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THE SYNTHESIS OF 8-HYDROXY- AND 8-METHOXY-ELLIPTICINES[1]

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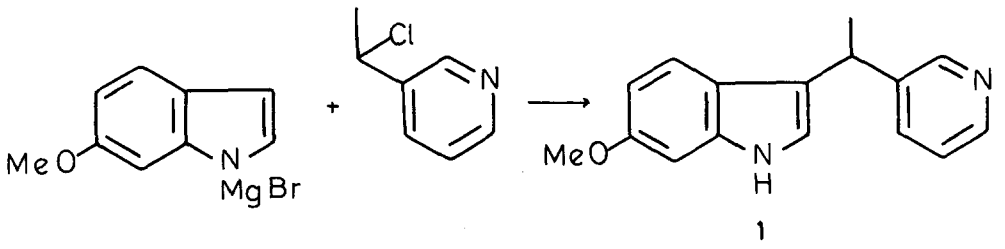
Abstract: The first synthesis of 8-hydroxyellipticine is described and its identity with an ellipticine metabolite from Aspergillus alliaceus confirmed.

When the anti-tumour agent ellipticine (5, R=H) was fed to the mould Aspergillus alliaceus two hydroxylated derivatives were formed, one of which was shown to be 9-hydroxyellipticine by direct comparison with an authentic specimen, whereas the other isomer was assumed to be 8-hydroxyellipticine (5, R=OH) on the basis of spectroscopic evidence.[2]

8-Hydroxyellipticine has not been synthesised and it is interesting that the rat liver microsomal enzyme hydroxylates ellipticine at positions 7- and 9.[3] Thus the unequivocal identification of the fungal metabolite is of some importance and here we report a synthesis of 8-hydroxyellipticine which is now shown to be identical in every respect with the compound previously obtained from A. alliaceus - confirming the original proposal.

6-Methoxyindolyl magnesium bromide was reacted with 3-(1-chloroethyl)pyridine in diethylether:tetrahydrofuran (4:1) at room temperature to give the indolylpyridylethane (1) (40%). This with O-mesitylene sylphonyl hydroxylamine, followed by N-acetylation with acetic anhydride and N-methylation with methyl iodide, afforded the salt (2), reaction of which with potassium cyanide in water, and photolysis of the intermediate 1,4-dihydropyridine (3) yielded the nitrile (4). Treatment of the nitrile with methyllithium and work-up in the presence of aqueous acetic acid gave 8-methoxyellipticine (5, R=OMe) m.p. 280-281°. Demethylation of this product with pyridinium chloride at 210-220° afforded 8-hydroxyellipticine (5, R=OH), m.p. and mixed m.p. 268° (dec.).[3] The overall yield from the indolylpyridylethane (1) to 8-methoxy-ellipticine was 42% but the productivity in the final O-demethylation step to

8-hydroxyellipticine was only 30%.



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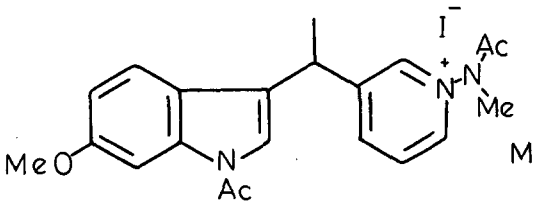

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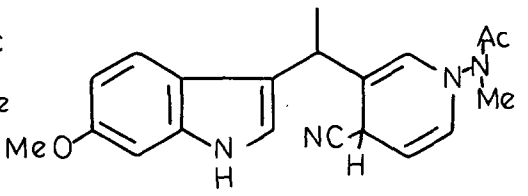

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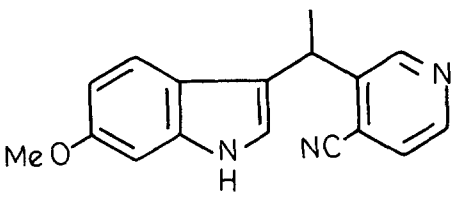

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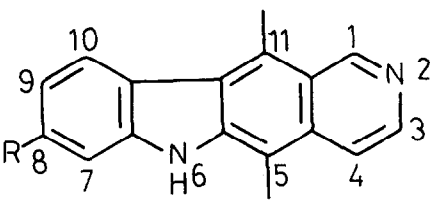

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(Satisfactory analytical data were obtained for all the compounds mentioned.)

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