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BROMINATION OF A REFORMATSKY ADDUCT TO 16-DEHYDROPREGNENOLONE ACETATE

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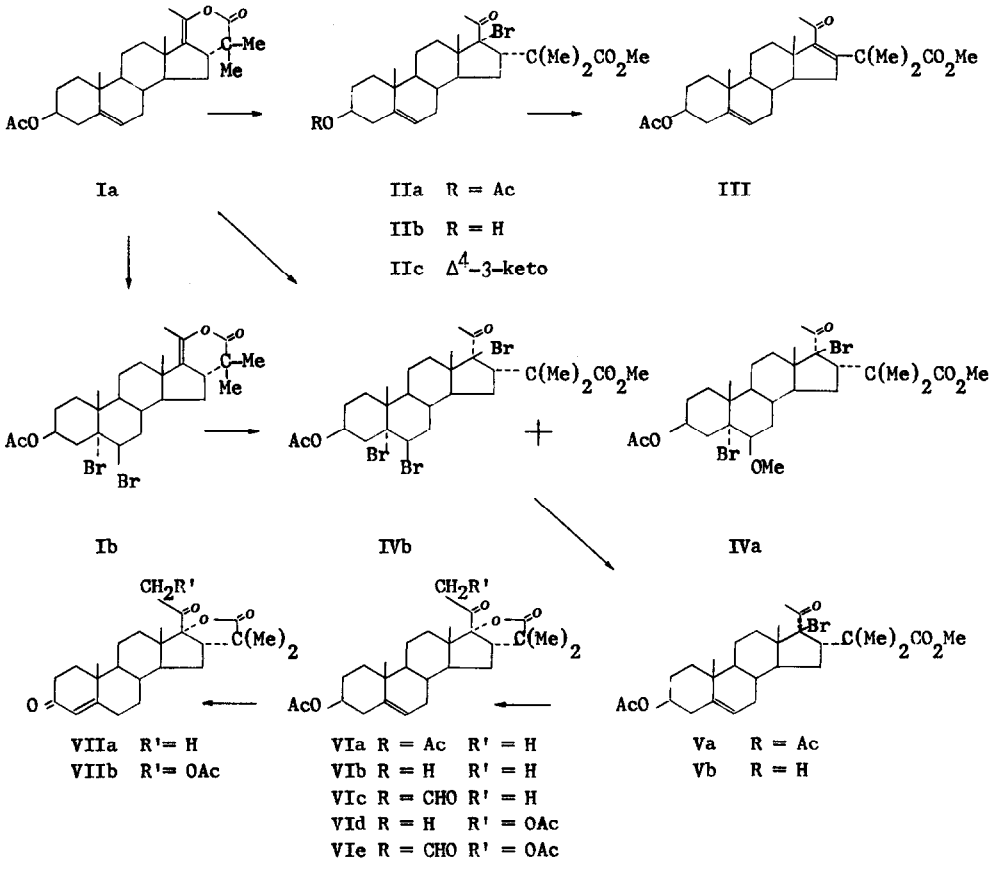
In a previous paper (1) we described the conjugate addition of Reformatsky reagents to 16-dehydropregnenolone acetate and we attributed 16α-configuration to the new substituent at C-16.

This hypothesis is now confirmed by further transformations of the adduct, 16a-dimethyl-pregna-5,17(20)-dien-3β,20-diol-16α-acetic acid-(16b→20)δ-lactone (Ia)(1), a structure presenting with a 16α-substituent, a potential 20-ketone function and an easily functionalized C-17 position.

