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# CONFORMATION AND PROPERTIES OF $\Delta^{5(10)}$-STEROIDS (1)

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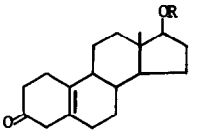
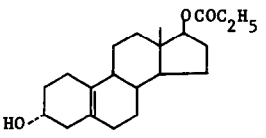
THE $LiAlH_4$ reduction of 17β-hydroxy-$\Delta^{5(10)}$-estrene-3-one (I, R = H) is reported to give mainly a single 3-alcohol, m.p. 208-209° (2). We considered this result (confirmed in our laboratory) to be surprising since the expected alternation of ring A between two half-chair conformers (3) would seem to preclude any net conformational control (4) over the direction of hydride attack. A first step toward understanding the selectivity of this reaction would be to establish unambiguously the C-3 configuration of the resulting diol. Our further work was done largely on 17-acylated steroids to facilitate chromatographic separations.




I

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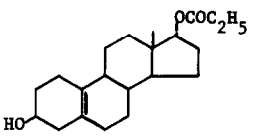



III

17β-hydroxy-$\Delta^{5(10)}$-estrene-3-one propionate (I, R = $COC_2H_5$) was treated with $LiAl(Ot\text{-}Bu)_3H$ in tetrahydrofuran at 25°. Chromatography of the reduction products on alumina gave epimer A (81-83%), m.p. 111-112°, $[\alpha]_D^{CHCl_3}$ +134° and epimer B (13-15%), m.p. 115-117°, $[\alpha]_D^{CHCl_3}$ +74. Saponification of the major epimer (A) produced an unsaturated diol, m.p. 205-207°, $[\alpha]_D^{CHCl_3}$ +186°, identical with the $LiAlH_4$ reduction

product of 17β-hydroxy-$\Delta^{5(10)}$-estren-3-one. Saponification of the minor epimer (B) gave a new unsaturated diol, m.p. 130-132°, $[\alpha]_D^{CHCl_3}$ +112°.

The 3-alcohol A was converted to a mixture of A/B cis 3,5,10-triols by treatment with $OsO_4$ in benzene. Chromatography on silica gel gave triol $A_1$, m.p. 201-202.5°, $[\alpha]_D^{CHCl_3}$ +14°, and triol $A_2$, m.p. 191-193.5°, $[\alpha]_D^{CHCl_3}$ +30°. Epimer B was similarly converted to triol $B_1$, m.p. 150.5-152°, $[\alpha]_D^{CHCl_3}$ +19° and triol $B_2$, m.p. 149.5-150.5°, $[\alpha]_D^{CHCl_3}$ +23°.

TABLE I

| Cpd. | Structure | $C_3$-H Conformation | Chemical Shift (τ) | $W_{1/2}$ (Cps) (approx.) |
|---|---|---|---|---|
| $A_1$ | IV | axial | 5.92 | 20 |
| $A_2$ | V | axial | 6.30 | 22 |
| $B_1$ | VI | equat. | 5.99 | 8 |
| $B_2$ | VII | equat. | 5.88 | 8 |
| A | II | (axial) | 6.23 | 19 |
| B | III | (equat.) | 6.00 | 11 |
| Lit. values for $C_1$-H of subst. cyclohexanols (5,6) | | equat. | ~5.9 | 7 |
| | | axial | ~6.4 | 20-22 |

The NMR spectra of the four isomeric $OsO_4$ products were examined with particular attention to the region from 5 to 7τ in which protons of the type -$\underline{C}$H(OH) are visible.* Table I records the chemical shift (τ) and half-height width ($W_{1/2}$) of this signal for the $C_3$-proton of these triols (and for the parent alcohols). It will be noted that isomers $A_1$ and $A_2$ each give rise to a broad band ($W_{1/2}$~21 c.p.s.) characteristic of axial protons whereas the relatively narrower ($W_{1/2}$~8 c.p.s.) $C_3$-H signal found for isomers $B_1$ and $B_2$ must arise from equatorial (weakly

*The 17α-proton signal (triplet) appears at approximately 5.4τ in each case; all spectra were run in $CDCl_3$ with internal TMS reference (τ = 10.00).

coupled) protons (5).

