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CONSTITUENTS OF NAUCLEA DIDERRICHII. PART VI. NAUCLEONINE AND NAUCLEONIDINE.

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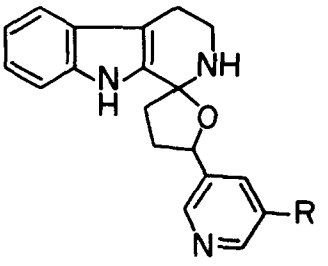
Among the constituents of N. diderrichii were two substances, designated ND-305B and ND-363C, which we characterized as indole-pyridine alkaloids and tentatively assigned structures Ia and Ib, respectively, primarily on the basis of spectroscopic evidence[1]. The evidence, particularly from the nmr spectra, indicated that each substance consisted of a pair of closely related and interconvertible isomers, and it was proposed that there existed a ready path for isomerism through a ring-opened hydroxy imine (II), which could reclose to two epimeric carbinolamine ethers of formula I. Two pieces of evidence were difficult to accommodate in this hypothesis: a peak near τ 8.22 in the nmr spectrum, readily removable by treatment of the sample with D_2O, had to be explained as resulting from an unusual type of hydration of each epimer, and the presence of a strong M-15 peak in the mass spectrum had to be attributed to an unusual fragmentation.

In order to test this hypothesis, several compounds of structure III have been prepared. However, none of the alcohols obtained by hydrolysis of III exhibited spectroscopic characteristics corresponding to those attributed in the case of the alkaloids to the presence of the carbinolamine ether. The non-identity with ND-305B of synthetic II (R=H) established conclusively that the original hypothesis was incorrect and that the alkaloids could not be represented by I. However, observations made during this synthetic study suggested how the original hypothesis could be revised to provide the true structure of the

alkaloids.

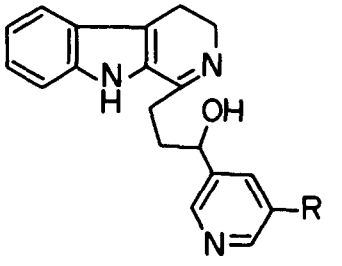
In a model study, harmalan was treated with ethylene bromohydrin and the salt that formed was made basic. The product isolated had the spectroscopic characteristics expected for the oxazolidine IVa, and furthermore they bore a strong resemblance to those of the alkaloids. The appearance of the uv spectrum and its behaviour in acidic, basic and neutral media showed that the indole chromophore had been modified in the same way as that of the alkaloids. The nmr spectrum showed the methyl resonance at τ 8.28 and, furthermore, it was rapidly removed by treatment of the sample with D_2O. When the model compound IVb was synthesized in a similar manner from styrene oxide, the resemblance was even more striking and included the "doubling" of nmr signals associated with the presence of two diastereoisomers[1]. In order to obtain the required pyridine-containing analogs, the epoxide Va was prepared by the reaction of 3-pyridinecarboxaldehyde with dimethyloxosulfonium methylide[2], and 3-carbomethoxy-5-chlorocarbonylpyridine was converted through the stages of diazo ketone, α-bromo ketone and bromohydrin to the epoxide Vb. These epoxides reacted with harmalan to provide materials identical in spectroscopic and chromatographic properties with natural ND-305B and ND-363C, and to which the formulae IVc and IVd can be assigned. Crystalline derivatives of the model compounds IVa (hydrobromide) and IVb (picrate) were obtained for analytical purposes, but IVc and IVd did not provide suitable crystalline derivatives. However, synthetic IVc and IVd gave satisfactory combustion analyses, supported by high resolution mass spectral molecular weight determinations, after they had been carefully purified by tlc and dried to glassy solids.

Consequently structures IVc and IVd can now be confidently assigned to ND-305B and ND-363C, respectively. However, each consists of a pair of epimers which have not yet been separated and, indeed, separation may prove to be impossible. Nevertheless, it appears to be advantageous for future reference to designate each alkaloid by a name, and under formula VI we define the structures and relative configurations of α- and β-naucleonine (ND-305B) and

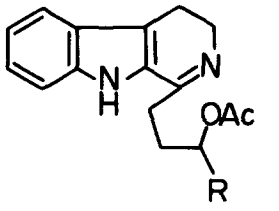


Ia R=H

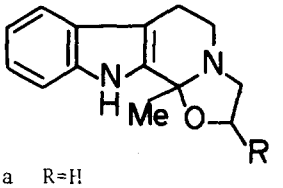
Ib R=CO_2Me



II



III

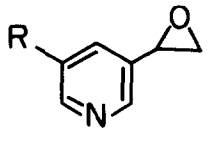


IVa R=H

IVb R=Ph

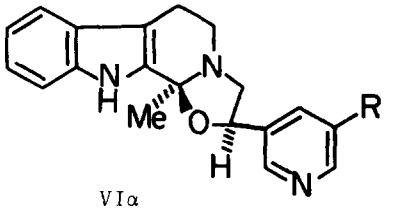
IVc R=3-pyridyl

IVd R=5-carbomethoxy-3-pyridyl



Va R=H

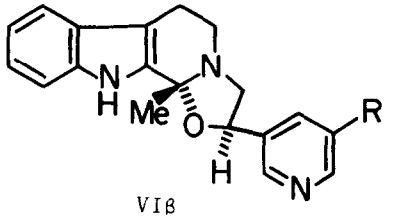
Vb R=CO_2Me



VIα

α-Naucleonine R=H

α-Naucleonidine R=CO_2Me



VIβ

β-Naucleonine

β-Naucleonidine

α- and β-naucleonidine (ND-363C). In the revised formulation it appears probable that equilibration of epimers proceeds through an iminium ion, and the nmr evidence that the methyl protons undergo rapid exchange with D_2O indicates that the corresponding enamine forms part of the equilibrium under the conditions used for observation. A closely related oxazolidine moiety has very recently been assigned to the alkaloid cadambine[3], and there is evidence that it occurs in other alkaloids of this general class.

ACKNOWLEDGMENTS

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