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CONFORMATIONAL PREFERENCE IN RING A OF RING B-AROMATIC STEROIDS

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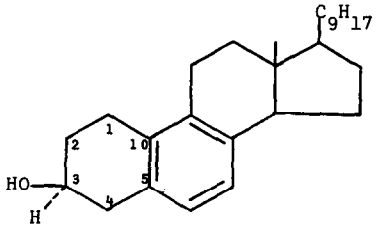
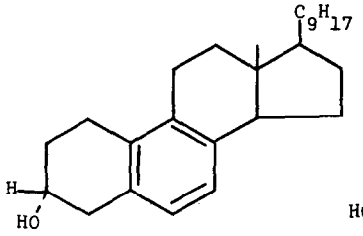
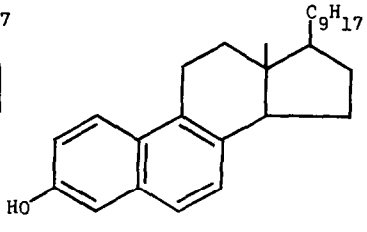
Our interest in conformational preference effects in ring A of 5(10)-unsaturated steroids (1) has led us to investigate the case of ring B aromatic steroids represented by neoergosterol(I) (2) and epineoergosterol(II) (3). It has already been deduced (4) from infrared spectral data that the epimeric hydroxyl substituents in I and II are both equatorial, suggesting that the respective conformations of ring A are as I' and II'. In agreement, we have concluded from inspection of models that these alternative half-chair conformers are about equally free of destabilizing interactions. In this light, however, it is difficult to explain the exclusive production (3) of II by treatment of "dehydroneoergosterol" III or neoergosterol itself with sodium in boiling amyl alcohol; the apparent stereoselectivity of these processes would seem to require a considerable degree of conformational preference for ring A in the ring B aromatic system. Our attempt to resolve this paradox began with the synthesis of epineoergosterol(II) by a new method.



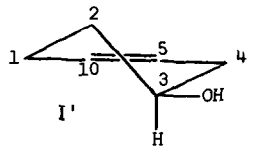
I



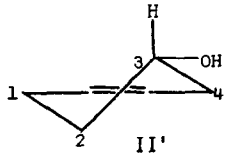
II



III



I'



II'

A sample of neoergosterol (m.p. 151-152°, $[\alpha]_D$ -6.0°) (5), after conversion to the 3-methanesulfonate IV* (6), m.p. 110-111°, was subjected to displacement by tetraethylammonium formate (7) in refluxing dry acetone. The resulting 3α-formate ester (V) was briefly heated with sodium bicarbonate in aqueous methanol, giving epineoergosterol (II)*, m.p. 173-174° [Lit. (3), m.p. 177°]. This is the first preparation of epineoergosterol to employ only stereospecific reactions. Using this product the following observations were made.

(a) Epineoegosterol, prepared as above, has $[\alpha]_D$ +50.7° whereas the highest value previously reported is +27°.

(b) The NMR spectra of neoergosterol and epineoergostergosterol are very similar. In the 6τ region (Fig. 1) a broad absorption pattern for the C-3 proton is observed

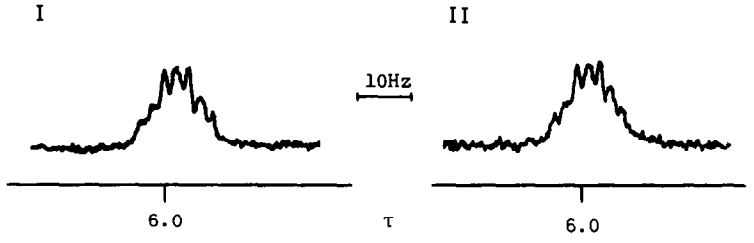


Fig. 1

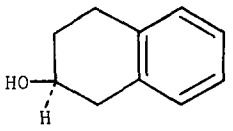
Partial NMR Spectra of Neoergosterol (I) and Epineoergosterol (II) at 100 Mc

in both cases, thus verifying that the OH groups are largely equatorial (axial protons) in both compounds. The infrared spectra of the two epimers are also almost identical.

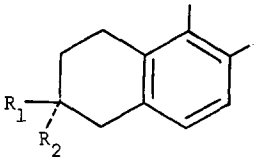
(c) Mixtures of neoergosterol and epineoergosterol gave no significant melting point depression and were not separable in our hands by any of the common chromatographic techniques.

From the above results we conclude that previous preparations of epineoergosterol have, in fact been mixtures of the epimeric 3-alcohols containing approximately 58% epineoergosterol based on the molecular rotation.

The ratio of epineoergosterol to neoergosterol was not greatly increased by conducting the synthesis under conditions of high stereoselectivity. Neoergosterone (8), m.p. 115° (from neoergosterol and the Jones' chromic acid reagent) was reduced with lithium tri-t-butoxyaluminum hydride in tetrahydrofuran at -70°. The resulting 3-alcohol mixture had m.p. 174-176° and $[\alpha]_D$ +30.3°, corresponding to 63% epineoergosterol.



VII



IV $R_1 = O_3SCH_3$, $R_2 = H$

V $R_1 = H$, $R_2 = OCHO$

VI $R_1, R_2 = O$

VIII $R_1 = R_2 = H$

The absolute configuration of (-)-β-tetralol($[\alpha]_D$ -72°) has very recently been determined (9) to be S as shown (VII). This is in qualitative agreement with the more negative rotation of neoergosterol (3-S) as compared with epineoergosterol (3-R).

Allowing that neoergosterol and epineoergosterol are both largely equatorial alcohols with opposite ring A conformation, it follows (Brewster's method (10)) that a ring A unsubstituted substance should have an optical rotation about midway between those of the epimeric alcohols. This was found to be the case. Neoergosterol mesylate IV, with lithium aluminum hydride, gave desoxyneoergosterol (VIII)*, m.p. 107-108°, $[\alpha]_D$ + 22.3°.

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