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HETEROCYCLIC STEROIDS VI[1].

Total synthesis of 4-aza-19-norsteroids.

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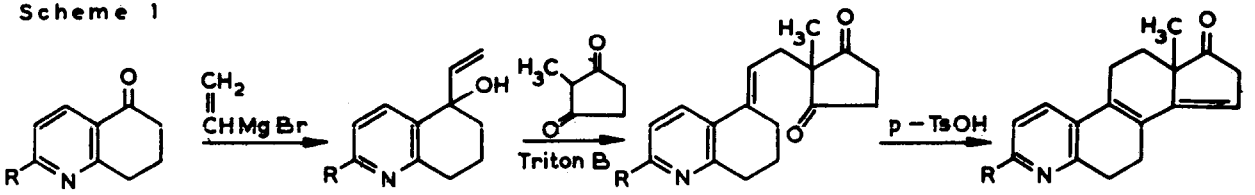
The total synthesis of several 6-azaestrogens has been recently reported from this laboratory[3]. The sequence of reactions which was employed for this synthesis is, in principle, potentially capable of affording a variety of heterocyclic steroids containing the hetero atom(s) in ring A or ring B of the steroid skeleton. In this communication we wish to report the synthesis of 4-aza-8,14-bisdehydroestrone ethyl ether (I)* via an adaption of the previously described reaction scheme (Scheme 1). Compound I is a key intermediate for the preparation of 4-aza-19-norsteroids.

The bicyclic ketone II, which incorporates in it the preformed AB ring system of the 4-azasteroid skeleton, was most conveniently obtained by the sequence of reactions described in Scheme 2.

Condensation of methyl propiolate with 3-aminocyclohexenone-2 yielded III (44%); m.p. 290-298°; IR spectrum (KBr) $\nu\,cm^{-1}$ 2800-3000 and 1600-1700, broad bands; ($CHCl_3$) $\nu\,cm^{-1}$ 1670 (C=O) and 1650 (pyridone C=O). Absence of characteristic pyridine bands in these spectra supports the assigned structure III. Refluxing the silver salt of III with ethyl iodide gave ketone II in 73% yield; m.p. 54-55°; IR spectrum ($CHCl_3$) $\nu\,cm^{-1}$ 1670 (C=O), 1590, 1570, 1465 (pyridine bands) and 1260 (OC_2H_5). Treatment of II with excess (fivefold) of vinylmagnesium bromide afforded the vinyl alcohol IV in high yield (95%).

Scheme 1



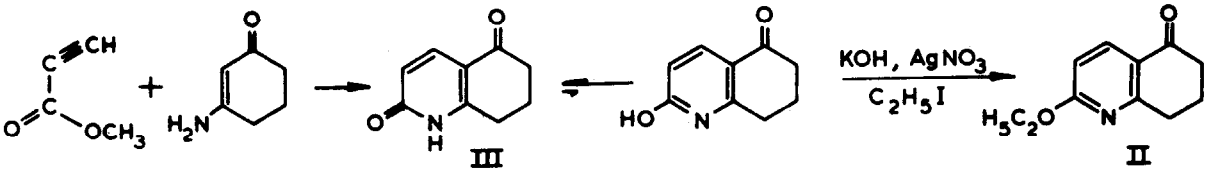
II R = OEt
VI R = H

IV R = OEt
VII R = H

V R = OEt
VIII R = H

I R = OEt
IX R = H

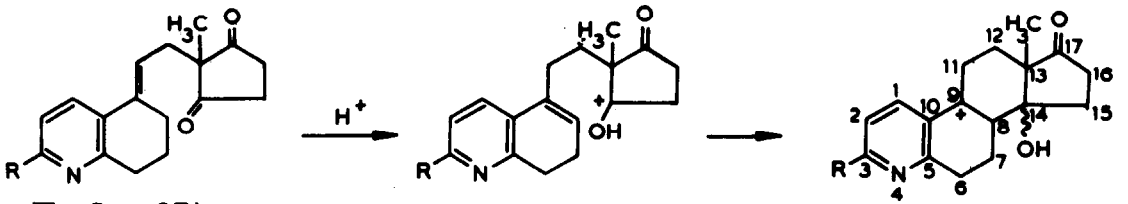
Scheme 2



III

II

Scheme 3



V R = OEt
VIII R = H

X R = OEt
XI R = H

The product was isolated as an oil and utilized in the following step without further purification. Structure of IV followed from its IR spectrum which showed absorptions at ($CHCl_3$) ν cm^{-1} 3620, 3450 (OH), 1590, 1570, 1460 (pyridine), 1250 (OC_2H_5) and 990, 920 (H_2C=CH-). Condensation of IV with 2-methylcyclopentanedione-1,3 gave crystalline tricyclic diketone V (m.p. 85-87°) in good yield.

IR spectrum of V showed the charateristic cyclopentanedione carbonyl bands at ($CHCl_3$) ν cm^{-1} 1760 and 1720. Cyclization of V to the 4-azasteroid skeleton (ketone I, m.p. 117-122°) was achieved by refluxing it in toluene in the presence of slightly over one equivalent of p-toluenesulfonic acid. IR spectrum of I is characterized by only a single ketone band at 1735 cm^{-1} ($CHCl_3$) and structure I is further supported by its UV spectrum: $\lambda_{max.(nm)}^{cyclohexane}$ 224 (9600), 303 (23200), 315 (29200) and 330 (21400) and the NMR spectrum: $\delta_{TMS}^{CDCl_3}$ 1.13 singlet (C_{15}-CH_3), 1.37 triplet (O-$CH_2\underline{CH_3}$), 4.36 quartet (O-CH_2CH_3), 5.88 triplet (C_{15}-H) and a pair of doublets at 6.54 and 7.46 ppm, J = 8.5 cps, (C_1 and C_2 pyridine protons).

In a model study involving the sequence of reactions starting from ketone VI[4], (undertaken prior to the successful synthesis of I), the condensation step with vinylmagnesium bromide, leading to vinyl-alcohol VII, proceeded in the expected manner. Coupling of alcohol VII with 2-methylcyclopentanedione-1,3 proved to be considerably more difficult than in the case of IV. However, after prolonged refluxing of the reactants in xylene (30 hrs), VIII was formed in fair yield. Attempts to cyclize diketone VIII under a very large variety of reaction conditions failed to show the presence of any IX in the IR spectra of the respective reaction mixtures. These results are in significant contrast to the behaviour of diketone V which undergoes a facile acid-catalyzed ring closure. A possible explanation of this difference may be sought in the details of the mechanism of cyclization.

As suggested by Smith, et.al[5], the latter presumably proceeds via an initial rearrangement of the exocyclic 9,11- double bond, in V, to the 8,9-endocyclic configuration, followed by an intramolecular electrophilic attack by a protonated carbonyl of the cyclopentanedione moiety. This sequence of events is described in Scheme 3. It is apparent from the latter scheme that the cyclization step results in the generation of a carbonium ion at C_9. While an electron-deficient centre can be amply sustained in system X, owing to delocalization of the electrons on the ether oxygen, a similar stabilization is not

possible for the analogous system XI. In fact, the proposed mechanism predicts that the pyridine nucleus, in view of its electronegative character, will resist the accomplishment of any reaction which may tend to create a positive charge on the carbon atom in α-position to the pyridine ring. These considerations suggest the most plausible explanation why V and VIII behave in such different manners. Conversion of I to various 4-azasteroids is currently underway in this laboratory.

References.

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* Satisfactory analyses have been obtained for all new compounds described herein.