Tetrahedron Letters No.36, pp. 3529-3533, 1967. Pergamon Press Ltd. Printed in Great Britain.

HETEROCYCLIC STEROIDS IX[1]

A Convenient Synthesis of 14-Aza-11-Keto Steroids

U.K.Pandit, (Mrs.) K.de Jonge, G.J.Koomen and H.O.Huisman,
Laboratory for Organic Chemistry, University of Amsterdam,
Nieuwe Achtergracht 129, Amsterdam, The Netherlands.

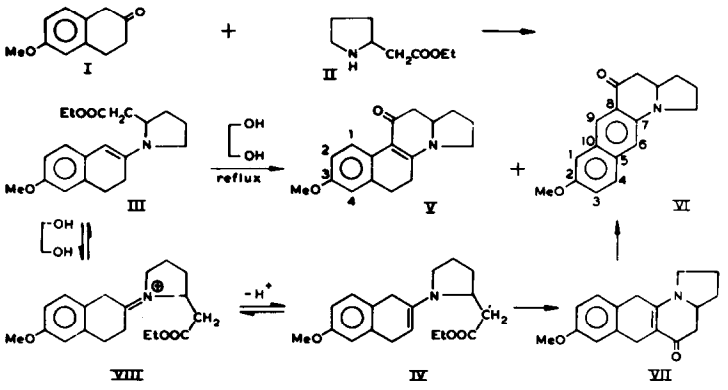
(Received in UK 12 June 1967)

The syntheses of several heterocyclic steroids have been previously reported from this laboratory[2]. In view of the potential pharmacological interest in 11-oxygenated heterocyclic steroids, we have recently directed our attention to the total synthesis of this class of compounds. This communication describes a convenient synthesis of the 14-aza-11-keto steroidal skeleton.

An attractive general approach for the preparation of 14-azasteroids was visualized via the condensation of 6-methoxytetralone-2 (I) with ethyl 2-pyrrolidylacetate (II), or an appropriately substituted derivative, followed by cyclization to complete the steroidal skeleton. The ring closure step of the sequence represents an intramolecular acylation of the enamine ester III. While several examples of intramolecular acylation of enamines have been described in the literature [3a,b], none of the cases studied is strictly analogous to that of enamine III; since, in the latter, the conjugation of the enamine function with the aromatic ring presents a distinctive structural feature. An attempt to cyclize the enamine ester formed from tetralone-2 and methyl 3-(N-methylamino)propionate was reported to result in the formation of an abnormal amide product[4].

Enamine III was readily formed by refluxing a solution of 6-methoxy-tetralone-2 (I) and ester II in xylene, using a Dean-Stark water-separator filled with molecular sieve (4A/XW). The NMR spectrum of the product showed a sharp singlet

at 5.18 δ for the vinyl proton, in agreement with structure III. The absence of any other absorption in the vinyl proton region ruled out the formation of isomeric enamine IV.



When III was heated for 19 hours in ethylene glycol, under reflux conditions, a reaction mixture was obtained from which a colourless product, m.p. 210.5 - 212°, could be isolated by fractional crystallization. Chromatography of the residual material over neutral alumina yielded a second crystalline substance, m.p. 191.5 - 192.5°. Based upon their spectra data, described in the sequel, structures V and VI are suggested for the high and low melting compound respectively[5]. Analytical data for V ($C_{17}H_{19}NO_2$) and VI ($C_{17}H_{17}NO_2$) are consistent with the assigned structures.

	Yield	IR (KBr)	UV (EtOH)	Mass Spec.
	%	C=O, cm^{-1}	λ max, mμ	M^+
V	28	1610	277 (18,200)	269
			366 (8,700)	
VI	23	1680	265.5 (48,400)	267

