AMYRIS OF JAMAICA. 2,5-DIARYLOXAZOLES AND A CHROMENE FROM AMYRIS PLUMIERI D.C (RUTACEAE)

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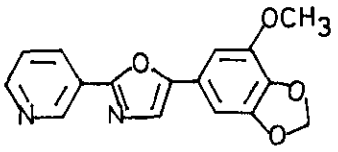
Abstract - The isolation and identification of three new heterocyclic compounds (two oxazoles and a chromene) from Amyris Plumieri is presented.

In connection with our taxonomic studies on the Jamaican Amyris genus[1-4], we have isolated the oxazoles (1) and (2) and the chromene (3) from Amyris plumieri. This genus has been classified by certain authors as belonging to the family, Burseraceae[5] and by others as belonging to Rutaceae[6]. The isolation and characterisation of these oxazoles and chromene, however, support our earlier chemical evidence[1-4] for placing the Jamaican Amyris in Rutaceae.



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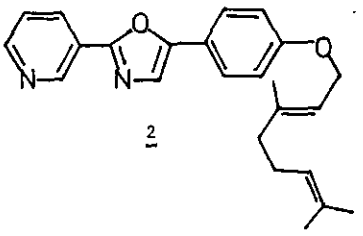

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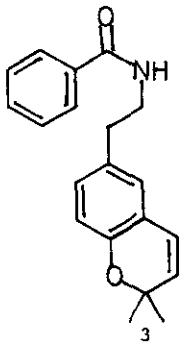

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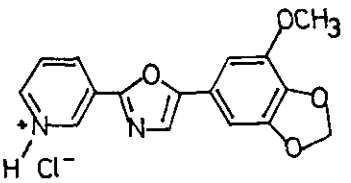

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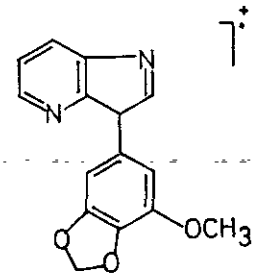
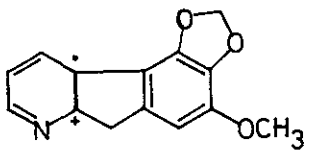
Toluene extraction of the milled aerial portion of A. plumieri followed by purification by column and preparativr layer chromatographies afforded the oxazole (1) as colorless needles, $C_{16}H_{12}N_2O_4$, mp 188-189°C, the oxazole (2) as an oil and the chromene (3) as colorless plates, $C_{20}H_{21}NO_2$, mp 133.5-134.5°C.

The infrared spectrum of (1) showed absorptions at 1608 and 1588 cm^{-1}, indicative of an aromatic nucleus while the ultraviolet spectrum with maxima at 205, 247 and 331 (log ε 4.37, 4.00 and 4.18 respectively) nm shifted in acid to 213, 267 and 347 (log ε 4.37, 4.01 and 4.03 respectively) nm. This unusual bathochromic shift of the maxima on addition of acid has been observed before[7,8] and has been attributed by Burke and Parkins[1] to the formation of the salt (4). The pyridinium cation in (4) being more electron-withdrawing than the unprotonated species (1) causes this shift to longer wavelength. The ^1H NMR (100 MHz) in $CDCl_3$ confirmed the structure (1) for this 2,5-diaryloxazole by showing an ABCD system between δ 7.46 - 9.35 for the 3-substituted pyridine fragment[9], a sharp one-proton singlet at δ 7.40 for the oxazole proton, H-4 and a two-proton singlet at δ 6.95 for the aromatic protons of the tetra-substituted phenyl ring. A three-proton singlet at δ 4.02 and a two-proton singlet at δ 6.08 were assinged to the aromatic methoxy and methylenedioxy groups respectively.

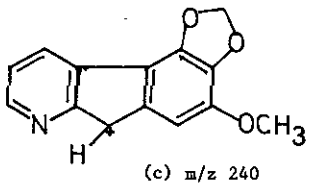
The mass spectral ions (a - e) of (1) fully concurred with the proposed structure. Loss of HCN and CO - typical cleavages of 2,5-diaryloxazoles[10] - from the molecular ion was the primary fragmentation process. The molecular ion at m/z 296 was the base peak.



