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THE STEREOCHEMISTRY OF THE C-3 ETHYL SIDE CHAIN IN ULEINE AND ITS ANALOGS

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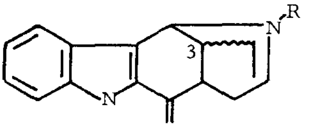
The uleine group of indole alkaloids involves seven bases which have been chemically interrelated (1). Besides uleine (I) itself, the group includes des-N-methyluleine (II), 1,13-dihydro-13-hydroxyuleine (III), dasycarpidone (IV), des-N-methyldasycarpidone (V), dasycarpidol (VI), and des-N-methyldehydrouleine (VII). Many of the essential structural features of these alkaloids have been elegantly derived through chemical degradations and nmr and mass spectral studies (1-3).

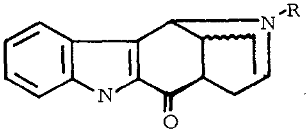
One point of uncertainty that remained, however, was the stereochemistry of the C-3 ethyl side chain in compounds I-VI. The clarification of this point is important for any further synthetic endeavor in this series, as well as for biogenetic considerations. The problem is compounded by the fact that uleine type alkaloids epimeric at C-3 are unknown; all of the bases available possessing the identical stereochemistry at this asymmetric center.

It was, therefore, decided to undertake a systematic study of the pseudo first order rates of methiodide formation for a variety of alkaloids, mostly of the indole type and including uleine, in the hope that comparison of these rates would throw some light on the asymmetry at C-3 in uleine and its analogs. The Table lists the alkaloids that were investigated together with their rates, and here it must be recalled that the kinetics will be primarily dependent upon steric hindrance around the basic nitrogen atom.

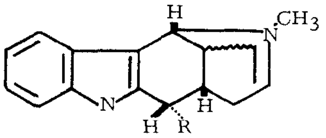
The extremely fast rate of 6×10^{-2} sec^{-1} exhibited by uleine is exceeded only by the



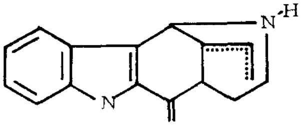
I, R = CH_3
II, R = H



IV, R = CH_3
V, R = H



III, R = CH_2OH
VI, R = OH



VII

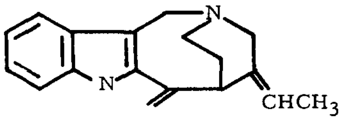
values for apparicine (4) and pseudoyohimbine (5). The only other alkaloid whose rate anywhere approached those for uleine (I), apparicine, and pseudoyohimbine, was akuammidine (6). These last three alkaloids share the common feature of possessing very unhindered basic nitrogen atoms, so that this aspect must also prevail in uleine. On the other hand, the slowest rates were exhibited by α-yohimbine, aspidospermine, and vallesine, where the basic nitrogens are highly hindered. That uleine exhibits a very rapid rate cannot be ascribed solely to the presence of an N-methyl group, since mesembrine which possesses such a group has a slow rate because of hindrance by the aromatic ring.

Considering now the two possibilities for uleine, in expression Ia below the basic nitrogen atom is almost completely unhindered, while in Ib appreciable steric hindrance prevails. In both expressions the N-methyl group was placed in the more stable equatorial configuration (7). Structure Ia, with the C-3 ethyl group pointing away from N_b, must therefore correspond to uleine, and that same steric relationship must also prevail in alkaloids II-VI. Dasycarpidol, for instance, can now be represented by expression VIa in accord with the chemical and spectral data also available for this molecule (1).

The present study demonstrates that kinetic measurements can allow assignments of stereochemistry even when only one of two possible diastereoisomeric forms is avail-

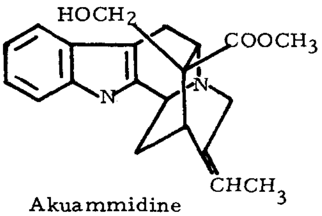
TABLE

Pseudo First Order Rates of Methiodide Formation in sec^{-1} Units



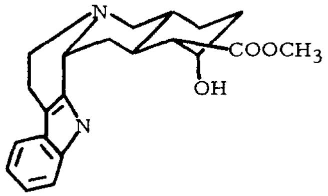
Apparicine

7×10^{-2}



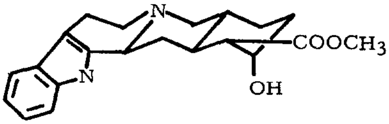
Akuammidine

3×10^{-2}



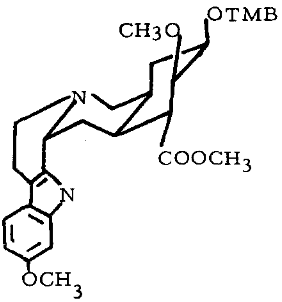
Pseudoyohimbine

7×10^{-2}



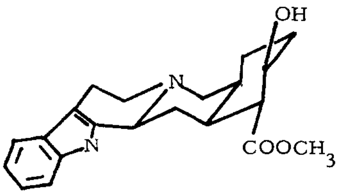
Yohimbine

49×10^{-4}



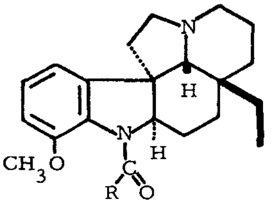
Reserpine

10×10^{-4}



α-Yohimbine

1×10^{-4}

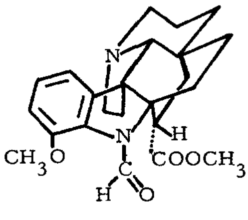


Aspidospermine, $R=CH_3$

1.7×10^{-4}

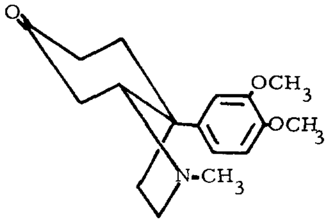
Vallesine, R=H

2.2×10^{-4}



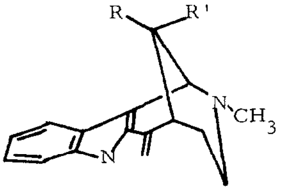
Refractine

22×10^{-4}

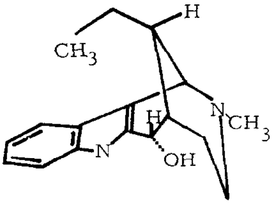


Mesembrine

8×10^{-4}



Ia, $R=C_2H_5$ and $R'=H$
Ib, $R=H$ and $R'=C_2H_5$



VIa

able. The rates were measured on 3 mg of each alkaloid, at 25° in acetonitrile solution as per Ref. 5.

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