

## Eniminium Salts as Protecting Groups in Steroid Synthesis†

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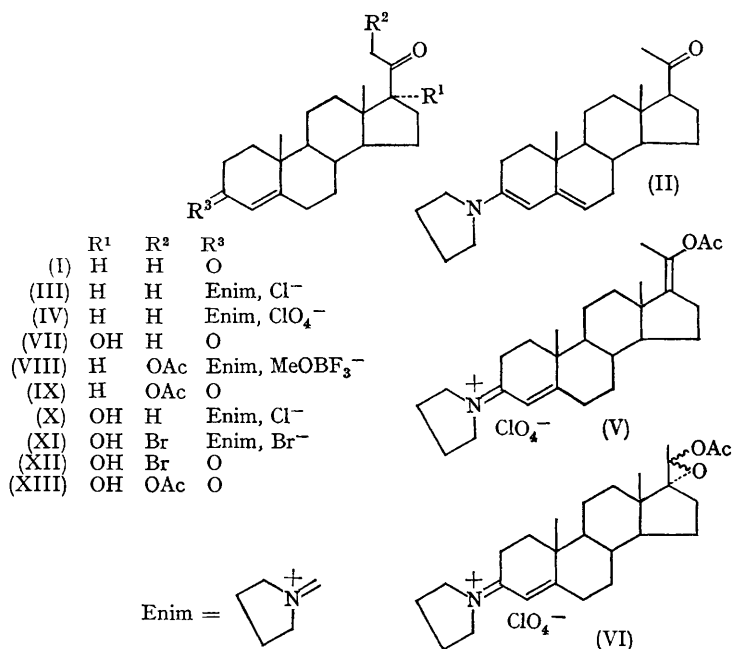
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WE describe the use of eniminium salts as selective and efficient protecting groups for the 4-en-3-one group in the synthesis of steroids oxygenated at C-17 and C-21, starting from compounds containing the 4-ene-3,20-dione system. It is well established<sup>1</sup> that pyrrolidine will react readily and quantitatively with a 4-ene-3,20-dione such as progesterone (I) to form a dienamine (II); and we noted that the eniminium salt (III), which is

produced by the action of strong acid on (II), should be unaffected by the various electrophilic species which could be used to introduce oxygen functions at C-17 or C-21. The 4-ene-3-one system may then be readily regenerated<sup>1</sup> from the eniminium salt by the action of mild alkali.

In order to introduce a hydroxyl group at C-17, the eniminium perchlorate (IV), formed in 95% yield from progesterone, was treated with acetic

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anhydride in the presence of a catalytic amount of 70% perchloric acid, to give the enol acetate (V), which reacted with *m*-chloroperbenzoic acid, in benzene, to give the epoxide (VI). The latter, on treatment with 0.2*N*-aqueous ethanolic sodium hydroxide<sup>2</sup> gave 17-hydroxypregn-4-ene-3,20-dione (VII) in 48% overall yield from progesterone. Previously this transformation was accomplished<sup>3</sup> in 7.5% yield by a route involving the selective hydrolysis of a di-enol acetate.

An acetoxy-group was introduced into (II) at C-21 by treating it or its salt (III) with excess lead tetra-acetate in 5% methanol-benzene containing boron trifluoride etherate. The crystalline salt (VIII) thus formed was hydrolysed with aqueous ethanolic sodium bicarbonate to give 21-acetoxypregn-4-ene-3,20-dione (IX), in 52% yield from (I). When this reaction was carried out directly on progesterone (I), an 11% yield was obtained.<sup>4</sup>

Finally, we have shown that the eniminium salt (X), prepared from (VII), may be brominated at

C-21 in ethanol containing hydrogen chloride,<sup>5</sup> to give the bromo-ketone (XI), in quantitative yield. Hydrolysis of (XI) with aqueous ethanolic potassium bicarbonate removed the protecting group to give (XII), which, on treatment with potassium acetate in refluxing acetone, gave 21-acetoxy-17-hydroxypregn-4-ene-3,20-dione (XIII) in 78% overall yield from (VII). This reaction sequence provides a convenient alternative to the Stork procedure,<sup>6</sup> which in our hands has proved extremely unreliable.

The above reactions demonstrate the stability of eniminium salts and it is felt that they may prove valuable when selective protection of an  $\alpha\beta$ -unsaturated ketone group is required during an electrophilic reaction.

After completion of this work the C-17 ketalisation of an eniminium salt derived from androst-4-ene-3,17-dione followed by basic hydrolysis to give 17,17-ethylenedioxyandrost-4-en-3-one was described.<sup>7</sup>

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