Tetrahedron Letters No.40, pp. 3901-3905, 1967. Pergamon Press Ltd. Printed in Great Britain.

HETEROCYCLIC STEROIDS X[1].

SYNTHESIS OF 12-AZA-11-KETO and 12-OXA-11-KETO STEROIDS

by

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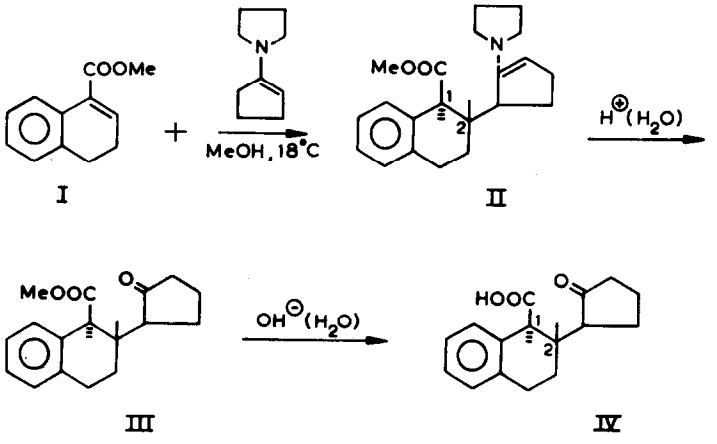
(Received in UK 28 June 1967)

In continuation of our interest in the total synthesis of 11-oxygenated heterocyclic steroids we wish to report a general synthetic approach for 11-keto steroids incorporating a hetero atom in the 12-position.

The most convenient procedure for introducing a hetero atom in ring C of the steroid nucleus is via a starting intermediate that comprises of preformed rings A, B and D and carries suitable substituents which can be cyclized with incorperation of a hetero atom. Ready availability of such a molecular system is a prerequisite for a facile synthesis.

A suitable intermediate for the synthesis of 12-heterosteroids may be recognized in the keto acid IV which possesses the necessary functional moieties. Synthesis of IV was achieved by the sequence of reactions shown in Scheme I. Addition of 1-pyrrolidinocyclopentene to methyl 3,4-dihydro-1-naphthoate (I), in methanol, followed by stirring at room temperature, afforded crystalline enamine ester II, m.p. 118 - 120°, in high yield. The structure of II followed from its

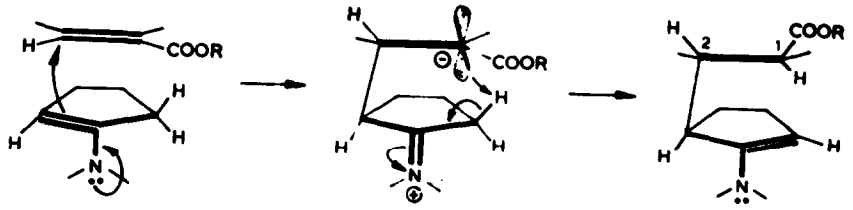
spectral data. IR spectrum (KBr) showed strong bands at 1720 ($-COOCH_3$) and 1630 cm^{-1} (-N-C=C-). NMR spectrum ($CDCl_3$) exhibited a triplet centred at 5.75 τ for



Scheme I

the vinyl proton, attesting to the fact that the enamine system contains a 'less substituted' double bond. The latter point is of some interest in view of recent observations that enamine additions to certain vinyl sulfones lead to the formation of the 'more substituted' enamine products[2].

Assuming the formation of the conventional dipolar intermediate A (Scheme II), between the enamine and the electrophilic olefin (I), ester II may arise either by an intramolecular hydrogen transfer from the cyclopentane ring, as shown in Scheme II, or via protonation-deprotonation equilibria involving intermediate A and the solvent. That the reaction in fact follows an intramolecular course was revealed by experiments carried out in CH_3OD. These showed that in accordance with the predictions of the intramolecular scheme there was essentially no incorporation of deuterium at C_1 of the enanime ester (II).