By reacting Ia with two molar equivalents of cupric bromide in refluxing methanol, and acetylating the crude reaction mixture, we obtained the 17α-bromo derivative IIa, with m.p. 205-206 C, $[\alpha]_D$ = -77°(2), ($\phi_{370°}$ = -1881, $\phi_{320°}$ = -5996, $\phi_{300°}$ = -806, $\phi_{274°}$ = +4165, $\phi_{260°}$ = +2957, a= -101,6); NMR at δ 0.78 (s,3H,18-Me), 1.02 (s,3H,19-Me), 1.156 and 1.264 (6H,16a gem-Me), 2.43 (s,3H,21-Me), 3.63 (s,3H,-CO_2Me), 2.03 (s,3H,-O-CO-Me); the process did not affect the integrity of the olefin bond at C-5 (3a,b). The product treated with $CaCO_3$ in DMA (4) or LiBr and Li_2CO_3 in DMF (5 a,b) was slowly converted to 16a-dimethyl-pregna-5,16-dien-3β-ol-20-one-16α-acetic acid methyl ester acetate (III), with m.p. 169-170 C, $[\alpha]_D$ = -116°, λ_{max} 207 and 255 mμ (ε=3,100 and 4,360), ($\phi_{390°}$ = -1552, $\phi_{360°}$ = -1918, $\phi_{330°}$ = -913, $\phi_{290°}$ = -9558, $\phi_{264°}$ = -17807, $\phi_{250°}$ = -11415; a_1 = -10.05 a_2 = +168.9) NMR at δ 1.057 (s,6H,18-Me and 19-Me), 1.29 and 1.34 (6H,16a gem-Me), 2.12 (s,3H,21-Me), 2.02 (s,3H,-O-CO-Me), 3.62 (s,3H,-CO_2-Me). From the crude mixture of the cupric bromide reaction we also isolated small amounts of 17α-H derivative (1), 17α-OCH_3 compound was not detected (3b).

After saponification to the crude 3β-ol derivative (IIb), $[\alpha]_D$ = -65° and Oppenauer oxidation, we obtained a 55% yield of 17α-bromo-16a-dimethyl-pregn-4-ene-3,20-dione-16α-acetic acid methyl ester (IIc), with m.p. 169-171 C, $[\alpha]_D$ =+8°, λ_{max} 241 mμ (ε=16,120).

On the other hand, when bromination of IIa was carried out in the same solvent with two molar equivalents of bromine in methanol or methanol-dioxane mixture at room temperature, the reaction products were the 17β-derivatives IVa and IVb. Chromatography of the crude reaction mixture on silica gel allowed separation of two crystalline products, namely 5α,17β-dibromo-6β-methoxy-

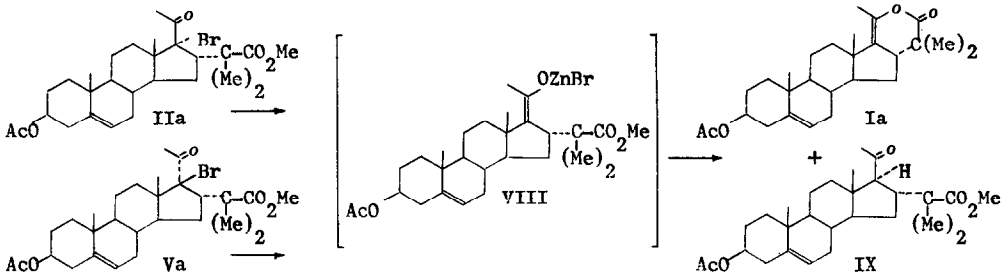


16a-dimethyl-17-iso-pregnan-3β-ol-20-one-16α-acetic acid methyl ester (IVa) with m.p. 176-178 C $[\alpha]_D$= -49° ($\phi_{340°}$= +1297, $\phi_{322°}$= +4475, $\phi_{300°}$= -2983, $\phi_{260°}$= -12645, $\phi_{250°}$= -12380, a = +171.2); NMR at δ 1.26 (s,3H,18-Me), 1.34 (s,3H,19-Me), 1.18 and 1.20 (6H,16a gem-Me), 2.46 (s,3H,21-Me), 2.00 (s,3H,-O-CO-Me), 3.16 (s,3H,6β-OMe), 3.66 (s,3H,-CO_2-Me) and 5α,6β,17β-tribromo-16a-dimethyl-17-iso-pregnan-3β-ol-20-one-16α-acetic acid methyl ester (IVb) with m.p. 146-148 C, $[\alpha]_D$= -60°, $[\alpha]_{365°}$= -35°. If the C-5 double bond was previously protected against the action of methoxide anion by the addition of one molar equivalent of bromine in CH_2Cl_2, giving the 5α,6β-dibromo derivative (Ib) with m.p. 148-150° C, $[\alpha]_D$= -43°, $[\alpha]_{365°}$= -170°, the only product of the reaction was the tribromo compound IVb. Subsequent treatment of IVb with sodium iodide in acetone gave 17β-bromo-16a-dimethyl-17-iso-pregn-5-en-3β-ol-20-one-16α-acetic acid methyl ester acetate (Va) with m.p. 128-130 C, $[\alpha]_D$= -35° ($\phi_{330°}$= +3547, $\phi_{320°}$= +4730, $\phi_{300°}$= -2042, $\phi_{265°}$= -10750, $\phi_{250°}$ = -10212, a = +154.8); NMR at δ 1.285 (s,3H,18-Me), 1.025 (s,3H,19-Me), 1.194 and 1.195 (6H,16a-gem-Me), 2.49 (s,3H,21-Me), 2.02 (s,3H,-O-CO-Me), 3.68 (s,3H,-CO_2-Me); subsequent saponification

gave the corresponding 3β-ol (Vb) with m.p. 139-140 C, $[\alpha]_D$ = +40°, $[\alpha]_{365°}$ = +44°.

