons as the AB portion of an ABX system. Catalytic hydrogenation of the olefin followed by hydrolysis of the non-crystalline dihydro compound (IVb) produced 5α,9β,10α-estrane-3β,17β-diol (IVc) (m.p. 209-210°; $(\alpha)_D$ ± 0° (pyridine); ν_{max}^{KBr} 3350 cm^{-1}. Found: C, 77.83; H, 10.94; O, 11.58).

Selective oxidation of the foregoing diol at C-3 with platinum and oxygen(8) in aqueous acetone provided 17β-hydroxy-5α,9β,10α-estran-3-one (IVd) (m.p. 213-214°; $(\alpha)_D$ ± 0° ($CHCl_3$). ν_{max}^{KBr} 3450 and 1705 cm^{-1}. Found: C, 77.20; H, 10.18; O, 12.78**). Low temperature bromination(9) of the monoketone (IVd) followed by immediate dehydrobromination (calcium carbonate in dimethyl-

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*This substance exhibited a negative Cotton effect curve ($(\Phi)_{350}$ -4830°; at the trough).

**This substance retained 0.25 mole of methanol of crystallization after drying at 70° for 72 hr.

formamide) gave 19-nor-retrotestosterone (I)* (m.p. 224-225°; $(\alpha)_D$ -89° (EtOH); λ_{max}^{EtOH} 243 mμ (log ε 4.22); ν_{max}^{KBr} 3500, 1660 and 1610 cm^{-1}. Found: C, 78.84; H, 9.45; O, 11.85). The identities of both 19-nor-retrotestosterone (I) and 17β-hydroxy-5α,9β,10α-estran-3-one (IVd) were rigorously checked (mixed m.p., $(\alpha)_D$, O.R.D., i.r., u.v., and gas chromatographic behavior comparisons) against samples synthesized by an alternative route. 3-Methoxy-estra-1,3,5(10),9(11)-tetraen-17-one (Va)** was converted to the 17-cycloethylene ketal Vb(10) and the latter successively hydrogenated and hydrolyzed with aqueous acid to afford 3-methoxy-9β-estra-1,3,5(10)-trien-17-one (Vc)*** (m.p. 85-86°; $(\alpha)_D$ +32° ($CHCl_3$); λmax 280 and 288 mμ (log ε 3.33 and 3.28); ν_{max}^{KBr} 1740, 1610 and 1580 cm^{-1}. Found: C, 80.43; H, 8.51; O, 11.38). Reduction with lithium and ammonia followed by acid hydrolysis gave 19-nor-retrotestosterone (I) (m.p. 224-225°; $(\alpha)_D$ -88° (EtOH). Hydrogenation then afforded a mixture from which 17β-hydroxy-5α,9β,10α-estran-3-one (m.p. 213-214°; $(\alpha)_D$ ± 0° ($CHCl_3$) was obtained by chromatographic separation.

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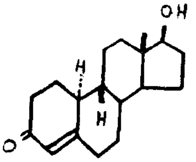
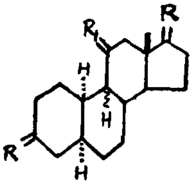
* Reported(2) for a sample prepared by total synthesis and resolution of the dl racemic mixture, m.p. 223° $(\alpha)_D$ -86° (EtOH).

** Prepared by the action of chloranil on estrone methyl ether in refluxing dioxan and t-butyl alcohol(10).

***The dl racemate has been prepared by total synthesis(11).



I.



II. a) 9α; R=αH,βOH; R_1=αOH,βH

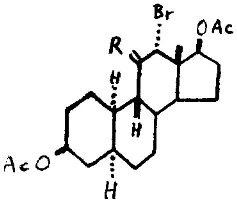
b) 9α; R=R_1 = O

c) 9α; R=αH,βOH; R_1=O

d) 9α; R=αH,βOAc; R_1=O

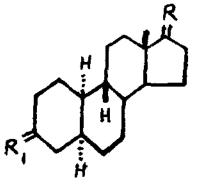
e) 9β; R=αH,βOH; R_1=O

f) 9β; R=αH,βOAc; R_1=O



III. a) R = O

b) R = H,OH

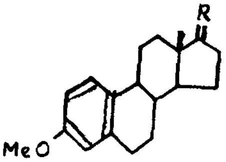


IV. a) 11,12-double bond; R=R_1=αH,βOAc

b) R=R_1 = αH,βOAc

c) R=R_1 = αH,βOH

d) R = αH,βOH; R_1=O



V. a) $\Delta^{9(11)}$; R=O

b) $\Delta^{9(11)}$; R= 

c) 9βH; R=O

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