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A FAVORSKI REACTION USING IODOSOBENZENE

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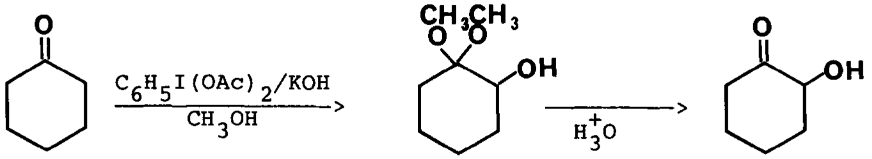
Abstract. Iodosobenzene or iodobenzene diacetate and excess base when reacted with 17β-hydroxy-5α-androstane-3-one (1a) unexpectedly gave a good yield of Favorski acid (3a) and some (3b). 17β-hydroxy-5α-19-norandrostan-3-one (1b) gave mainly the expected dimethylketal of the 2α-hydroxy-3-keto steroid (5).

We found it necessary to prepare steroidal 2-hydroxy-3-ketones, and to that end, a method described recently[1,2,3,] employing iodosobenzene ($C_6H_5I{=}O$)[4] as a means of generating α-hydroxy ketones was attempted.

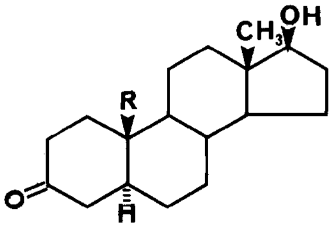
In a typical experiment, the authors describe the reaction of an α-methylene or α-methyl ketone with either $C_6H_5I{=}O$ and an equivalent of base (OH^-) in MeOH or iodobenzene diacetate [$C_6H_5I(OAc)_2$] and at least 3 equivalents of base (OH^-) in MeOH, followed by an acid work up, to afford an α-hydroxyketone. An example cited is the conversion of cyclohexanone to α-hydroxycyclohexanone (80% yield).[1]



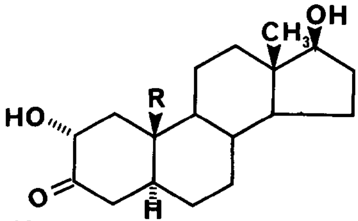
17β-hydroxy-5α-androstan-3-one (1a) when treated with an excess of KOH and an equivalent of $C_6H_5I(OAc)_2$ in MeOH at R.T. overnight, followed by an acid (3N HCl) work up afforded a mixture of the known acids (3a)[5] and (3b)[6] (tlc) and not the desired (2a). Direct recrystallization of the crude product from MeOH afforded a 65% yield of (3a)[7], mp 270-272°; M^+ 306; C^{13}mr(DMSOd_6) δ 177.9 ppm ($\underline{C}$OOH); ir (KBr) 1693 cm^{-1}, (Lit.[5] mp 263-268°[8]).

Reduction of (3a) with BH_3/THF affords the known 2α-hydroxymethyl compound (4a).[5,7]; mp 155-156° (MeOH), M^+ 292; ir (no carbonyl); nmr (DMSOd_6) δ 3.2 (m, 1H, C$\underline{H}$OH), 3.4 ppm (m, 2H, C$\underline{H}_2$OH), (Lit.[5] mp 148-155°[9]).

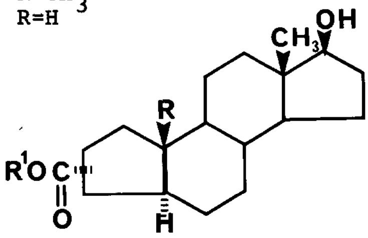
Reduction of (<u>3a</u>) mother liquor with BH_3/THF afforded after preparative HPLC separation 12% more of (<u>4a</u>) and 12% of the 3α-hydroxymethyl compound (<u>4b</u>);[6,7] mp 199-200° (MeOH); M^+ 292; ir (no carbonyl); nmr (DMSOd_6) δ 3.2 (m, 2H, C<u>H</u>$_2$OH) 3.4 ppm (m, 1H, C<u>H</u>OH). The assignment of 3α-hydroxymethyl for (<u>4b</u>) is based upon the expected Favorski products.[6]



