

HETEROCYCLIC STEROIDS XIV¹

. Total synthesis of d,1-8,9-dehydro-13-azaestrone methyl ether

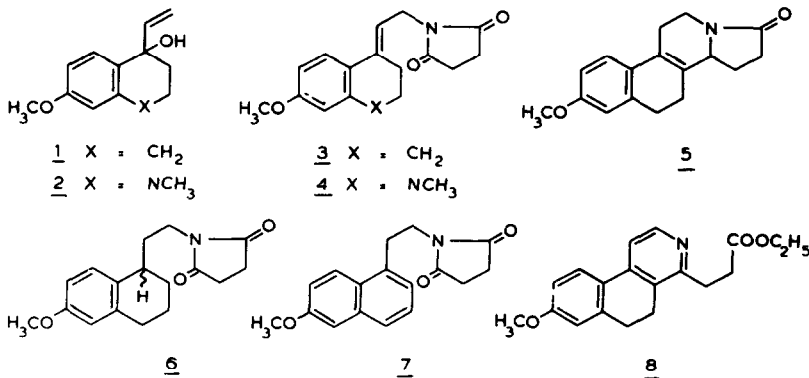
by

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Several 13-azasteroidal heterocyclics³, including 13-azaequilenin⁴, have been synthesized recently. The synthesis of a 13-azaestrone derivative will be the subject of this communication.

One of the prominent synthetical routes for the total synthesis of estrone and derivatives consists of the addition of a cyclopentanedione-1,3 system to an activated tertiary vinyl alcohol⁵. The important factors involved in this condensation are -amongst others- the acidity of the dione⁶ and the reactivity of the vinyl alcohol. Some information about the latter factor has been obtained from the reactions of a series of heterocyclic analogues⁷. On the other hand with a view to the recently reported activity of a γ -lactone derivative⁸ in this type of condensation, the possibility of a similar type of addition between 1-vinyl-1-hydroxy-1,2,3,4-tetrahydro-6-methoxynaphthalene and succinimide could be anticipated.



When the tetralol 1 and succinimide are refluxed in methanol for 6 hrs, a confirmation of this assumption is found in the IR spectrum of the reaction product, in which

a weak band at 1700 cm^{-1} is indicative for the presence of the seco-steroid 2. Unfortunately, as a result of the weak acidity of the succinimide, the addition reaction was too slow to compete favourably with the imide methanolysis. In a series of other solvents tried, the desired reaction did not take place. Stepwise changes of the acidity of the methanol solution either resulted in formation of dimers of vinyl dihydronaphthalene - formed as a consequence of the acid-catalyzed elimination of water from the tetralol - or in acceleration of the solvolysis. However, the addition occurred, albeit in rather low yield (20-30 %) when a molten mixture of succinimide, its potassium salt and the tetralol 1 were stirred at a temperature of about 110° C for a period of 12-24 hrs, to afford the seco-steroid 2, m.p. $118-120^{\circ}\text{ C}$, IR (KBr) : 1770 and 1700 cm^{-1} (C=O) ; NMR (CDCl_3) : δ 1.85 multiplet ($\text{C}_3\text{-CH}_2$), 2.61 singlet ($\text{CO-CH}_2\text{-CH}_2\text{-CO}$), 2.66 multiplet (C_2 and $\text{C}_4\text{-CH}_2$), 3.77 singlet (OCH_3), 4.23 doublet (N-CH_2), 5.88 triplet ($=\text{C-H}$) and 6.5-7.5 (aromatic protons).

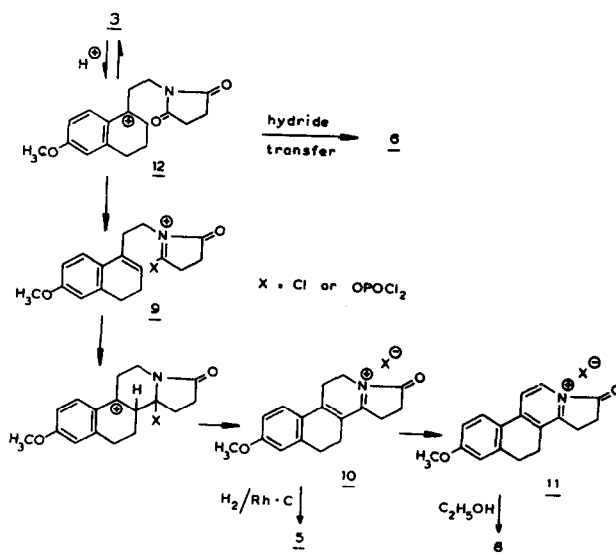
Although the mechanism of this type of addition reaction is not established with certainty, some evidence in favour of the proposed ion-pair mechanism⁹ was obtained through the condensation of the vinyl tetrahydroquinoline 2 with succinimide. The electron-releasing capacity of the nitrogen atom is well known to contribute to a more rapid addition of methylcyclopentanedione-1,3¹⁰. Upon reaction of 2 with a molten mixture of succinimide-potassium succinimide a high yield of the addition product 4 was obtained, IR (CHCl_3) 1760 and 1700 cm^{-1} (C=O) ; NMR (CDCl_3) : δ 2.70 singlet ($\text{CO-CH}_2\text{-CH}_2\text{-CO}$), 2.92 singlet (N-CH_3), 3.83 singlet (OCH_3), 4.29 doublet (CO-N-CH_2), 5.83 diffused triplet ($=\text{C-H}$), thus indicating the operation of similar electronic factors in the addition process.

Ring closure of the adduct 2 was achieved by means of phosphorus oxychloride containing 2.5 % of water. The crude reaction product was directly hydrogenated over Rh/C in acetic acid to afford the d,1-8,9-dehydro-13-azaestrone methyl ether 5, m.p. $125-127^{\circ}\text{ C}$, IR (KBr) 1660 cm^{-1} (C=O); UV (EtOH) λ_{max} 216 (18.000) and 274 13.000 nm; NMR (CDCl_3) δ 2.0-3.3 multiplet (11 protons), 3.77 singlet (OCH_3), 4.0-4.6 multiplet (N-CH), 6.5-7.2 (aromatic protons). A mass spectrum showed the molecular ion peak at m/e 269.

Some evidence on the cyclization mechanism was obtained from the following experiments. When the reaction was carried out in the absence of water and the crude product subsequently hydrogenated, no ring closure occurred and the seco-steroid 6 was isolated

quantitatively. On use of a mixture of phosphorus oxychloride-water 4 : 1 one of the products of the reaction was the ring B aromatized seco-steroid 7. Furthermore, on treatment of the reaction mixture before hydrogenation with ethanol, a substantial amount of the ester 8 was isolated, IR (CHCl_3) 1720 cm^{-1} . A likely explanation for the observed process which is in accordance with the above-mentioned facts is outlined in Scheme I :

Scheme I



After initial isomerization of the $\text{C}_9\text{-C}_{11}$ double bond under the influence of an acid ($\text{H}_2\text{O-POCl}_3$), cyclization of the iminium salt 9 occurs to yield the tetracyclic product 10. This in turn can be either hydrogenated to estrone 5 or oxidized to the N-acyl pyridinium salt 11, the latter of which is known¹¹ to give the ester 8 on treatment with ethanol. It should be noted that an increase of the acid concentration results in disproportionation of the carbonium ion 12, a process which was recently found to occur easily in a variety of substituted 3,4-dihydronaphthalenes¹². Further investigations on the exact mechanism of the addition and cyclization process are in progress.

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