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INDOLE ALKALOIDS. XXI: A REVISED STRUCTURE FOR GENESERINE.

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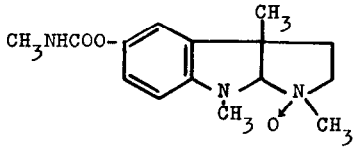
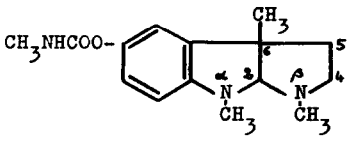
Since the work of M. POLONOVSKI on the alkaloids of the Calabar bean (Physostigma venenosum) geneserine is considered as the N-oxide of physostigmine and is therefore represented by I [1]. This structure was infered mainly from the following observations: a-geneserine behaves in many ways similarly to physostigmine (eserine) [II]; b- geneserine differs in constitution from II only by the addition of one oxygen atom; c- reduction of geneserine by zinc and acetic acid affords II, which in turn can be oxidized by hydrogen peroxide to geneserine.



I



II

However, though structure I is consistent with these observations, it does not account satisfactorily for some of the physical properties of geneserine such as polarity, NMR and mass spectra.

As pointed out by Polonovski [2], geneserine is not hygroscopic and its solubility in water is very low. This is in contrast with the polar properties of true N-oxides (e.g. in the field of indole alkaloids, pleiocarpoline, pleiocarpolinine, kopsinoline [3], venoxidine [4],... are soluble in water).

The mass spectrum of geneserine does not show the $M^+ - 16$, $M^+ - 17$ and $M^+ - 18$ peaks which are generally observed for N-oxides [9].

Comparison of the chemical shifts ($CDCl_3$ solutions) between physostigmine [II], geneserine and the model compounds III and IV is given in table 1.

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Table 1: Chemical shifts (cps) in $CDCl_3$ solution (60 Mc).

	II	geneserine		III	IV
$N_{(\alpha)}$-CH_3	174 (s)	171 (s)			
$C_{(2)}$-H	245 (s)	283 (s)			
$N_{(\beta)}$-CH_3	152 (s)	152 (s)	N-CH_3	141 (s)	200 (s)
$C_{(4)}H_2$	ca 160 (t)	ca 155 (m)	$C_{(2)}H_2$	ca 148 (m)	ca 210 (m)
$C_{(5)}H_2$	116 (t?)	ca 125 (m)	$C_{(3)}H_2$	ca 106 (m)	ca 130 (m)
$C_{(6)}$-CH_3	84 (s)	71 (s)			

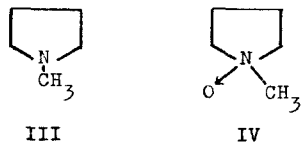
These values deserve some comments:

- The chemical shift of $N_{(\beta)}$-CH_3 of geneserine is unexpectedly low on the basis of structure I. In fact, $N\overset{O}{<}CH_3$ signals generally appear at about 190-200 cps (some examples in the field of alkaloids may be found in ref. 5 and 8). Moreover, it would be expected that the chemical shift of the $N_{(\beta)}$-CH_3 group in geneserine must be roughly comparable with that of physostigmine methiodide (see for instance (8). This is not observed: the $N_{(\beta)}CH_3$ groups of physostigmine methiodide appear at 205 and 215 cps.

- Surprisingly, the two $C_{(4)}H_2$ protons have about the same chemical shifts in geneserine and in physostigmine [II] (compare with III and IV), the major difference consisting in a change in the multiplicities.

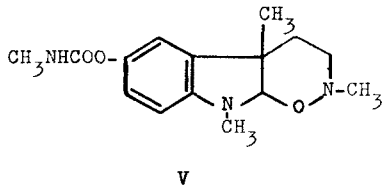
- The only proton which appears to have experienced a significant down-field shift, compared with the corresponding proton in II, is $C_{(2)}$-H.

As these observations are not in agreement with a N-oxide structure for geneserine, structure V was adopted as a working hypothesis and found to be correct. Structure V



III

IV



V

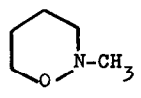
may be considered as resulting from nucleophilic attack of the oxygen atom of a transient N-oxide [I] on $C_{(2)}$ with consecutive enlargement of the C ring; on this basis, geneserine appears as a tetrahydro-1,2-oxazine derivative. The chemical properties of geneserine are in agreement with structure V: for instance, reduction of geneserine

to physostigmine by zinc and acetic acid may be considered as an hydrogenolysis of the $C_{(2)}O$ - N bond (as observed for VII [7]) and nucleophilic substitution of the OH at $C_{(2)}$ by the $N_{(\beta)}$ nitrogen atom.

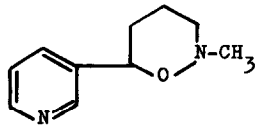
The above discussed physical properties of geneserine (water solubility, NMR and mass spectra) can now be explained on the basis of structure V.

Bearing in mind that physostigmine [II] is only slightly soluble in water, there is no reason to expect an important difference in passing from II to V.

In the NMR spectrum of (neat) N-methyltetrahydro-1,2-oxazine [6] [VI], the chemical shifts of $N-CH_2$ (156 cps) and $N-CH_3$ (148 cps) closely resemble the values observed for geneserine. The same applies to the comparison of geneserine with the model compound VII (obtained from nicotine-1'-oxide [7]) in $CDCl_3$ and in other solvents (see table 2). The solvent effects on the chemical shifts of the $N-CH_3$ protons are found to be small but parallel for geneserine and for VII.



VI



VII

Table 2: Compared solvent effects on geneserine and VII.

Solvent	Geneserine $N_{(\beta)}CH_3$	VII $N-CH_3$
-	-	154 cps
$CDCl_3$	152 cps	161 cps
Pyridine	147 cps	158 cps
Acetone	146 cps	156 cps
DMSO	145 cps	155 cps
Acetonitrile	145 cps	155 cps
Benzene	142 cps	152 cps

On the basis of structure V, $C_{(2)}$-H is the only proton which is expected to experience an important down-field shift (being now attached to a carbon flanked by an oxygen and a nitrogen atom instead of two nitrogen atoms) compared with the corresponding proton in II, as indeed observed.

Though a general study on the fragmentation of tetrahydro-1,2-oxazines under electronic impact is lacking, the absence of $M^+ - 16$, $M^+ - 17$ and $M^+ - 18$ peaks in the

mass spectrum of geneserine is not surprising in view of the fact that these ions are also missing in the mass spectrum of the model compound VII.

The sample of geneserine (m.p. 129 - 130°; $[\alpha]_D^{22}$: -174° (ethanol; c = 1,3); litt[1]: m.p. 128 - 129°; $[\alpha]_D$: -175° (ethanol) used in this work was obtained according to the method of M. Polonovski [1] from well identified physostigmine (m.p. 105 - 106°; $[\alpha]_D^{22}$: -78° (chloroform; c = 1,4) kindly supplied by " Etablissements Coutelier frères, S.A."

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