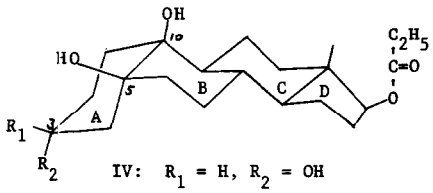
It is clear from steroid models that a C-3 axial proton will possess a 3β-configuration in either of the two (all chair) A/B cis systems. Correspondingly, a $C_3$-equatorial proton will have a 3α-configuration in each of the A/B cis ring systems. It follows that the $OsO_4$ products $A_1$ and $A_2$ both possess a 3β-proton (3α-OH) and that the predominant hydride reduction product (A) is 3α,17β-dihydroxy-$\Delta^{5(10)}$-estrene-17-propionate (II).* Similarly, the isomeric triols $B_1$ and $B_2$ must be 3β-alcohols and the minor reduction product (B) is 3β,17β-dihydroxy-$\Delta^{5(10)}$-estrene-17-propionate (III).

The C-3 configurations assigned to the four 3,5,10-trihydroxy-17-propionates on the basis of half-height line width are also seen (Table I) to be in accord with the corresponding chemical shift values except for triol $A_1$. This compound gives rise to a signal at 5.92 τ, approximately 0.5τ toward low field from the expected position. We propose that this deshielding effect is caused by the presence of a C-5 hydroxyl group located 1,3-cis, diaxial with respect to the proton in question. In confirmation, we have found that the axial 3α-proton of cholestane-3β,5α-diol appears at 5.86τ (7).

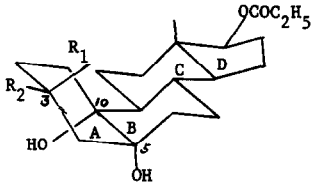
A 1,3-cis relationship between the $C_3$-H and $C_5$-OH of isomer $A_1$ would identify it as the 3α,5β,10β-triol (IV). This structure was confirmed by the following transformation. Catalytic oxidation ($O_2$/Pt in HOAc) of triol $A_1$ to a 3-ketone (not further characterized) followed by treatment with KOH in $CH_3OH$ gave 10β-hydroxy-19-nor-testosterone, m.p.

*Drs. A. Bowers and A. D. Cross have concluded that sodium borohydride reduction of $\Delta^{5(10)}$-estrene-3,17-dione also gives mainly the 3α-alcohol. We wish to thank the above investigators for this information and for providing a comparison sample of their reduction product, m.p. 203-205° undepressed on admixture with our sample of 3α,17β-dihydroxy-$\Delta^{5(10)}$-estrene, m.p. 205-207°, obtained by saponification of the 17-propionate II.

213-217°, identical (by IR and mixture m.p.) with an authentic sample.* The assignment of structure IV to the triol $A_1$ now requires that we formulate the companion product $A_2$ as the 3α,5α,10α-triol V.




IV: $R_1$ = H, $R_2$ = OH
VI: $R_1$ = OH, $R_2$ = H



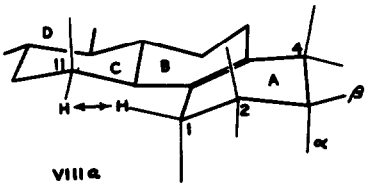

V: $R_1$ = H, $R_2$ = OH
VII: $R_1$ = OH, $R_2$ = H

Of the four well characterized 3-monoacetates which could be prepared from triols IV, V, $B_1$ and $B_2$, only the one derived from the 3β,5,10-triol $B_1$ displayed an acetate carbonyl band in the infrared (1752 $cm.^{-1}$) separate from 17-propionate absorption (1738 $cm.^{-1}$). This high frequency shift must result from H-bonding between the ether oxygen of the axial 3β-acetoxy group and a hydroxyl group situated in a 1,3-cis, diaxial relationship (8). This finding requires that isomer $B_1$ be assigned the 3β,5β,10β-triol structure VI; isomer $B_2$ must then be the 3β,5α,10α-triol (VII).

