AMYRIS OF JAMAICA. A NEW NICOTINAMIDE FROM AMYRIS PLUMIERI D.C. (RUTACEAE)

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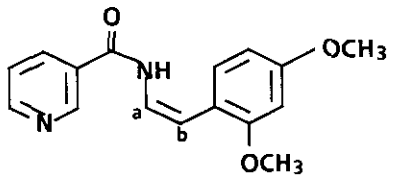
Abstract - A new nicotinamide, isolated from Amyris plumieri is assigned the structure (*1*) on the basis of spectroscopic and chemical evidence. Compound (*1*) was converted to a hydroxy oxazoline, a possible biogenetic precursor of oxazoles.

In the course of our studies[3-6] on the constituents of Amyris, a genus with three species in Jamaica, we have isolated an array of secondary metabolites which have resolved the taxonomic dispute relating to this genus and substantiated the hypothesis[7,8] that β-phenylethylamides are precursors of the 1,5-diaryloxazoles. Our continued efforts to determine the complete range of phytochemical intermediates between these structural extremes have led to the isolation of a new Z-α-styryl nicotinamide from Amyris plumieri.

Dried, milled leaves and twigs of A. plumieri were percolated with toluene. The solvent on evaporation yielded a gum which upon trituration with ethyl acetate afforded compound (*1*) as the residue. Recrystallization from methanol gave pale yellow plates, mp 124.5 - 125.5°C, which analyzed for $C_{16}H_{16}N_2O_3$. UV maxima at 212, 253 and 313 nm (log ε 4.45, 4.18 and 4.13, respectively) indicated an aromatic and styryl moiety while absorption at 3322 and 1653 cm^{-1} in the IR spectrum suggested an amide group.



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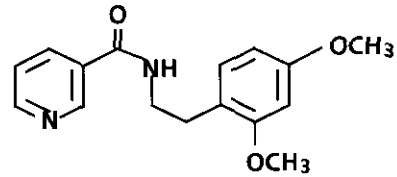

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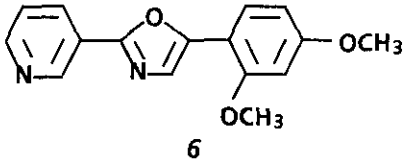
The ^1H NMR (400 MHz) spectrum of (*1*) in $CDCl_3$ gave signals diagnostic of a 3-pyridyl system between δ 7.44 - 9.99 for the nicotinamide segment,[9] while a one-proton doublet (J = 10Hz) at δ 9.16 which exchanged slowly (deuterium oxide) and two resonances at δ 7.07 (one-proton triplet, J = 10Hz, collapsing to a doublet upon deuterium exchange of the amide proton) and δ 5.79 (one proton doublet, J = 10Hz) indicated the

fragment Ar-CO-NH-CH=CH-Ar. The Z-geometry of the unsaturated linkage was based on the coupling constant (J=10Hz) displayed by the olefinic protons. This latter value compares favorably with the value (14.5Hz) for the E-isomer. Both values however are in the lower range expected for the respective isomers because of the electronegativity of the nitrogen atom attached to the olefinic linkage. The 1,2,4-substitution pattern on the benzene ring was revealed by signals at δ 3.86 (3H,s,OCH_3), 3.95 (3H,s,OCH_3), 6.57 - 6.63 (2H,m) and 7.8 (1H,d,J=8Hz).

Chemical confirmation of the olefinic system in (*1*) was achieved by catalytic hydrogenation to (*2*) using 10% Pd/C. Recrystallization of (2) from methanol furnished plates, $C_{16}H_{18}N_2O_3$, mp 113 - 113.5°C. The UV spectrum of this compound no longer showed the absorption at 313 nm, indicating loss of the styryl moiety. The ^1H NMR (60 MHz) spectrum was consistent with structure (*2*), the olefinic protons being replaced by a two-proton triplet (J=6Hz) at δ 2.88 and a two-proton quartet (J=6Hz, collapsing to a triplet after addition of D_2O) at δ 3.68. An exchangeable proton was present at δ 6.59 (broad multiplet). The E-isomer of (*1*) had previously been converted to (*2*)[3]. The two are thus correlated chemically.



