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# THE SYNTHESIS OF NOVEL BRIDGED A RING STEROIDS

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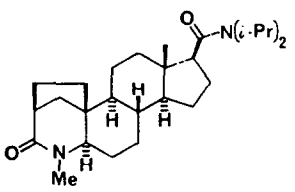
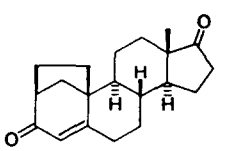
*Summary: The novel bridged A ring steroid 1 was synthesized as a potential inhibitor of steroid 5α-reductase. The structure of the key synthetic intermediate, pentacyclic enedione 2 was confirmed by x-ray analysis.*

In connection with an interest in the inhibition of steroid 5α-reductase[1] we were intrigued by a recent report of Rasmussen *et al*[2] that in a series of 4-aza steroid inhibitors, the 19-nor analog demonstrated considerable inhibitory activity against the rat prostatic enzyme. As the x-ray structure of 19-nortestosterone shows that the A ring arches upward in the β direction relative to testosterone itself,[3] and making the assumption that this effect would hold true for both the solution conformation and the 4-aza series we decided to synthesize a novel bridged 4-aza steroid 1. It was anticipated that the bridge would eliminate the known flexibility of 19-nor steroids,[3] and as a consequence of the constraint between C-2 and C-10, would promote upward arching of the A ring relative to the parent. This latter prediction was supported by MM2 calculations using the SYBYL molecular modelling system.[4] The synthesis of 1 was projected to proceed *via* the novel bridged analog 2 of androst-4-ene-3,17-dione. Since androst-4-ene-3,17-dione is a substrate for enzymes such as steroid 5α-reductase and aromatase, the effect of 2 on these enzymes was also considered to be of interest.

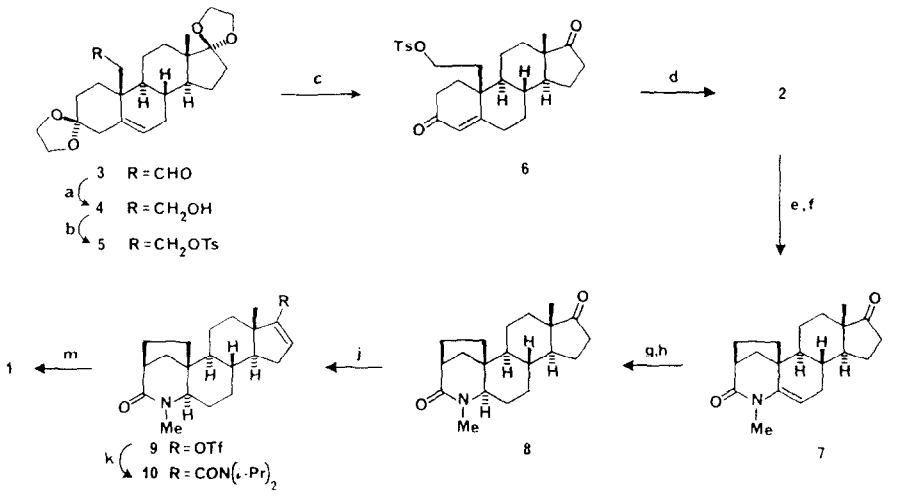



1




2

SCHEME 1




Reagents: (a) $NaBH_4$, EtOH, 0°C; (b) *p*-TsCl, pyr., 0°C; (c) *p*-TsOH, acetone; (d) LDA, THF/hexane, -78°C→r.t.; (e) $KMnO_4$, $NaIO_4$, $H_2O$/t-BuOH; (f) $MeNH_2$, ethylene glycol, Δ; (g) $H_2$, $PtO_2$, AcOH; (h) Jones' oxidation; (j) $(CF_3SO_2)_2O$, 2,6-di-t-butyl-4-methylpyridine, $CH_2Cl_2$, r.t.; (k) $Pd(PPh_3)_2(OAc)_2$, CO, $(i\text{-}Pr)_2NH$, $CH_2Cl_2$; (m) $H_2$, $PtO_2$, EtOAc.

Scheme 1 shows the synthetic approach to the bridged 4-aza steroid 1. The starting material 3 was prepared from commercially available 19-hydroxyandrost-4-ene-3,17-dione[5] according to the procedure of Jeger *et al.*[6] Reduction of 3 with sodium borohydride afforded the alcohol 4 in 96% yield which upon reaction with *p*-toluenesulfonyl chloride in pyridine gave the corresponding tosylate 5 in quantitative yield. Deprotection of 5 was carried out with *p*-toluenesulfonic acid to give the tosylate 6 in 85% yield. The crucial cyclization reaction was achieved by treatment of tosylate 6 with LDA in THF/hexane.[7] The bridged enone 2 was obtained in 58% yield after column chromatography and its structure was confirmed by x-ray analysis (see ORTEP drawing in Figure 1).