The positive Cotton effect in the o.r.d. curves of IVa and Va, the negative Cotton effect of IIa provide definite information as to the stereochemistry of the bromine atom at C-17 and as to the axial or quasi-axial orientation of the C_{17}-Br bond in IIa, IVa and Va (6).

Dehalogenation of IIa (17α-Br) and Va (17β-Br) with Zn in 90% acetic acid gave the same 2:1 mixture of Ia and 16a-dimethyl-pregnenolone-16α-acetic acid methyl ester acetate (IX) (1).



It is well accepted (7a,b) that during α-dehalogenation and α-deacetoxylation reactions the formation of an intermediate enolate anion occurs. In our case we think that the enolate anion (VIII) is partly protonated to give the 17α-H-20-keto compound (IX) (1) and partly combined with the ester function to give the 17(20)δ-enol-lactone Ia. In addition to confirm that all differences between IIa and Va are only related to the stereochemistry at C-17, our results suggest that the same intermediate enolate anion might occur in the course of the conjugate addition of Reformatsky reagents to 16-dehydropregnenolone acetate. Furthermore we found that pyrolysis of the trans-δ-keto-γ-bromo ester (Va) at 140-145 C proceeds smoothly to give methyl bromide, derived from the alcohol moiety of the ester, and high yields of the δ-keto-γ-lactone 16a-dimethyl-pregn-5-en-3β,17α-diol-20-one-16α-acetic acid-(16b→17)γ-lactone acetate (VIa) with m.p. 212-214 C $[\alpha]_D$ = -42° ($\phi_{330°}$ = +4315, $\phi_{322°}$ = +5754, $\phi_{300°}$ = -2655, $\phi_{270°}$ = -11724, $\phi_{260°}$ = -11507, a = +174.83); IR CO (lactone) 1765 cm^{-1}; NMR at δ 0.73 (s,3H,18-Me), 1.015 (s,3H,19-Me), 1.09 and 1.18 (6H,gem-Me) 2.28 (s,3H,21-Me), 2.02 (s,3H,-O-CO-Me). The positive Cotton effect in the o.r.d. curve of VIa and the chemical shift associated with C-18 methyl absorption (8) in its NMR spectrum are well consistent with β-orientation of the 17-acetyl group. It is also well known (9 a,b) that the pyrolysis of acyl-γ-bromo-esters to lactones proceeds smoothly only if the oxygen atom of the ester can reach the rear of the carbon carrying the bromine atom. Furthermore this reaction is characterized by nearly complete retention of optical activity and inversion of configuration at the carbon carrying the alkyl oxygen (10). So the 17-hydroxy compound is α-oriented; and since a stable trans-fused five-membered-ring lactone appears very unlikely (11), this finding may safely be taken as evidence of 16α-substitution in these products and in the original adduct. In addition, as previously shown, in the cis-δ-keto-γ-bromo-ester (IIa) trans-diaxial hydrogen bromide elimination is preferred.

Subsequent selective cleavage of the 3β-acetoxy group in VIa produced the 3β-ol derivative VIb with m.p. 226-228 C, $[\alpha]_D$ = -39°. This was then converted by Oppenauer oxidation to the Δ^4-3-keto compound VIIa with m.p. 199-201 C, $[\alpha]_D$ = +74°, λ_{max} 240 mμ (ε=16,000).

C-21 bromination of VIb (or 3-formate VIc: m.p.245-247 C, $[\alpha]_D$ = -50°) followed by treatment with triethylamine in acetic acid (12), lead to the 21-acetoxy compounds: VId (3β-ol) m.p.232-233 C, $[\alpha]_D$ = -26° and VIe (3β-formate) m.p. 189-191 C, $[\alpha]_D$ = -25°, from which we obtained 16a-dimethyl-pregn-4-en-17α,21-diol-3,20-dione-16α-acetic acid-(16b→17)γ-lactone-21-acetate (VII b) with m.p. 172-174 C, $[\alpha]_D$ = +78°, λ_{max} 239 mμ (ε=18,000).

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