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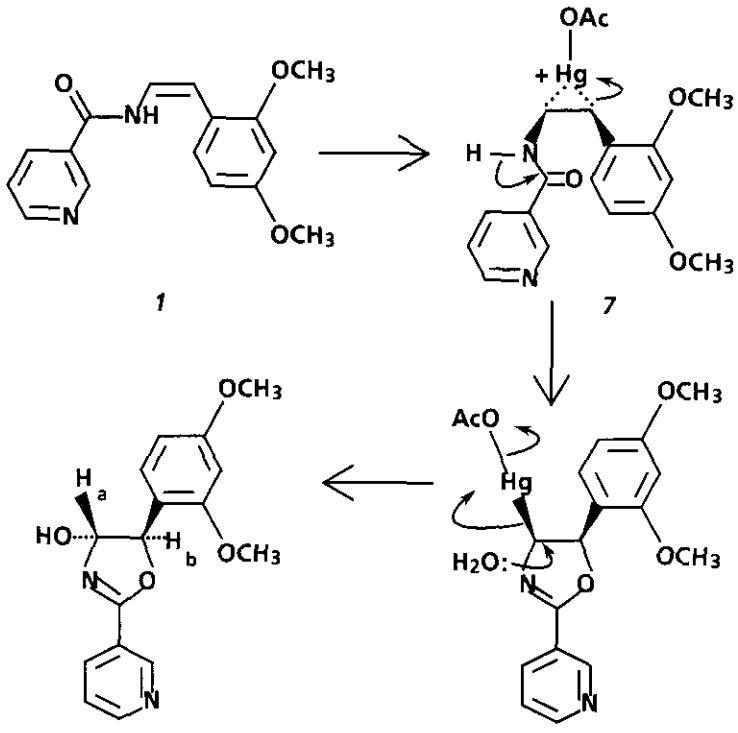
In an attempt to mimic the possible biogenetic-like oxidative conversion of enamide to oxazole (*6*), the styrylamide (1) in THF was treated with an aqueous solution of mercury-II acetate[10]. The reaction was virtually instantaneous and the product was identified as trans-4-hydroxy-5-(2,4-dimethoxyphenyl)-Δ^2-oxazoline (*9*). This interesting oxidative cyclization may be rationalized by a pathway represented by Scheme I. An electrophilic attack by mercuric acetate on the olefinic bond forms the adduct (*7*) which upon subsequent intramolecular attack of the entropically poised nucleophilic oxygen of the carbonyl group on the benzylic carbon bearing the dimethoxyphenyl group gives the acetoxymercurio derivative (*8*). The intermediate (*8*) then undergoes demercuration by a bimolecular process in which water displaces the acetoxymercurio group with concomitant inversion to give the trans-Δ^2-oxazoline (*9*). The reaction proceeded with good yield (75%).



Scheme I

Compound (*9*) crystallized from methanol as needles, mp 144-144.5°C and analyzed for $C_{16}H_{16}N_2O_4$. The UV maxima [269, 227 nm (log ε 3.92 and 4.32 respectively)] and IR absorptions (1613, 1590 cm^{-1}) of (*9*) indicated that the aromatic nuclei were retained. The ^1H NMR (60 MHz) spectrum was in accordance with the proposed structure. Present at δ 7.32 - 9.22 were the signals typical of the 3-substituted pyridine segment. A six-proton singlet at δ 3.78(OCH_3 x 2), a multiplet δ 6.30 - 6.63(2H) and a doublet (1H, J = 9Hz) at δ 7.12 identified the 1,2,4-trisubstituted phenyl species. A pair of mutually coupled AB doublets (J = 4Hz) at δ 5.63 and 5.84 for the trans-coupled protons on the five membered-heterocyclic ring and a broad multiplet at δ 5.87, exchangeable on addition of D_2O, for the hydroxyl proton signalled the hydroxyoxazoline moiety. The small value for the trans coupling on the five membered ring of oxazolines is expected[11]. In addition to the molecular ion (M^+, 300) the mass spectrum of (*9*) showed facile loss of water (m/z 282, 100%). This latter peak and the remainder of the spectrum displayed the pattern expected of the oxazole (*6*) formed from such a dehydration[3].

Attempts to dehydrate the hydroxyoxazoline led to the recovery of starting material or fragmented products. This is not unexpected as a cis elimination of water would be required. Nevertheless the synthetic utility of the styrylamide - oxazoline conversion and its relevance to the overall biosynthetic sequence is of importance in our studies. It illustrates that the styrylamides may indeed be true intermediates in the

pathway from the β-phenylethylamides to the 2,5-diaryloxazoles. These latter compounds were also found in the Jamaican variety of A. plumieri.[3,5,12]

REFERENCES

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