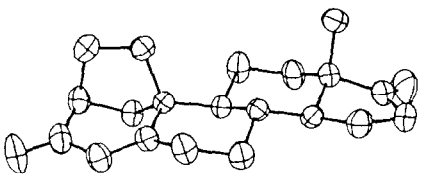
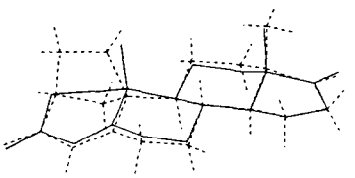


FIGURE 1

The structural effects of the bridge can be evaluated most rigorously in comparison to the observed structure of androst-4-ene-3,17-dione.[8] Figure 2 represents an overlay of the two structures generated by a least-squares fitting of C-9, C-15 and C-17 using the SYBYL program.[4] As may be seen from this diagram, there is a close correspondence between the B, C and D rings of the two molecules as determined in the solid state. In contrast, there are dramatic differences between features of the A-rings. In particular the position of C-1 is displaced 0.4Å toward the $\alpha$-face compared to its placement in the parent. Additionally, the ethano bridge distance appears to constrain C-19 such that its location is oriented more towards the center of the A-ring as compared to the parent structure, with a computed difference of 0.6Å in their locations.



——— androst-4-ene-3,17-dione
- - - - compound 2

FIGURE 2

The conversion of enone 2 into the 4-methyl-4-aza steroid 8 was carried out analogously to the reported route.[2] Thus, oxidative A-ring cleavage with $KMnO_4/NaIO_4$ in $H_2O$/t-BuOH led to the seco acid which upon treatment with methylamine in ethylene glycol provided the $\Delta^5$-lactam 7 (50% yield for the two steps). Hydrogenation of 7 ($PtO_2$/AcOH/$H_2$, 1-atm.) yielded the desired 5$\alpha$(H)-4-aza compound with concomitant reduction of the 17-ketone in 94% yield. Reoxidation of the 17$\beta$-alcohol with Jones' reagent afforded the ketone 8 in 80% yield. Elaboration of the 17$\beta$-diisopropylcarboxamide side chain was effected *via* carbonylation of the enol triflate 9 in the presence of a palladium (0) catalyst.[9] Thus, treatment of compound 8 with triflic anhydride and 2,6-di-t-butyl-4-methylpyridine provided the desired 17-enol triflate 9[10] in 75% yield. Carbonylation of the enol triflate 9 ($Pd(PPh_3)_2(OAc)_2$, 1 eq./CO, 1-atm./diisopropylamine, 40 eq./$CH_2Cl_2$) gave the $\Delta^{16}$-17-diisopropylcarboxamide 10 directly. Finally catalytic hydrogenation of 10 ($PtO_2$/EtOAc/$H_2$, 1-atm.) afforded the target compound 1[11] (70% yield from 9). The biochemical effects of 1 and 2 will be reported elsewhere.

Acknowledgement.

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References.

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4. SYBYL version 3.4b produced by Tripos, Inc., St. Louis, MO.

5. The 19-hydroxyandrost-4-ene-3,17-dione was purchased from Biosynth International, P.O. Box 541, Skokie, IL 60077.

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7. The procedure for the cyclization reaction shown in Scheme 1 is as follows: To a stirred solution of dry diisopropylamine (13.2 ml, 0.1 mol) in dry THF (20 ml) was added n-butyllithium (2.5M solution in hexane, 38 ml, 0.095 mol) at 0°C under argon. After 15 min the solution was cooled to -78°C. The tosylate 6 (4.7g, 0.01 mol) in dry THF (40 ml) was added dropwise and after 30 min at -78°C, the mixture was warmed to room temperature and left to stir overnight. Extractive work-up followed by column chromatography on silica gel (eluant: EtOAc/hexane, 2:3) gave 1.7 g of 2 as a white solid (58%). mp. 174-175°C. $[\alpha]_D$ + 223.3° (c. 0.7, MeOH). $\nu_{max}$ 1738 $cm^{1}$ (ketone), 1660 $cm^{-1}$ (enone). $^1$HNMR (360 MHz) $\delta$ ($CDCl_3$) *inter alia*, 0.90 (s, 3H, 18-$CH_3$), 5.65 ppm (s, 1H, 4-H). MS m/z 299 (M+H) (100), 298 (M) (2.84). Found: C, 80.82; H, 8.58. $C_{20}H_{26}O_2$ requires: C, 80.50; H, 8.78%.

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11. $[\alpha]_D$ -10.0° (c. 0.5, MeOH). $\nu_{max}$ 1630 $cm^{-1}$ (amide). $^1$HNMR (250 MHz) $\delta$ ($CDCl_3$) *inter alia*, 0.73 (s, 3H, 18-$CH_3$), 2.79 ppm (s, 3H, N-$CH_3$). MS m/z 429 (M+H) (100), 427 (M-H) (13.12). Found: (M) 429.3491. $C_{27}H_{45}N_2O_2$ requires: 429.3481.

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