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Mendeleev Commun., 1991, **1(2)**, 42–43
Mendeleev Communications

A Novel Microbial Transformation of γ-Carboline Derivative 3,6-Dimethyl-9-[2-(2-methylpyrid-5-yl)ethyl]-1,2,3,4-tetrahydro-γ-carboline

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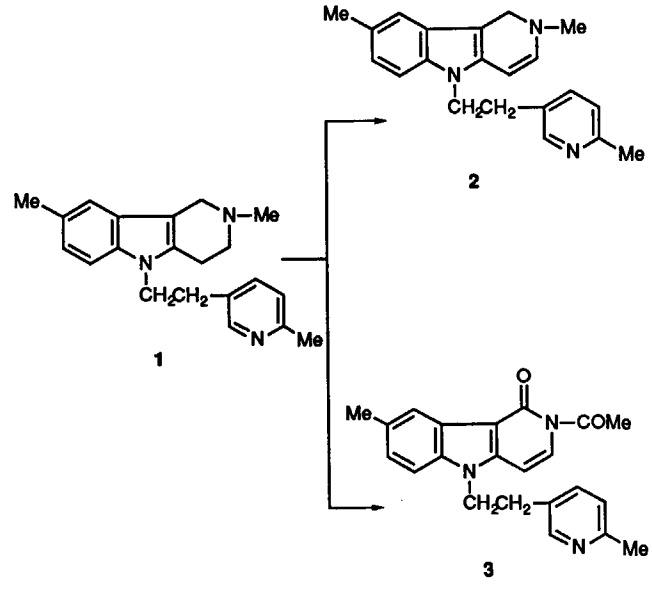
The transformation of 'Dimebon', a γ-carboline derivative, has been accomplished by *Penicillium simplicissimum* and involves dehydrogenation of the γ-carboline ring, followed by *N*-demethylation, formation of a carbonyl group at C-4 and *N*-acetylation.

Microbial transformation is known to provide both a model process for drug metabolism in animals and in humans, and also a method for the synthesis of potentially physiologically active metabolites.[1]

Thus, the biotransformation of the carcinostatic drug acronicine by *Cunninghamella bainieri* ATCC 9244 and *C. echinulata* NRRL-3655,[1,2] along with the transformation of nalidixic acid by *Penicillium adametzi* 737,[3] completely mimics the metabolism of these compounds in humans and animals. In all cases the hydroxy derivatives were obtained in 30–60% yields.

To our knowledge, the microbial transformation of γ-carboline derivatives has never been described previously. We have investigated the transformation of 3,6-dimethyl-9-[2-(2-methylpyrid-5-yl)ethyl]-1,2,3,4-tetrahydro-γ-carboline **1**, which possesses strong antihystaminic activity (USSR trade mark 'Dimebon').[4]

In order to achieve the transformation, we chose the following fungal cultures: *Beauveria bassiana* ATCC 7159 which is able to transform β-carboline derivatives,[5] along with *Aspergillus niger* VKMF-1119, *A. awamori* VKMF-758, *B. bassiana* VKMF-3111D, *C. verticillata* VKPMF-430 and *P. simplicissimum*, which perform stereoselective hydroxylation of ethylpyridines[6] and of 1-benzoylpiperidine.[7] Biotransformations were carried out following the known methods for culture growth and with previously grown cells.[6] *P. simplicissimum* proved to be the only species among those listed capable of transforming **1**. From a



Scheme 1

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chloroform extract of the fermentation medium two products **2** and **3** were isolated in 10% yields by column chromatography. Both differ distinctly from **1** in their chromatographic properties [**2**: R_f 0.25, **3**: R_f 0.17; solvent system ethanol–aqueous ammonia (5:4)] (Scheme 1).

The IR spectrum of **2** showed a weak band at 1600 cm^{-1} ($\nu_{C=C}$) and no absorption in the 3200–3600 cm^{-1} region, ruling out the possibility of the involvement of the hydroxylation process. The mass spectrum of **2**† showed that the β-pyridylethyl moiety was left unchanged, but the mass of the molecular ion was 2 amu less than that of **1**. The latter fact made us think that **2** is the dehydrogenation product of **1**. This hypothesis also explains the high intensity of the (M – H)† peak in the mass spectrum of **2** due to hydrogen loss from the dihydropyridine ring. A similar enzymatic dehydrogenation was noted in the biotransformation of the alkaloid glaucine by *Fusarium solani* ATCC 12823.[8] Analogous processes are known to take place in humans.[9]

The IR spectrum of **3** showed no absorption in the 3200–3600 cm^{-1} region, but there were two carbonyl bands at 1650 and 1715 cm^{-1}. The mass of the molecular ion of **3**† and the fragmentation pattern showed that the β-pyridylethyl moiety was still intact and that a carbonyl and an acetyl group had been introduced into the γ-carboline ring. All the conclusions drawn from the IR and MS data are in agreement with the structure proposed for **3**. Compound **3** may have been produced by demethylation of **2** followed by oxidation of C-4 of the carboline ring and acetylation of the nitrogen atom. Such processes also take place during the biotransformation of the alkaloid vindoline by *Streptomyces albogriseus* NRRL 5748 and of α-tetrandine by *C. blakesleeana* 8688a.[8] Demethylation of nicotine and of doxylamine has been observed previously in humans,[9] and microbial *N*-acetylation is described, for example, by Kieslich.[10]

In conclusion, the microbial transformation of the γ-carboline antihystaminic drug 'Dimebon' by *P. simplicissimum* involves the dehydrogenation of its saturated ring followed by demethylation, *C*-oxidation and *N*-acetylation, unlike the known biotransformation of similar heterocycles such as β-carboline.

We thank Dr Marina A. Yurovskaya (Moscow State University) for a sample of 'Dimebon'.

Received in USSR, 20th December 1990
Received in UK, 25th January 1991; Com. 1/00063B

† *Mass spectrum* of compound **2**: *m/z* (rel. intensity, %) 317(34) (M), 316(100) (M – H), 315(12) (M – 2H), 210(9) (M – H – C_7H_8N), 209(14) (M – 2H – C_7H_8N), 195(22) (M – 2H – $C_8H_{10}N$), 120(9) ($C_8H_{10}N$), 119(8) (C_8H_9N).

For **3**: *m/z* (rel. intensity, %) 359(19) (M), 317(22) (M – C_2H_2O), 316(36) (M – C_2H_3O), 289(100) (M – C_2H_2O – CO), 183(22) (M – C_2H_2O – CO – C_7H_8N), 170(18) (M – C_2H_2O – CO – C_8H_9N), 120(32) ($C_8H_{10}N$).

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