(a) m/z 268



(b) m/z 241



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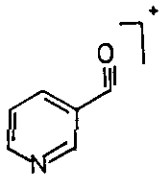
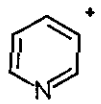


(d) m/z 106



(e) m/z 78

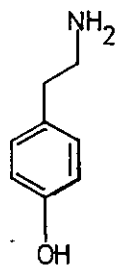
The oxazole (2) showed infrared absorptions at 1615 and 1607 cm^{-1}, these being aromatic peaks. The ^1H NMR spectrum (60 MHz) was in agreement with the structure (2). This was deduced from four sets of signals: the first set being the familiar ABCD system (δ 7.43 - 9.25) for the 3-substituted pyridine moiety; the second set consisting of a sharp singlet at δ 7.30 for the H-4 oxazole proton; the third set consisting of an A_2B_2 system at δ 6.95 and δ 7.60 for the para-disubstituted phenyl ring and the fourth set indicative of the geranyl side chain {δ 1.62, 1.68, 1.75, (9H, each s, =C(CH_3) × 3); 1.95 - 2.45 (4H, m, =CH-CH_2- × 2); 4.57 (2H, d, J = 6Hz, -OCH_2-): 4.95 - 5.62 (2H, m, =CH- × 2)}

The oxazole moieties of (1) and (2) were easily identified in the crude toluene extract because of the characteristic fluorescence displayed by them when subjected on the chromatoplate to long wavelength (366 nm) ultraviolet radiation. This behaviour is not surprising, for it is well known that 2,5-diaryloxazoles possess the best scintillation properties of all compounds[11].

The chromene (3) displayed ultraviolet maxima at 224, 264 (shoulder), 273 (shoulder) and 313 (log ε 4.56, 3.70, 3.53 and 3.36 respectively) nm while its infrared spectrum showed absorptions suggestive of a secondary amide function (3298, 1628 cm^{-1}). The presence of the 2,2-dimethylchromene moiety was evident from the ^1H NMR spectrum. This was indicated by a six-proton singlet at δ 1.42 and an AB quartet (J = 10Hz) centered at δ 5.59 and δ 6.28. Two multiplets, one at δ 7.61 - 7.81 (2H) and other at δ 7.18 - 7.58 (3H), were the signals for the benzoyl group while a three-proton multiplet between δ 6.71 - 6.98 (aromatic protons of a monosubstituted chromene moiety), a two-proton triplet (J = 6.5Hz) at δ 2.81 and a two-proton quartet (J = 6.5Hz) at δ 3.66, collapsing to a triplet on deuterium exchange of the amide proton present at δ 6.21, were the PMR resonances representing the remainder of the molecule.

Conformation of the benzoyl portion in (3) was achieved by acid hydrolysis employing concentrated hydrochloric acid. The product obtained was benzoic acid, identified by comparison with an authentic sample.

The structure (3) for this natural product was finally confirmed by synthesis from tyramine (5). Condensation of (5) with excess benzoyl chloride followed by hydrolysis under basic condition yielded the amide (6). Treatment of (6) with 3-chloro-3-methylbut-1-yne in the presence of potassium iodide and potassium carbonate provided the propargyl ether (7) which then rearranged to the chromene



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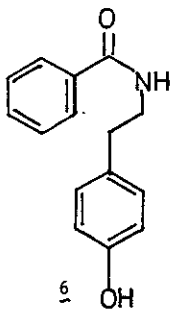

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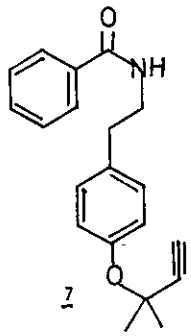

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(3) in boiling N,N-diethylaniline. The synthetic chromene proved to be identical in all respects to the naturally occurring compound.

The co-occurrance of the oxazoles (1) and (2) and the chromenylated tyramide (3) gives credence to the suggestion of Crow and Hodgkin[7] who claimed a biogenetic relationship between these two compounds. Oxazoles are rare as natural products and are of importance as they are known to show marked mitoinhibitory activity[12]. However, the biological activity of the two new oxazoles reported here has not yet been examined.

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