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A BIOGENETICALLY PATTERNED SYNTHESIS OF (±)-EUSIDERIN

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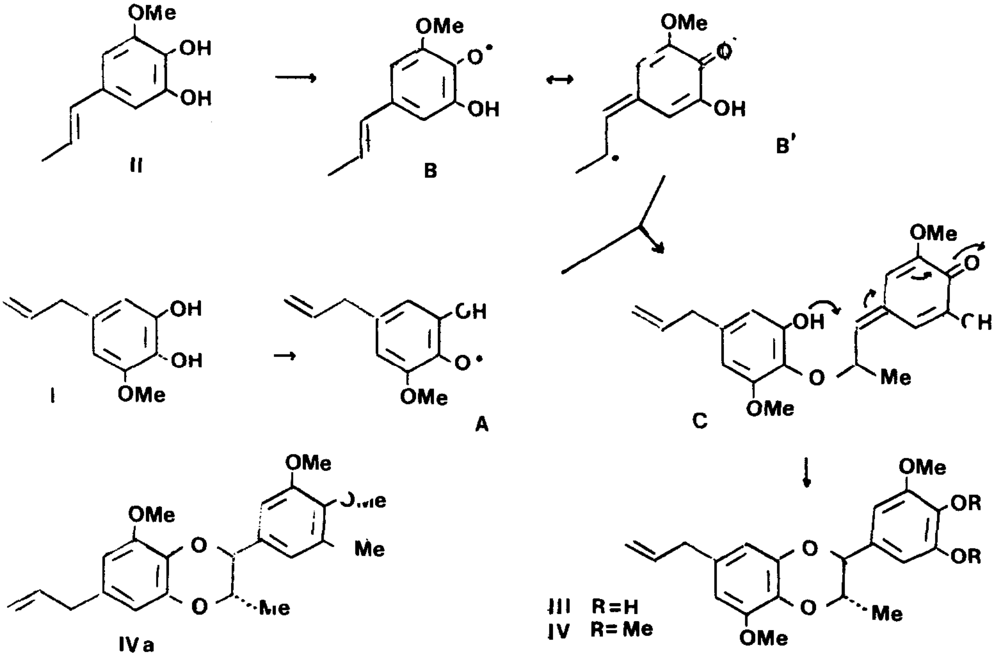
(-)-Eusiderin is a rare structural example of a neolignan[1] with a benzodioxane nucleus, that was isolated by Hobbs and King[2] from *Eusideroxylon zwageri* (Lauraceae) and again recently by Gottlieb[3] from *Licaria aurea*. The only other natural products containing a similar structural unit are the flavanolignans of the group of silybin.[4]

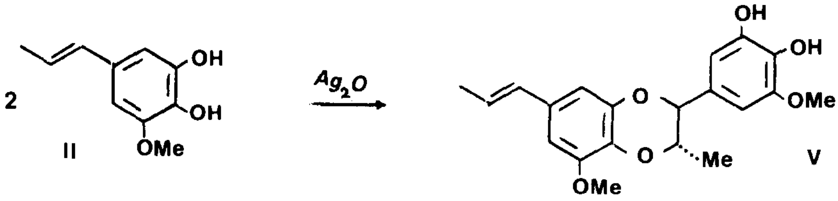
The structure (IV) or (IVa) is assigned to eusiderin,[1,2] the choice between the two being rather difficult even on the basis of NMR spectra.[5]

According to Erdtman's hypothesis,[6] shared by many other Authors,[7] eusiderin might be biosynthesized by oxidation of a p-allylphenol (e.g. I) and of a p-propenylphenol (e.g. II), to the corresponding phenoxy radicals, followed by O-β coupling of the two radicals A and B', and by nucleophilic attack of OH onto the quinone methide system of the intermediate C. Formation of a m-allylphenoxy instead of a p-allylphenoxy radical from I would lead to the isomer (IVa).



We now report the first *in vitro* reproduction of this biosynthetic scheme. Oxidation of equimolar amounts of I and II in benzene with 0.55 mole/mole of Ag_2O at room temperature gave a mixture from which, by acetylation and preparative TLC, the diacetate of III was isolated. By reaction with CH_2N_2 in ether-MeOH for 2 days[8] it was converted quantitavely into (±)-eusiderin, mass: 386, 208, 193; NMR ($CDCl_3$, 100 MHz): 1.26 (Me-3, J = 6), 3.32 (benzylic CH_2, d with allylic coupling), 3.96-4.00 (4 OMe), 4.10 (H_3), 4.58 (H_2, J = 7), 5.08, 5.12 and 5.98 (CH_2=CH-, J_{cis} = 9.5, J_{trans} = 16.5, J_{vic} = 6.5), 6.40 and 6.50 (H_6 and H_8, dec. from CH_2), 6.60 δ (s, 2 arom. H). TLC, m.p. and NMR comparison with an authentic sample of (-)-eusiderin, kindly provided by prof. F.E. King established the identity with the natural product.

Similar oxidation of II (300 mg) with 0.55 mole/mole of Ag_2O in benzene (8 ml) and traces of MeOH for 2 hrs. gave in good yield the compound V, NMR ($CDCl_3$): 1.23 (Me-3, J = 6), 1.80 (Me chain), 3.97 (2 OMe), 4.1 (m, H_3), 4.53 (H_2, $J_{2,3}$ = 7), 6.2-6.6 (4 arom. H), diacetate m.p. 173°, mass: 442, 400, 358, 315, 283, 222, 205, 191, 180. Catalytic hydrogenation of III diacetate and V diacetate with PtO_2 in MeOH afforded the same dihydroderivative (TLC, NMR), thus confirming the identity of the structural unit and of the coupling pathway in both cases.



We believe that the mechanism of the reactions parallels closely that reported in the scheme, coupling between the radicals A and B' occurring in the crossed reaction, and between B and B' in the oxidation of II alone. We favour the formation of a *para*-propenylphenoxy radical over a *meta*-propenylphenoxy one in the oxidation of II, due to the B ↔ B' resonance stabilization of the former, and therefore structures IV, III and V with respect to IVa and similar ones. The absence of coupling products other than V in the oxidation of II alone supports this hypothesis. X-ray analysis of eusiderin or of a derivative is in programme, in order to confirm the structures proposed.

REFERENCES

[&] Centro del C.N.R. per le Sostanze Organiche Naturali

[1] O.R. Gottlieb, *Rivista Latinoamer. Quim*. 5, 1 (1974)

[2] J.J. Hobbs and F.E. King, *J. Chem. Soc*. 4732 (1960)

[3] Unpublished results, quoted in ref. 1

[4] R. Hänsel, J. Schulz and A. Pelter, *Ber*. 108, 1482 (1975) and refs. quoted therein

[5] See ref. 4 for a similar problem.

[6] H. Erdtman, in "Recent Advances in Phytochemistry", Vol 1, p.29, Appleton-Century-Crofts, New York 1968

[7] O.R. Gottlieb, *Phytochemistry* 11, 1537 (1972); "Oxidative Coupling of Phenols", E.C. Taylor and A.R. Battersby ed., Arnold, London 1967

[8] H. Bredereck, R. Sieber and L. Kamphenkel, *Ber*.89, 1169 (1956)