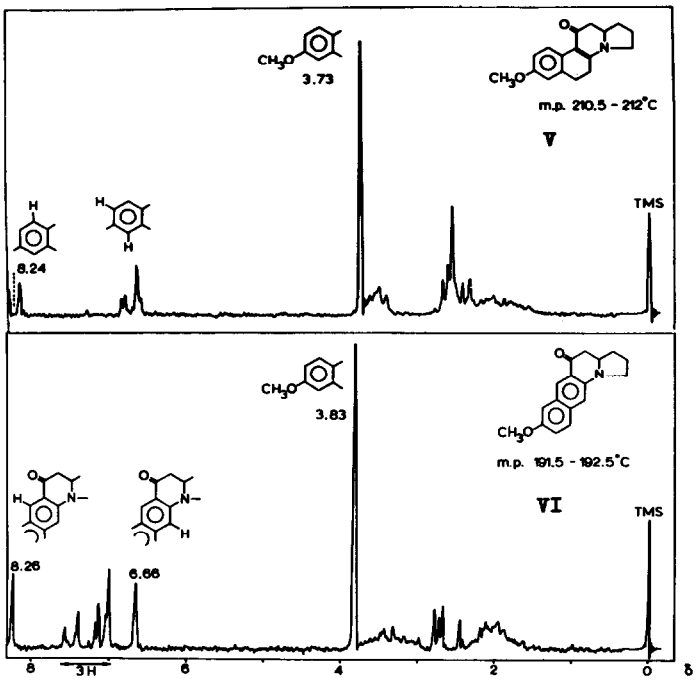


Fig.I

The NMR spectra of V and VI (Fig.I) were particularly revealing. The C_1-H of azasteroid V is observed as doublet centred at 8.24δ. This low field resonance signal arises from the expected anisotropic influence of the 11-carbonyl function. The spectrum of aza-anthrasteroid system VI, on the other hand, exhibits two sharp singlets at 8.26 and 6.66δ for the C_6 and C_9 hydrogens respectively, in accordance with its proposed structure.

While azasteroid V is the expected product of the normal cyclization reaction of enamine III, the formation of VI deserves some comment. The skeletal constitution of VI indicates that under the conditions of the reaction (refluxing ethylene

glycol) the enamine ester III can also adopt an 'abnormal' cyclization path. The mechanistic details of the latter process, while under investigation, have not yet been established. However, the available evidence prompts us to suggest that the 'abnormal' product (VI) most likely arises by a cyclization of the 'out of conjugation' enamine IV - which would be expected to undergo a rapid ring closure - followed by oxidation of the resulting 1,4-dihydronaphthalene system VII, in the course of the reaction itself or, during workup of the reaction mixture. Formation of IV may occur via the invervention of iminium ion VIII[6] which would be in equilibrium with enamine III in alcoholic solutions. Support for the involvement of VIII is derived from the observed influence of the character of the solvent upon the course of the cyclization reaction. It was found, for example, that whereas cyclization of III in n-butanol proceeded with the formation of a mixture of V and VI in which V was the major product, addition of a few drops of trifluoroacetic acid to the solvent diverted the reaction path so as to render an inversion in the proportion of the two substances. Furthermore, the ratio of normal/abnormal cyclization product in the reaction mixture was found to be sensitive to the dielectric constant of the solvent employed, showing a significant increase with the decrease in value of the dielectric constant.

The principle illustrated in the succesful synthesis of V and VI, coupled with the relative ease with which the formation of one or the other product can be controlled by means of reaction conditions, provides a convenient general method for the synthesis of 14-aza-11-keto steroids and anthrasteroids. The preparation of such steroids containing suitable substituents, for example at the 17-position, is currently in progress.

References

1. Part VIII. J.A.van Velthuysen, M.A.Douw, W.N.Speckamp, U.K.Pandit and H.O.Huisman, Tetrahedron Letters, 27, 3081 (1966).
2. See for example, J.G.Westra, W.N.Speckamp, U.K.Pandit and H.O.Huisman, Tetrahedron Letters, 24, 2781 (1966); (Miss) M.A.T.Sluyter, U.K.Pandit, W.N.Speckamp and H.O.Huisman, Tetrahedron Letters, 1, 87 (1966); W.N.Speckamp, H.de Koning,

U.K.Pandit and H.O.Huisman, Tetrahedron, 21, 2517 (1965).

3. (a) A.I.Meyers and J.C.Sircar, Tetrahedron, 23, 785 (1967); (b) F.Bohlmann and O.Schmidt, Chem.Ber., 97, 1354 (1964).

4. Zen-Ichi Horii, C.Iwata, Y.Tamura, N.A.Nelson and G.H.Rasmusson, J.Org.Chem., 29, 2768 (1964).

5. Condensation of I with ethyl 2-piperidineacetate followed by cyclization of the resulting enamine follows an analogous reaction pattern. These results will be described elsewhere.

6. Structure VIII represents one of the two possible isomeric iminium salts. However, this does not affect the argument concerning the mechanism of formation of VI.