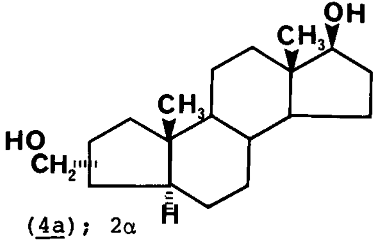
(<u>1a</u>); R=CH$_3$
(<u>1b</u>); R=H



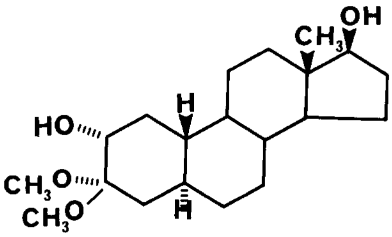
(<u>2a</u>); R=CH$_3$
(<u>2b</u>); R=H



(<u>3a</u>); 2α, R=CH$_3$, R'=H
(<u>3b</u>); 3α, R=CH$_3$, R'=H
(<u>3c</u>); 2α, R=R'=CH$_3$
(<u>3d</u>); 3α, R=R'=CH$_3$
(<u>3e</u>); 2α, R=R=H



(<u>4a</u>); 2α
(<u>4b</u>); 3α



(<u>5</u>)

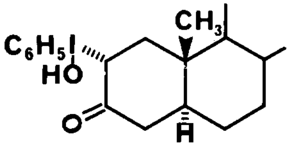
When 17β-hydroxy-5α-androstan-3-one (1a) was treated with $C_6H_5I{=}O$ and one equivalent of KOH in MeOH overnight at R.T., work up after acidification afforded a mixture of mostly 2α-ester (3c)[10] and some 3α-ester (3d) (tlc); ir (CCl_4) 1732 cm^{-1}; MH^+ 321; [Lit.[10] ir (KBr) 1730 cm^{-1}].

Reduction of (3c) and (3d) with Ca/NH_3 afforded after work up and preparative HPLC 83% and 17% yields respectively of hydroxymethyl compounds (4a) and (4b).

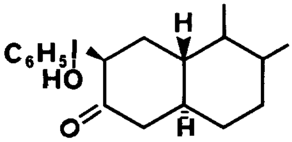
When 17β-hydroxy-5α-19-norandrostan-3-one (1b) was treated with an excess of KOH and an equivalent of $C_6H_5I(OAc)_2$ in MeOH at R.T. overnight, work up afforded from the organic layer before acidification a 40% yield of the 2α-hydroxy-3,3-dimethoxyketal (5)[7]; mp 129-131° (Et_2O-Hexane); M^+ 338; nmr ($CDCl_3$) δ 3.5-3.8 (m, 2H, C$\underline{H}$OH), 3.4 and 3.3 ppm (d, 6H C$\underline{H}_3$O). Acidification of the alkaline layer (3N HCl) gave after recrystallization an 18% yield of the Favorski acid (3e)[7]; mp 194-195 (Et_2O-Hexane); M^+ 292; C^{13}mr ($CDCl_3$ δ 178 ppm ($\underline{C}$OOH).

Compound (5) after stirring with Dowex 50W-X8 in MeOH, afforded the 2α-hydroxy-3-keto compound (2b)[7]; mp 153-154° (Et_2O); M^+ 292; ir (KBr) 1725 cm^{-1}; nmr ($CDCl_3$) 4.2 (J7, 12, 1H, C$\underline{H}$OH) 3.7 ppm (m, 1H, CHOH).[11]

Conclusion. We suggest that iodosobenzene when reacted with 17β-hydroxy-5α-androstan-3-one (1a) gives exclusively a 2α-adduct (6), as in the case of bromination.[12] The 17β-hydroxy-5α-19-norandrostan-3-one (1b) with iodosobenzene affords mainly the 2β-adduct (7), because of less steric compression as a result of the smaller angular hydrogen, together with some 2α adduct.



(6)



(7)

The 2α-adduct as in the case of a 2α-bromo steroid[6] undergoes a Favorski rearrangement by way of a trans anti planar displacement of the 2α-phenyl iodoso intermediate in the presence of methoxide ion whereas the 2β-adduct undergoes the anticipated conversion to the intermediate 2α,3α-epoxy-3β-methoxy structure which is further converted to the dimethyl ketal of the acyloin (5) as suggested by Moriarty.[2]

Acknowledgements.

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References.

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8. Probably a mixture of (3a) and (3b).
9. Probably a mixture of (4a) and (4b).
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