A

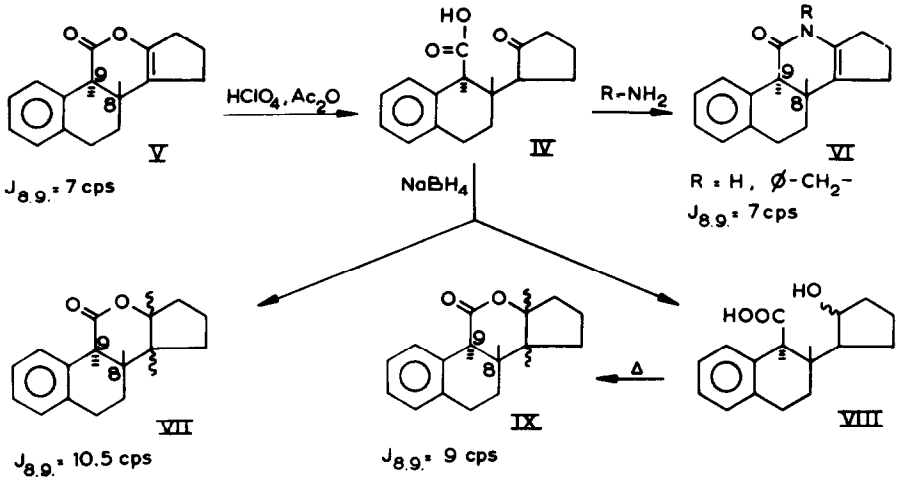
Scheme II

The mechanistic details of the intramolecular process carry definite implications for the stereochemical course of the reaction. Thus, it is apparent that, in a cyclic system, such as is implied in A, both the newly generated C-C and C-H bonds will develop from the same side of the plane of the ring. The resulting stereochemistry for the C_1 and C_2 protons in product II will therefore be trans in character. The NMR spectrum ($CDCl_3$) of the ester displays C_1-H as a diffused doublet (centred at 6.18 τ) with a coupling constant of 3.5 cps. The latter result is consistent with a trans-ee configuration for the C_1 and C_2 hydrogens. This conclusion, while initially somewhat unexpected, is reminiscent of the observation that bulky substituents located in a trans configuration on adjacent carbons of a six-membered ring frequently tend to assume a diaxial geometry[3]. Furthermore, it has also been noted that groups with large steric requirements at the C_6-position of a 1-substituted cyclohexene system, primarily acquire an axial configuration[4].

Hydrolysis of II in two steps via III led to the formation of IV as a colourless crystalline product, in reasonable yields. The trans assignment for the protons at positions 1- and 2- in IV rests on, (a) the deduced stereochemistry of the starting ester II, (b) the conditions of formation of the acid; alkaline hydrolysis being expected to form the thermodynamically favourable trans product[5] and (c) NMR spectrum ($CDCl_3$) of IV, which showed a neat doublet for the benzylic

proton (centred at 5.95 τ) with a $J_{1,2}$ value of 8 cps. The latter coupling constant is indicative of a trans diaxial H_1, H_2 configuration and strongly suggests that a reduction in the bulk of the substituents, as would be achieved by hydrolytic removal of the pyrrolidine and the alkoxy ($OCH_3 \longrightarrow OH$) moieties, leads to a change in conformation of the cyclohexene ring.

Transformations of IV involving cyclization to several heterosteroids are described in Scheme III. Treatment with ammonia or benzyl amine gave the corresponding 12-azasteroid systems VI (R = H, R = $-CH_2Ph$). Enol lactone V representing



Scheme III

the 12-oxasteroid skeleton was obtained upon treatment of the keto acid with acetic anhydride and perchloric acid. Reduction of IV with sodium borohydride resulted in a mixture of lactone VII and hydroxy acid VIII. When a solution of VIII in xylene was refluxed a second lactone (IX) which was isomeric with VII, was obtained in high yields. Comments on the stereochemistry at C_{13} and C_{14} in systems VII and IX are deferred to a more detailed discussion which shall be presented elsewhere.

The trans stereochemistry of the B/C ring junction in heterosteroids V, VI, VII and IX is derived from their NMR spectra. The C_9-H in each case appears as a doublet with $J_{8,9}$ varying from 7 to 10.5 cps. These values are consistent with a trans diaxial coupling, although in the case of compounds V and VI they represent the lower end of the scale of magnitude for such spin-spin interaction. Two factors may contribute to this deviation from more conventional values. Firstly, the presence of an electronegative substituent (O=C-O-), (which may be expected to diminish the coupling constants[6] from values predicted by the Karplus equation) and secondly, the influence arising from the electronic and steric effects of the C_{13}-C_{14} double bond. The contribution from the latter source may be appreciated by a comparison of the $J_{8,9}$ value for V with those of VII and IX.

We should like to comment upon the importance of enamine ester II as a useful intermediate in the synthesis of ring C heterosteroids. As an enamine system, II is capable of undergoing further substitution on the cyclopentane ring at a position which, after cyclization, becomes C_{17} of the steroid nucleus. Several electrophilic additions of appropriate substituents to II have been successfully achieved in our laboratory and the synthesis of corresponding 17-substituted heterosteroids is in progress.

Acknowledgment - The technical assistance of Mr H.M.P.Tambach is gratefully acknowledged.

* Satisfactory analytical data have been obtained for all compounds described in this communication.

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5. Equilibration of IV with sodium ethoxide, in a deliberate attempt to epimerize the benzylic proton, caused no change in the acid. Had IV a cis-H_1H_2 structure a conversion to the trans product would have been expected.
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