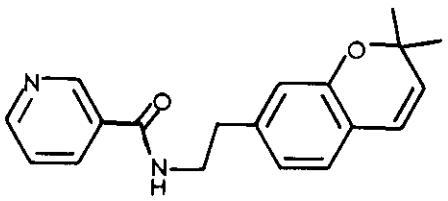
AN OXAZOLE AND ITS PRECURSOR IN AMYRIS BALSAMIFERA

Basil Burke*, Helen Parkins, and Ann Marie Talbot

Department of Chemistry, University of the West Indies, Mona, Kingston 7, Jamaica

Abstract -- The discovery of the oxazole, balsoxin (6), and the β-hydroxy-β-phenylethylamide, balsamide (4), constitutes further evidence for the biogenetic relationship between these types of compounds. The structures and correlation of these compounds are presented.

During a recent taxonomic investigation of the Amyris species of Jamaica, we discovered the nicotinamides (1) and (2) to be co-metabolites of the oxazole (3) in A. plumieri.[1] This co-occurrence of amide and oxazole lends credence to the ideas of Crow and Hodgkin[2] who suggested a possible *biogenetic relationship between these two types of compounds.*



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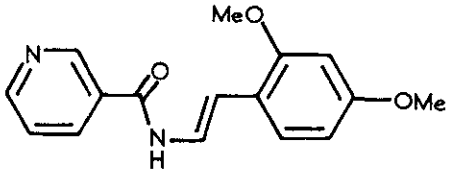

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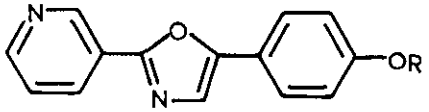
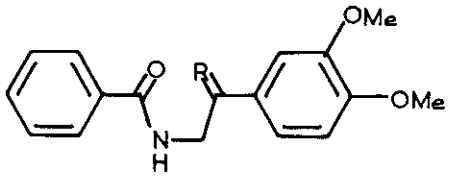


3, R = $CH_2CH = C(CH_3)_2$

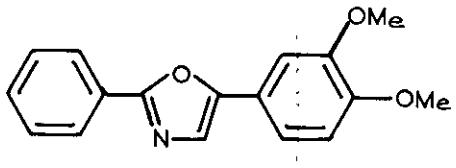
Another interesting feature is that the plant, A. plumieri, is purported to be useful against cancer.[3] This practice may soon find a serious scientific basis when it is considered that certain substituted oxazoles show marked mitoinhibitory activity.[4] Recently also, Wehrmeister has extended the biological uses of oxazole derivatives by producing tranquilizers, the composition of which are based on the dihydrooxazole nucleus.[5]

Our investigations on A. plumieri have not yet yielded further oxazoles. However, A. balsamifera has produced a new naturally occurring oxazole (6) as well as the amide (4) as an obvious biogenetic precursor of the former. Both compounds were obtained from the benzene extract of the dried milled aerial portion of A. balsamifera. After the usual purification by column and preparative thin layer chromatography we isolated the amide (4) which we have named balsamide as colourless prisms, $C_{17}H_{19}NO_4$, m.p. 135-136°, and the oxazole (6), balsoxin, as pale yellow plates, $C_{17}H_{15}NO_3$, m.p. 99-100°.



4, R = H,OH

5, R = O



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The u.v. spectrum of (4) showed maxima at 229.5, 275.5 and 283 (log ε 4.26, 2.66 and 3.51 respectively) nm for the aromatic nuclei, while the carbonyl band at 1643 cm^{-1} in the i.r. was reminiscent of the aromatic amides of A. plumieri.[1] The p.m.r. spectrum of balsamide clearly showed the signals for a benzoyl group as multiplets at δ 7.68 (2H) and 7.34 (3H) respectively.

A multiplet centered at δ 6.8 (3H) was shown to belong to the 3,4-dimethoxybenzyl moiety by its similarity with the signals in the p.m.r. spectrum of 3,4-dimethoxybenzyl alcohol, and its disagreement with those in the spectra of 2,4-dimethoxybenzyl alcohol and the α,β-dihydroderivative of (2).[1] The other signals at δ 7.55 (1H, exchanged with D_2O, -NH), 4.82 (1H, dd, J = 8.0 and 4.0 Hz, H-β), 3.78 (1H, exchanged with D_2O, -OH), 3.78 (2H, m, H-α), and 3.78 (6H, s, 2x $-OCH_3$) were confirmed to represent the remainder of the molecule by decoupling experiments.

The relationship between the hydroxy group and the other groups linking the two aromatic rings was confirmed by Jones' oxidation of (4) to the keto-amide (5), $C_{17}H_{17}NO_4$, m.p. 150-151°, which showed the expected i.r., u.v. and p.m.r. spectra, and subsequent transformation of (5) to the oxazole (6) by treatment with phosphorus oxychloride.[6]

The oxazole (6) showed u.v. maxima at 255 and 323 (log ε 4.02 and 4.39 respectively) nm for a 2,5-diarylsubstituted oxazole. Its i.r. spectra showed no carbonyl bands but aromatic peaks at 1603 and 1508 cm^{-1}. The p.m.r. spectra confirmed the structure (6) to be a 2,5-disubstituted oxazole by showing a multiplet (3H) for H-2' and H-6' of the phenyl ring and H-6" of the catechol moiety at δ 8.04, and a multiplet (4H) for H-3', H-4' and H-5' of the phenyl ring and H-2" of the

catechol ring at δ 7.33. The oxazole proton, H-4, had its characteristic sharp singlet at δ 7.28, while H-5" of the trisubstituted phenyl ring appeared as a well resolved doublet (J = 8 Hz) at δ 6.87.

This synthetic oxazole proved to be identical in all respects with the naturally occurring compound, balsoxin, - a new natural product.

The oxazole moiety of balsoxin was easily identified in the benzene extract of A. balsamifera because of its striking fluorescence on the chromaplate under long wavelength ultraviolet light. This behavior is not surprising in view of the fact that 2,5-diaryloxazoles have been found to possess among the best scintillation characteristics of all compounds.[7] In fact it was this property of fluorescence which prompted the isolation of the first naturally occurring oxazole, annuloline,[6,8] from Lolium multiflorum (annual rye grass), the seedlings of which are morphologically indistinguishable from those of Lolium perenne. Seedlings of the two plants could only be differentiated by subjecting the roots to long wavelength ultraviolet light, when the roots of L. multiflorum fluoresced brightly.

Oxazoles are rare as natural products. Thus the Amyris of Jamaica is outstanding in the ability of this genus to produce oxazoles as well as to provide a crucial link in the biogenetic relationship between β-phenylethylamides and oxazoles in nature. In addition, a closer look at the metabolite, balsamide, shows that it is a simple derivative of noradrenaline which is well established as a neurotransmitter substance. This interesting area of biological activity is yet to be examined.

References

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