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

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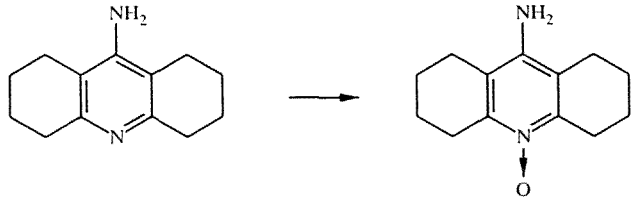
Microbiological transformations of medicinals are known, on the one hand, to mimic processes for their conversions in animals and man and , on the other hand, to be methods for preparing materials which are potentially active metabolites [1].

Transformation of the antitumour agent acronicin by *Cunninghamella baineri* ATCC 9244 and *C. echinulata* NRRL-3655 [1] and also the conversion of nalidixic acid by cultures of *Penicillium adametzi* 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.



I II

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

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

^1H NMR spectra of compounds I and II were similar but the signals of the NH_2 and CH_2 groups in positions 4 and 5 were shifted to weaker field for compound II. It follows from the ^{13}C NMR spectra that atoms $C_{(4a)}$ and $C_{(8a)}$ 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 $carbon_{(9)}$ 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 $M^{\cdot +}$, $[M - H]^+$ and $[M - 2H]^{+\cdot}$ have smaller intensity for compound II.

Mass spectra (*m/z*, relative intensity, %): compound I 202 (100) (M), 201 (45) (M-H), 200 (8) (M-2H), 174 (15) (M-C_2H_4), 173 (12) (M-H — C_2H_4), 146 (5) (M-C_2H_4 — C_2H_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 — C_2H_4), 173 (8) (M-O — H — C_2H_4).

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The mass spectrum of deuterated II has the molecular mass increased by two which indicates that the compound is not a hydroxylated aminoacridine. Ions with *m/z* 203 $[M + 3H - H_2O]^+$ and 221 $[M + 3H]^+$ were observed in the secondary ion mass spectrum of compound II. The latter is formed by additional protonation of the $[M + H]^+$ at the oxygen atom of the N-O group and at the nitrogen atom of the amino group.

There is therefore no doubt about the structure of compound II.

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