Aza-steroids: Synthesis of an 18-Nor-9-aza-androst-13(14)-en-6-one and Related D-Homo-Derivatives

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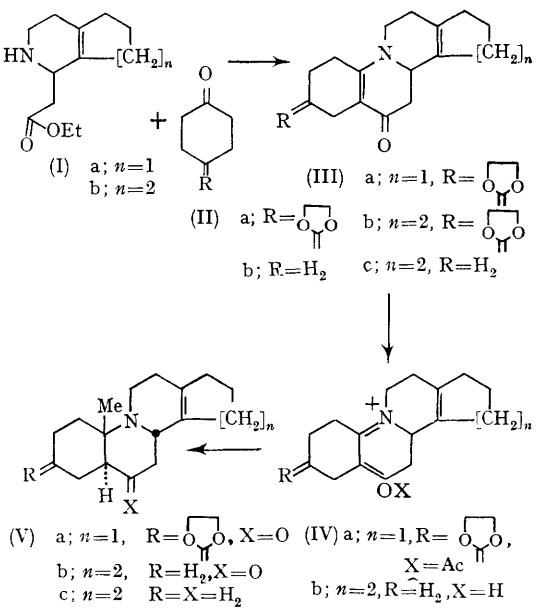
IN view of the unsuccessful attempts at total synthesis of 9-aza-steroids[1] and the recent interest in 6-keto-steroids,[2] we report an approach to 3,3-ethylenedioxy-18-nor-9-aza-androst-13(14)-en-6-one (Va) and the related D-homo-derivatives, (Vb) and (Vc).

Treatment of the piperidine esters, (Ia) and (Ib),† with the monoketal of cyclohexane-1,4-dione (IIa) in refluxing toluene[3] produced the tetracyclic systems, (IIIa) [m.p. 150—151°; i.r. ($CHCl_3$) 1550, 1610 cm.$^{-1}$; u.v. (EtOH) 333 mμ (log ϵ 4·13)] and (IIIb) [m.p. 172—173°; i.r. ($CHCl_3$) 1550, 1611 cm.$^{-1}$; u.v. (EtOH) 333 mμ (log ϵ 4·11)], respectively. In a similar fashion, (Ib) and cyclohexanone yielded the 3-nor-derivative, (IIIc) [m.p. 131—132°; i.r. ($CHCl_3$) 1548, 1610 cm.$^{-1}$; u.v. (EtOH) 336 mμ (log ϵ 4·14)]. Introduction of the C-10 methyl was accomplished smoothly when the perchlorate salt (IVb) [m.p. 205—206°; i.r. (Nujol) 3115, 1642 cm.$^{-1}$; u.v. (EtOH) 336 mu (log ϵ 4·14)] was treated with an excess of methylmagnesium iodide in hexane, affording (Vb) (97%) as a mixture of 5α- and 5β-isomers. Base-catalysed equilibration resulted in the pure 5β-isomer [m.p. 110—111°; i.r. ($CHCl_3$) 1704; n.m.r. ($CDCl_3$) τ 6·61 (b, C-8, 1H), 6·72 (b, C-5, 1H), 9·13 (s, C-19, 3H)].

Angular methylation on (IIIa) (or IIIb) could not be accomplished *via* the perchlorate salts, since the ketal linkage at C-3 readily cleaved during salt formation. Reaction of (IIIa) with acetyl chloride produced the *O*-acetyl derivative (IVa) (hygroscopic and air sensitive), which was used *in situ*[4] in the reaction with methylmagnesium iodide forming (Va) [oil, purified by t.l.c.; i.r. (neat) 2800, 2750 (Bohlmann bands) 1705 cm.$^{-1}$; n.m.r. ($CDCl_3$) τ 6·09 (s, ketal, 4H), 6·59 (b, C-8, 1H), 6·89 (b, C-5, 1H), 9·09 (s, C-19, 3H).

The data for (Va) supported the AB-*trans*, BC-*trans*-configuration whereas the BC-*trans* fusion for (Vb) received support from n.m.r. but not from i.r. evidence (lack of Bohlmann bands). However, Wolff–Kishner reduction of the C-6 keto-function in (Vb) resulted in the deoxy-derivative, (Vc) [oil, perchlorate m.p. 184°; i.r. (neat) 2770, 2730 cm.$^{-1}$ (Bohlmann bands); n.m.r. ($CDCl_3$) τ 6·87 (b, C-8, 1H), 9·11 (s, C-19, 3H)] which indeed possessed the AB-*trans*, BC-*trans*-configuration. The lack of Bohlmann bands in *trans*-quinolizidine systems has previously been noted.[5]



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† Prepared by the usual Bischler–Napieralski ring closure on the amide obtained from cyclopent-1-enylethylamine or cyclohex-1-enylethylamine and diethyl malonate. The C=N link in the resulting cyclized product was reduced with sodium borohydride, producing (Ia) and (Ib).

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