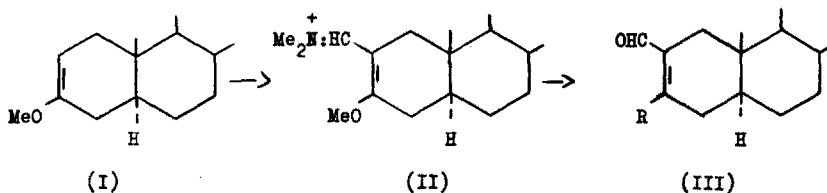


STEROIDAL 3-ALKOXY-2-FORMYL-2-ENES AND SOME OF THEIR TRANSFORMATIONS

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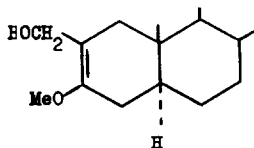
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We wish to report the introduction of a carbon substituent in position 2 in the steroid molecule by reaction of either a 3-alkoxy-2-ene of the 5 α -H series, or more conveniently of a 3,3-dialkoxy-5 α -H steroid, with the Vilsmeier reagent⁽¹⁾.

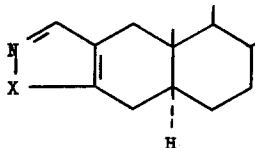


17 β -Acetoxy-3-methoxy-5 α -androst-2-ene (I), [m.p. 132-134°, [α]_D + 45°]* in anhydrous ethylene dichloride was treated with a Vilsmeier reagent prepared from dimethylformamide and phosgene. Hydrolysis of the intermediate (not isolated) iminium salt (II) with aqueous sodium acetate gave 17 β -acetoxy-2-formyl-3-methoxy-5 α -androst-2-ene (III; R = OMe) m.p. 210-214°, [α]_D + 95° $\lambda_{\text{max}}^{\text{EtOH}}$ 278.5 m μ (ϵ 13,560), which, on reduction with lithium borohydride passed into 17 β -acetoxy-2-hydroxymethyl-3-methoxy-5 α -androst-2-ene (IV), m.p. 120-122°, [α]_D + 41°.

* Rotations were determined in CHCl₃ solution unless otherwise stated.



(IV)

(V) a: X = NH
b: X = O

17 β -Acetoxy-3,3-dimethoxy-17 α -methyl-5 α -androstane [m.p. 114-116°, $[\alpha]_D + 7^\circ$] and 21-acetoxy-3,3-dimethoxy-17 α -hydroxy-5 α -pregnane-11,20-dione⁽²⁾ were similarly converted by 2 moles of the Vilsmeier reagent into iminium salts (II) from which the corresponding 2-formyl-3-methoxy-2-enes (III; R = OMe), having m.p. 182-183°, $[\alpha]_D + 95^\circ$, λ_{\max} 279 μ (ϵ 13,910) and m.p. 263-265°, $[\alpha]_D + 151^\circ$ (in pyridine), λ_{\max} 278.5 μ (ϵ 13,790) respectively, were obtained by hydrolysis with aqueous sodium acetate. Reduction of the former compound with lithium aluminium hydride gave 17 β -hydroxy-2-hydroxymethyl-17 α -methyl-3-methoxy-5 α -androst-2-ene (IV), m.p. 137-141°, $[\alpha]_D + 33^\circ$.

Compounds of type (IV) readily suffered dehydration on treatment with warm acetic acid. The products obtained, were dimeric materials⁽³⁾ which probably arise from acid-labile intermediate 2-methylene-3-ketones.

Reaction of 17 β -acetoxy-2-formyl-17 α -methyl-3-methoxy-5 α -androst-2-ene (III; R = OMe) with hydrazine or semicarbazide gave the pyrazole (Va), m.p. 219-220°, $[\alpha]_D + 44^\circ$, λ_{\max} 224 μ (ϵ 5,000), and with hydroxylamine the isoxazole (Vb), m.p. 142-143°, $[\alpha]_D + 55^\circ$, λ_{\max} 227.5 μ (ϵ 5,160). Treatment of the same 2-formyl derivative (III; R = OMe) with aniline afforded 17 β -acetoxy-3-methoxy-17 α -methyl-2-phenyliminomethyl-5 α -androst-2-ene, m.p. 197-198°, $[\alpha]_D + 135^\circ$, λ_{\max} 355 μ (ϵ 27,200). An exchange reaction between 17 β -acetoxy-2-formyl-3-methoxy-5 α -androst-2-ene (III; R = OMe) and dimethylamine furnished the 2-formyl-3-enamine

(III; R = NMe₂), m.p. 205-207°, $[\alpha]_D + 222^\circ$, λ_{\max} 339 m μ (ϵ 14,590).

We have also observed, inter alia, the formation of 2-dimethylaminomethyl 3-enol ether derivatives and their borane adducts when iminium intermediates (II) are reduced with lithium borohydride.

A range of 2-substituted steroidal derivatives has been satisfactorily prepared by the foregoing general processes.

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