

## MICROBIOLOGICAL TRANSFORMATIONS OF 9-AMINO-1,2,3,4,5,6,7,8-OCTAHYDROACRIDINE

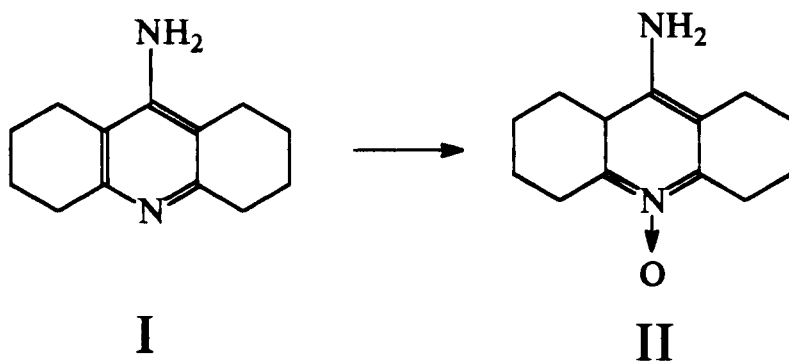
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Microbiological transformations of medicinals are known, on the one hand, to mimic processes for their conversions in animals and man and, on the other hand, to be methods for preparing materials which are potentially active metabolites [1].

Transformation of the antitumour agent acronicin by *Cunninghamella baireri* ATCC 9244 and *C. echinulata* NRRL-3655 [1] and also the conversion of nalidixic acid by cultures of *Penicillium adametii* 737 [2] are completely the same as the metabolism of these compounds in animals and man and produce hydroxylated products in 30-60% yields.

With the objective of functionalizing it, we have investigated microbiological transformations of 9-amino-1,2,3,4,5,6,7,8-octahydroacridine (I), an analog of 9-amino-1,2,3,4-tetrahydroacridine (the medicinal "Tacrine") which regulates transmission of nerve impulses by inhibition of choline esterase and by changing the permeability of the cell membrane to calcium.

Of the six strains of fungi from the genera *Beauveria*, *Aspergillus*, *Cunninghamella*, and *Penicillium* known to transform nitrogen heterocycles which we investigated, only a suspension of nonreproducing cells of *Cunninghamella verticillata* VKPM F-430 transformed compound I under standard conditions [1]. A single transformation product — 9-amino-1,2,3,4,5,6,7,8-octahydroacridine 10(N)-oxide (II) — was isolated in 90% yield by column chromatography of the dried chloroform extract ( $R_f$  0.38 with 70:30:10 chloroform-methanol-saturated aqueous ammonia).



Comparison of the IR spectra of compounds II and I showed that the doublet absorption for the amino N-H ( $3200-3300\text{ cm}^{-1}$  in compound I) was shifted to higher frequency.

Even larger shifts were observed for the C=N stretch ( $1620$  and  $1580\text{ cm}^{-1}$  for compounds II and I respectively) and aliphatic C-H deformation. The absorption bands in the  $1200-1300\text{ cm}^{-1}$  were more intense for compound II.

$^1\text{H}$  NMR spectra of compounds I and II were similar but the signals of the  $\text{NH}_2$  and  $\text{CH}_2$  groups in positions 4 and were shifted to weaker field for compound II. It follows from the  $^{13}\text{C}$  NMR spectra that atoms  $\text{C}_{(4a)}$  and  $\text{C}_{(8a)}$  are more strongly shielded in compound II. The shielding of the hydrogen and carbon atoms is connected to the inductive effect of the N-oxide unit and in part to the magnetic anisotropy of the N-O bond. Localization of the negative charge at carbon<sub>(9)</sub> in compound II causes to be deshielded which was confirmed spectroscopically.

The mass spectra of compounds II and I are almost completely the same but the ions  $\text{M}^+$ ,  $[\text{M}-\text{H}]^+$  and  $[\text{M}-2\text{H}]^+$  - have smaller intensity for compound II.

Mass spectra (w/z, relative intensity, %): compound I 202 (100) (M), 201 (45) (M-H), 200 (8) (M-2H), 174 (15) (M-  $\text{C}_2\text{H}_4$ ), 173 (12) (M-H -  $\text{C}_2\text{H}_4$ ), 146 (5) (M- $\text{C}_2\text{H}_4$  -  $\text{C}_2\text{H}_4$ ); compound II 218 (10) (m), 127 (15) (M-H), 216 (48) (M-2H), 202 (100) (M-O), 201 (73) (M-O - H), 200 (10) (M-O - 2H), 174 (14) (M-O -  $\text{C}_2\text{H}_4$ ), 173 (8) (M-O - H -  $\text{C}_2\text{H}_4$ ).