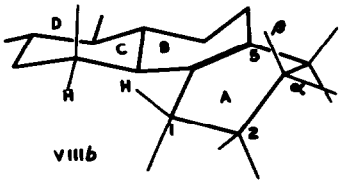
We propose that the observed stereoselectivity in hydride reduction of 3-keto-$\Delta^{5(10)}$ steroids has its basis in the existence of a preferred conformation of ring A. Inspection of Dreiding models reveals that one of the two expected half-chair conformations of ring A involves a particularly severe non-bonded interaction (indicated by the double-headed arrow in VIIIa) between the equatorial 11α-H and the quasi-equatorial 1β-H. This internuclear distance, estimated from measurements (9) on

*Kindly supplied by Dr. A. D. Cross, Syntex, S. A.

the model, is approx. 1.8 Å. The alternative half-chair form (VIIIb) appears to be free of any serious repulsion effects. In the latter (presumably preferred) conformation of the molecule, a 3α-substituent is equatorial and a 3β-substituent is axial. The preferential reduction of a $\Delta^{5(10)}$-3-ketone to the 3α-alcohol then follows from the amply demonstrated property of the common hydride reducing agents to produce a preponderance of the equatorial alcohol from an unhindered ketone (4).



VIII a



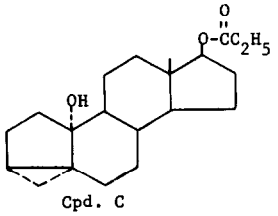
VIII b

Diret evidence for conformational preference in ring A of $\Delta^{5(10)}$-steroids has been provided by spectral data. The line width and chemical shift values (Table I) for the epimeric alcohols II and III are seen to approach the values typical for axial and equatorial protons, respectively. In addition, the IR spectrum (O-H stretching region)* of the "equatorial" alcohol II displayed only a single sharp band at 3625 $cm.^{-1}$ whereas the "axial" alcohol III gave rise to a main band at 3628 $cm.^{-1}$ and a shoulder at 3605 $cm.^{-1}$, indicative of OH to olefin H-bonding (cf. epicholesterol: main band at 3619 $cm.^{-1}$, shoulder at 3589 $cm.^{-1}$) (10).

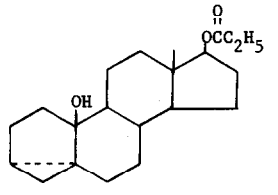
An attempt to uncover chemical evidence for conformational preference in ring A has led to new findings of particular interest. The 3α-alcohol II was converted to the corresponding 3α-mesylate (IX), m.p. 115-116°, $[\alpha]_D^{CHCl_3}$ +118°; the 3β-alcohol III afforded a 3β-mesylate (X), m.p. 83.5-

*We are very grateful to Dr. H. Fales for these high resolution measurements ($CCl_4$ solvent) and their interpretation.

85.5°, $[\alpha]_D^{CHCl_3}$ +69°. Both mesylates were subjected to solvolysis in buffered, aqueous acetone at 80°. The 3α-mesylate gave cpd. C (32% yield), m.p. 131-132.5°, $[\alpha]_D^{CHCl_3}$ +17° and the 3β-mesylate gave cpd. D (39%), m.p. 113-114°, $[\alpha]_D^{CHCl_3}$ +63°. (The other products, in each case, consisted almost entirely of the 3-alcohols II and III as well as diene elimination products.) Cpds. C and D were (a) isomeric with the original $\Delta^{5(10)}$-3-ols (b) U.V. transparent down to 200 mμ (c) alcohols, $\nu_{max}$ 3600 cm.$^{-1}$ (d) unattacked by $CrO_3$/pyridine or $AC_2O$/pyridine. The IR spectra of both compounds showed bands at 3030-3070 cm.$^{-1}$ and the NMR spectra included multiplets at 9-10τ, indicating the presence of cyclopropane hydrogens in cpds. C and D. These results point to 10-hydroxy-3,5-cyclosteroid structures for cpds. C and D, and tentative analogy with the stereochemistry of the familiar "i-steroid rearrangement" would call for configuration assignments as in formulas XI and XII (11).




Cpd. C




Cpd. D

Participation by the $\Delta^{5(10)}$ double bond was also evidenced by enhanced rates of solvolysis of the 3α- and 3β-mesylates in buffered HOAc at 80°. These kinetic results and the details of product composition will be included in a full report along with further chemical evidence bearing on the structures and conformations of the 3,5-cyclosteroid solvolysis products.

Satisfactory elemental analyses were obtained for all new compounds.

Thin layer chromatography was routinely employed to distinguish isomeric products and as a general index of purity.

Acknowledgement. We take pleasure in thanking Dr. M. E. Wall, Director of this Laboratory, for his encouragement and stimulating discussions throughout the course of this work.

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