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THE STRUCTURE OF PEEPULOIDIN, AN ALKALOID FROM PIPER PEEPULOIDES.

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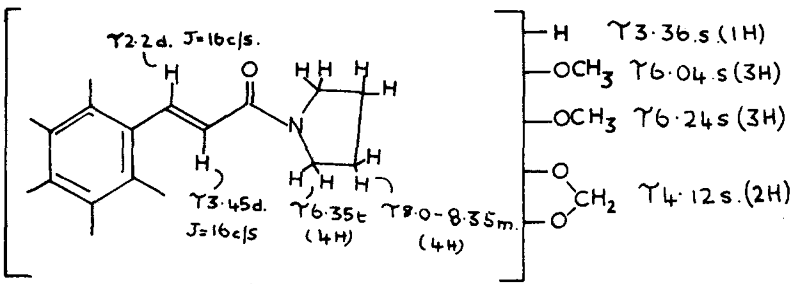
Due to its importance in the Ayuvedic system of medicine, the plant Piper peepuloides Roxb. is being subjected to a thorough chemical analysis, the novel (±)-dia-eudesmin having been already isolated and characterised[1]. Light petroleum extraction of the dry ground leaves, followed by chromatography on alumina yielded a fraction (eluted with methanol) which recrystallised from benzene/light petroleum as colourless prisms, m.p.149-150°.

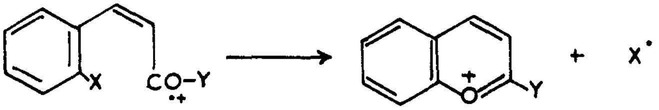
The substance, named peepuloidin, analysed for $C_{16}H_{19}NO_5$ and this was confirmed by an accurate determination of the molecular weight as 305.126807. In the I.R. spectrum a band at 1642 cm.$^{-1}$ showed the compound to be an amide, and lack of an N-H stretching frequency demonstrated that it was a tertiary amide. A band at 1380 cm.$^{-1}$ was assigned to a methylenedioxy group, whilst two peaks at 932 cm.$^{-1}$ and 996 cm.$^{-1}$ indicated a trans-disubstituted double bond. Peaks at 1597 cm.$^{-1}$ and 1608 cm.$^{-1}$ showed the substance to be benzenoid. The U.V. spectrum had $\lambda_{max.}$ 333(10,000), 305(10,800) and 240(12,700) mμ.

The NMR spectrum was only consistent with part structure (I), the τ values of the various groupings being as shown and all the supposed couplings being supported by spin-spin decoupling experiments. The positions of all the protons are in accord with expectation[2].

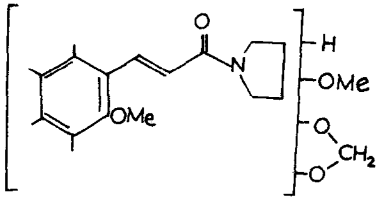


(I)

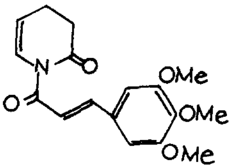
The mass spectrum of peepuloidin was of great interest at this point. There is a transition from m/e 305 to m/e 235 which may be written as $[I]^{\cdot+} \rightarrow ArCH{:}CHCO^{+}$, confirming the basic grouping. The unusual loss of an aromatic methoxyl group, however, to give the base peak at 274.108893 ($C_{15}H_{16}NO_4$) is the dominating feature of the spectrum. We have shown that cinnamic acid derivatives lose specifically an ortho-substituent very readily, presumably by cyclisation to yield a pyrillium ion.



This is not confined to an o-methoxy group, but is quite general; an account of this work will be given elsewhere. On this basis the part structure (I) may be expanded to (II).



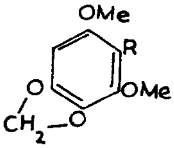
(II)



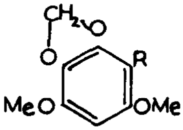
(III)

It is always difficult to assign a full structure to a pentasubstituted benzene derivative, and in this connection the τ value of the aromatic proton becomes important. Applying the figures of Ballantine and Pillinger[3] for deriving the probable position of an aromatic proton, to the closely related alkaloid piperlongumine[4] (III) (which incidentally did not lose a methoxyl group under electron bombardment) it was found that a correction of -0.4τ had to be used to allow for tne effect of the cinnamic amide grouping.

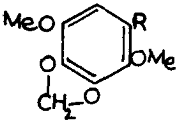
Of the five possibilities (a) - (e), only (c) and (d) have the theoretical value close enough to that found to make them possible structures. Structure (e) could also be rejected on biogenetic grounds.



(a)

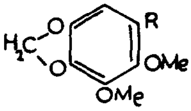


(b)

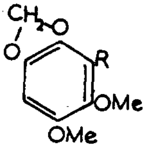


(c)

Aromatic proton (theory)	τ4.10	τ4.10	τ3.25
OMe shifts ($CDCl_3 \rightarrow C_6H_6$)	1	2	1



(d)

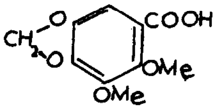


(e)

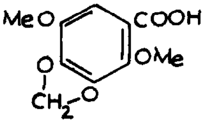
Aromatic proton (theory)	τ3.25	τ3.75
OMe shifts ($CDCl_3 \rightarrow$, C_6H_6)	0	1

The method of methoxy shifts in the NMR spectrum on changing solvent from $CDCl_3$ to C_6H_6[5] proved unreliable in distinguishing between (c) and (d). There were very many shifts in the spectrum, the most dramatic being the progressive separation of the triplet due to the four α-protons of the pyrrolidine ring into two triplets. At 20% $CDCl_3$ in C_6H_6 these were at τ6.58 and 7.06. In view of the widespread effects little faith could be placed on the comparatively minor shifts in the positions of the methoxy protons.

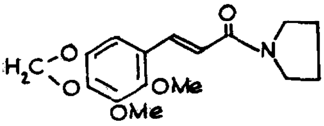
Potassium permanganate oxidation of peepuloidin gave an acid m.p.148-149°, identical in all respects with a sample of dill-apiolic acid (IV) m.p.148°, obtained by oxidation of dill apiole. On admixture of the oxidation product with apiolic acid (V) m.p.175-176° (kindly supplied by Professor Highet) the mixed melting point was 125-152°.



(IV)



(V)



(VI)

Peepuloidin then is represented by (VI) and is a further, highly oxygenated, example of a cinnamic amide elaborated by a *Piper* species.

References

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