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THE REACTION OF 3-METHYLBUT-2-ENAL WITH TRYPTAMINE AND ITS DERIVATIVES. A SUGGESTION FOR THE BIOSYNTHESIS OF AUSTAMIDE

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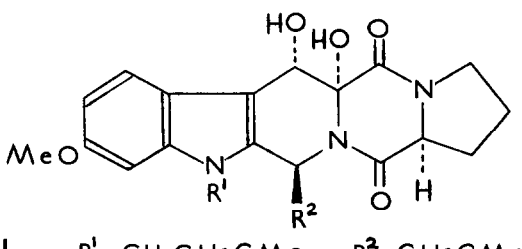
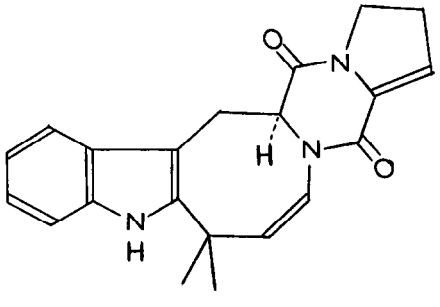
SUMMARY. Tryptamine and 3-methylbut-2-enal furnished the conjugated imine 3b which cyclised with pyridine-tosyl chloride to yield the N-tosyl-tetrahydro-β-carboline 10; alternatively in pH 6.2 aqueous buffer the hydroxyisobutyl derivative 9b was formed. The reaction of L-tryptophan methyl ester with the same aldehyde and the possible biosynthetic relevance of these studies are discussed.

1-Alkyltetrahydro-β-carbolines may be synthesised by the Pictet-Spengler-like condensation of a tryptamine derivative with an appropriate aldehyde.[1] Hitherto no example has been reported of the use of a simple α,β-unsaturated aldehyde in a condensation of this type. I suggest that the fungal metabolites fumitremorgin B[2] 1a and the indole 2 related to austamide,[3] may arise biosynthetically from tryptophan and 3-methylbut-2-enal via alternative modes of cyclisation of a common precursor, the α,β-unsaturated imine 3.



1 a; $R^1 = CH_2CH{:}CMe_2$, $R^2 = CH{:}CMe_2$
b; $R^1 = H$, $R^2 = CH_2CMe_2OH$



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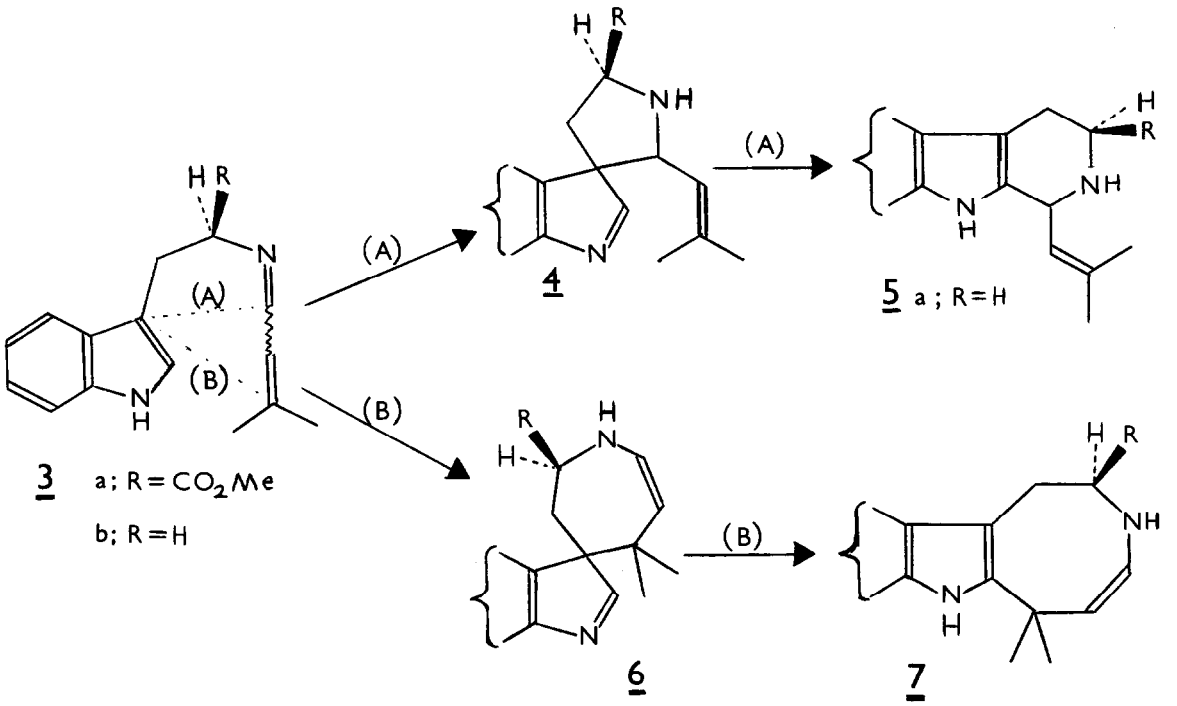
It is suggested that the early stages of the biosynthesis of fumitremorgin B follow the unexceptional Pictet-Spengler-like sequence 3→4→5 (Scheme 1A). Alternatively the α,β-unsaturated imine 3 may, in principle, undergo an unprecedented conjugate cyclisation 3→6. Further transformation of the indolenine 6

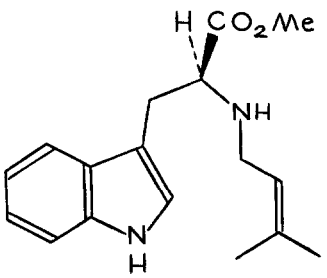
could lead via 7 to the fungal product 2 (Scheme 1B). The possible existence of the latter cyclisation route is consistent with stereoelectronic considerations.[4] Thus with respect to the C=N moiety of 3 the conversion 3→4, although well-precedented,[1] involves a 5-endo-trig ring closure and so should be disfavoured with respect to the postulated 7-endo-trig cyclisation 3→6. On the other hand it is unlikely that the latter cyclisation could occur in one step owing to severe steric hindrance in the required conformation of the syn imine 3. The study outlined below of the chemistry of imines related to 3 was prompted by these biosynthetic considerations.

