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THE PREPARATION AND CHEMISTRY OF THE 10α-ESTRA-4-EN-3-ONES

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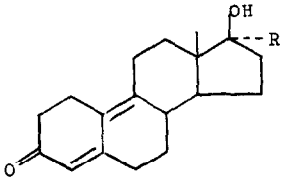
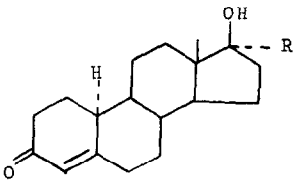
Recent work toward the preparation of biologically active steroids has resulted in several compounds with interesting biological properties whose structures possess unnatural stereochemistry at various ring-juncture carbons of the steroid nucleus. The preparation and biological activity of 9β,10α-pregna-4,6-diene-3,20-dione (1) is an example of the interesting changes in biological properties that can result by modification of the stereochemistry of the nucleus. Other representative compounds possessing unnatural stereochemistry that have been prepared include: 10α-testosterone (2); various 5α,10α-estranes (3a and b); 9β,10α-19-nor steroids (4a and b); 9β-progesterone (5); and 19-hydroxy-10α-testosterone (6). Here we will describe the preparation and chemistry of the 10α-estra-4-en-3-ones.

Utilizing the selective partial catalytic hydrogenation of a dienone (7), the substituted estra-4,9(10)-dien-3-ones (I) (8) were reduced with one equivalent of hydrogen to give in 20-30% yield the corresponding 4-en-3-ones (II) using palladium supported on barium sulfate or alumina catalyst and alcohol solvent. Small amounts of the appropriately substituted 5α,10α-estrane

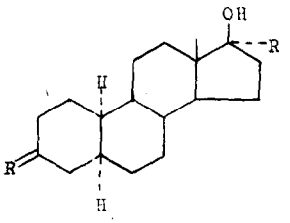
(III) were also isolated. In general, higher yields, 60-80%, of the 10α-4-en-3-ones can be obtained through the use of 2% palladium supported on strontium carbonate catalyst with benzene as the solvent (7). Because of solubility differences, these alternate conditions were not applicable in all cases.



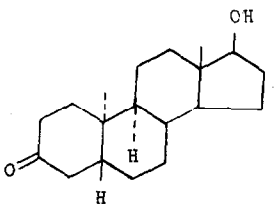
Ia, R = H
Ib, R = CH_3



IIa, R = H
IIb, R = CH_3



IIIa, R = H
IIIb, R = CH_3



IV

The 10α-19-nortestosterone (IIa) obtained, m.p. 172-173° C.; $\lambda_{max.}^{EtOH}$ 245; ϵ 15,800, has an R.D. curve almost identical to the corrected curve for 10α-testosterone (2). The $\pi - \pi^*$ region of this curve, which indicates the chirality of the chromophore (9), shows a negative Cotton effect.

This result can best be accommodated with the B ring assuming a boat form and the A ring the half-chair conformation which has the 2α and 10α protons cis and diaxial. This conformation can be considered as a limiting structure with small alterations in this conformation occurring in order to minimize the various resultant strain interactions.

In the N.M.R. spectrum of IIa, the 18-methyl protons are shifted upfield with their resonance occurring at 42 c.p.s. as compared to a chemical shift of 50 c.p.s. for the corresponding protons of 19-nortestosterone. This upfield position is in agreement with the B-ring boat conformation since the 18-methyl group is situated on the concave surface of the molecule which results in increased shielding.

The 10α-19-nortestosterone can readily be isomerized to 19-nortestosterone by treatment with hydrogen chloride in chloroform or with potassium butoxide solution. These experiments indicate the relatively greater stability of this latter stereochemistry. Further support for the 10α structure assignment was obtained by catalytic hydrogenation of the remaining double-bond which gives the known 5α,10α-estran-3-one-17β-ol (IIIa) (3a and b) in high yield.

Acetylation results in preparation of 10α-19-nortestosterone acetate, m.p. 143-144° following the usual conditions indicating the system is stable to pyridine. Oxidation (10) of the parent compound (IIa) in pyridine similarly gives high yields of 10α-estra-4-ene-3,17-dione, m.p. 162-164°.

Metal-ammonia reduction of 10α-19-nortestosterone (IIa) resulted in preparation of two estranes; one isomer, the 5β,9α,10α-estrane (IV), m.p. 121-122° C., was obtained in about 60% yield. IV gave an R.D. curve having a negative Cotton effect, $[\alpha]_{314} = -1022$, in agreement with Octant Rule (11) predictions. The other isomer, IIIa, 5α,10α-estran-3-one-17β-ol, was obtained in 20% yield. The preparation of the strained 5β,10α-estrane accompanied by the all-chair 5α,10α-estrane presents an interesting result when viewed in the context of recent discussions of the stereochemistry of the products from this type of reduction (12a, b, and c).

Hydrogenation of 17α-methylestra-4,9(10)-dien-3-one-17β-ol (Ib) affords 17α-methyl-10α-estra-4-en-3-one-17β-ol (IIb), m.p. 193-195° ($\lambda_{max.}^{243}$ 16,400). The R.D. and N.M.R. spectra contain the salient features of the parent compound (Ia). The over-reduction product, 17α-methyl-5α,10α-estran-3-one-17β-ol (IIIb), was isolated as a side product.

Other derivatives of this novel system are currently being prepared.

The 10α-19-nortestosterone in biological assays gives a spectrum of activity differing from that of 19-nortestosterone. The 10α isomer shows no androgenic activity while maintaining high pituitary gonadotrophin inhibitory activity. A weak uterotrophic response was also noted (13).

Satisfactory elemental analyses were obtained for all new compounds.

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13. The biological assays were performed by Drs. R. J. Kraay and D. M. Brennan. Additional biological data will be published elsewhere.