L-Tryptophan methyl ester condensed smoothly with 3-methylbut-2-enal to yield the imine 3a, m.p. 131-132.5°, ν_{max}^{KBr} 1740, 1662, and 1610 cm.$^{-1}$, δ($CDCl_3$) 7.78 (1H, d, J 10Hz, N=CHCH=) and 6.03 (1H, d, J 10Hz, N=CHCH=). Additional evidence for the structure assigned to this imine was furnished by its reduction with sodium borohydride in methanol which gave the expected N-dimethylallyl derivative 8, m.p. 103.5-104°, $[\alpha]_D^{21}$ + 16.5°, δ($CDCl_3$) 5.2 (1H, t, J 6Hz, $NHCH_2CH$=), 3.16 (2H, d, J 6Hz, $NHCH_2CH$=), M^+ 286. However attempts with acid catalysis or under neutral conditions[5] to effect Pictet-Spengler-like cyclisation of the imine 3a were uniformly unsuccessful. In contrast, the saturated aldehyde 3-methylbutanal smoothly condensed with L-typtophan methyl ester in refluxing benzene[5] to yield the expected diastereoisomeric tetrahydro-β-carbolines 9a.

Tryptamine was similarly converted to the imine 3b which also failed to cyclise under acid catalysis but underwent a smooth reaction on treatment with p-toluenesulphonyl chloride-pyridine[6] to form the N-tosyl-tetrahydro-β-carboline 10, m.p. 175-176°, δ($CDCl_3$) 5.85 (1H, d, J 10Hz, NCHCH=), 4.10 and 3.25 (each 1H, m, CH_2CH_2N) and 2.65 (2H, m, CH_2CH_2N), M^+ 380. Tryptamine also condensed with 3-methylbut-2-enal in aqueous phosphate buffer at pH 6.2[7] to give in 50% yield the tertiary alcohol 9b, m.p. 194-195.5°, δ($CDCl_3$) 7.6-7.0 (4H, m, aromatic), 4.38 (1H, m, $NHCHCH_2$), 3.15 and 2.75 (each 2H, m, CH_2CH_2), 1.88 (2H, m, $NHCHCH_2$), 1.41 and 1.28 (each 3H, s, Me_2), M^+ 244. Conclusive evidence for the structure of this product was furnished by the ^{13}C n.m.r. spectrum ($CDCl_3$) which showed inter alia resonances at 22.4 and 44.6 ppm. (CH_2CH_2N), 49.5 ($CHCH_2CMe_2OH$), 39.7 ($CHCH_2CMe_2OH$), 70.6 (CH_2CMe_2OH), 29.0 and 31.3 ppm. (CH_3)$_2$ with the appropriate multiplicities and relative to TMS at 0.0 ppm. It is inconceivable under the reaction conditions used that the alcohol 9b could have been formed by hydration of the expected product 5a; hence it is suggested that the intermediate imine 3b undergoes Michael addition of water followed by normal Pictet-Spengler cyclisation. The recently reported isolation of the natural alkaloid 1b,[8] which contains a hydroxyisobutyl substituent equivalent to that in 9b, suggests that this Michael addition may have biosynthetic relevance also. While no evidence was found in this study for the postulated conjugate cyclisation 3→6, the isolation of 9b and 10 represent the first successful Pictet-Spengler cyclisations performed with α,β-unsaturated imines.



SCHEME 1



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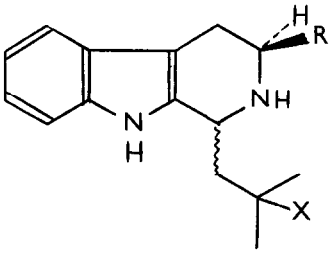
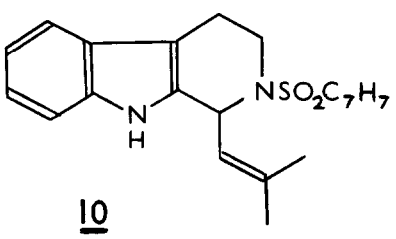


9 a; R = CO_2Me, X = H
b; R = H, X = OH



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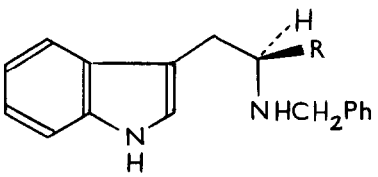

11 a; R = CO_2Me
b; R = H

The imines 3a and 3b presumably both possess the anti configuration. It was expected that the N-benzyl-tryptamines 11a and 11b would undergo Pictet-Spengler cyclisation with 3-methylbut-2-enal via the syn and anti imminium cations. In the event 11a and 11b were recovered unchanged after prolonged refluxing with 3-methylbut-2-enal in benzene or toluene solutions. Under the same conditions[9] 11a and the saturated aldehyde 3-methylbutanal gave the expected tetrahydro-β-carboline derivative. The reactions of the hydroperchlorate salts of 11a and 11b with 3-methylbut-2-enal are presently under investigation.

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