

THE DETECTION OF ARYLOXY RADICALS IN THE OXIDATION OF RETICULINE

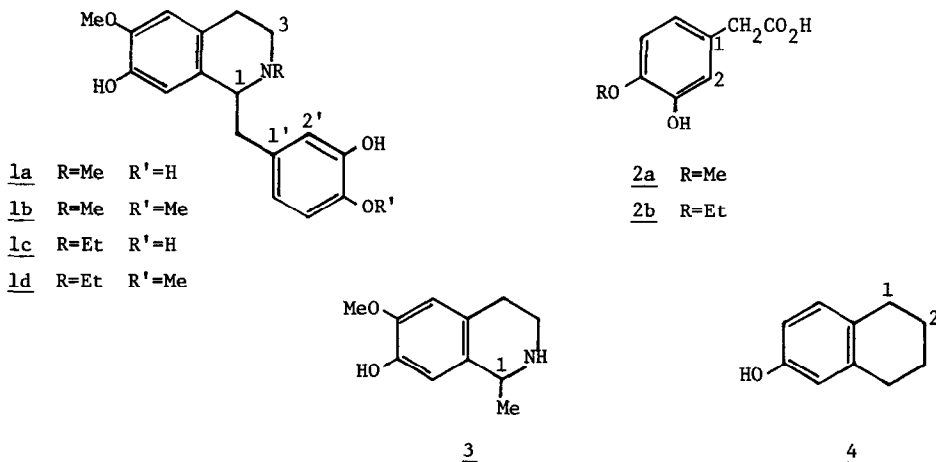
F. Richmond Hewgill* and Michael C. Pass

Department of Organic Chemistry, University of Western Australia,
Nedlands, Western Australia. 6009

Summary. In suitably substituted reticulines radicals derived from the oxidation of both phenolic rings can be observed by ESR.

The biosynthesis of morphine by intramolecular oxidative coupling of (-)-reticuline along the lines of Robinson's original suggestion has been clearly established by extensive tracer experiments,^{1,2} and imitated, albeit in low yield, *in vitro*.³ Although there has been general acceptance of the proposal by Barton and Cohen⁴ that aryloxy radicals are involved in this oxidative coupling, we know of no published attempt to reveal their presence. Indeed, several authors^{5,6} have pointed out that other mechanisms are possible.

In an attempt to detect radical intermediates by ESR we have used the technique developed by Stone and Waters,⁷ and oxidised the (\pm)-reticulines 1a - 1d⁸ in a flow system with alkaline ferricyanide or acidified ceric sulphate. Although ferricyanide was unsuccessful because of a build-up of solid paramagnetic material in the cell, the experiments with ceric sulfate resulted in the observation of radicals, whose spectra (Table 1) were assigned by comparison with those of the model compounds 2 - 4 and by computer simulation.



The spectrum obtained from reticuline 1b shows only the phenoxy radical derived from the 1-benzyl substituent, its overall width and splitting constants approximating those of the radical derived from the model compound 2a. The spectrum from norreticuline 1a was similar, but in this weak lines on either side the main spectrum indicate the presence of a small proportion of the tetrahydroisoquinoline aryloxy radical. Oxidation of the ethoxy homologue 1c

of norreticuline however gave a spectrum which closely matched that obtained from an equimolar mixture of (\pm)-isosalsole 3 and 3-hydroxy-4-ethoxyphenylacetic acid 2b, representing models for the phenolic portions of 1c. The spectrum of 1c was successfully simulated using the splitting constants shown in Table 1 and a molar radical ratio of 1:1. This apparent, and fortuitous, equivalence in the rates of oxidation of the two phenolic rings was lost again in the N-methyl compound 1d, where the spectrum was that of the 1-benzyl moiety with only a trace of the isoquinoline radical.

Table 1. Splitting constants (mT) for the ESR spectra of radicals from compounds 1 - 4

Compound	g-value	a_{H-1}	a_{H-4}	a_{H-5}	a_{H-6} (OMe)	a_{H-8}	$a_{H-2'}$	$a_{H-4'}$ (OR')	$a_{H-5'}$	$a_{H-6'}$
<u>1a</u>							0.40	0.20	0.19	0.865
<u>1b</u>	2.0042						0.40	0.20	0.19	0.865
<u>1c</u>	2.0044*	0.135	1.245	0.165	0.165	0.514	0.59	0.20	0.20	0.83
<u>1d</u>							0.59	0.20	0.20	0.83
<u>2a</u>	2.0043						0.39	0.19	0.20	0.88
<u>2b</u>	2.0044						0.40	0.19	0.19	0.84
<u>3</u>	2.0043	0.135	1.245	0.17	0.165	0.514				
		a_{H-4}	a_{H-1}	a_{H-8}	a_{H-7}	a_{H-5}				
<u>4</u>		0.165	1.86	0.165	0.61	0.61				

*

Ring A

While these experiments provide for the first time *prima facie* evidence for the intramolecular radical coupling of these bisphenols, we have not been able to rule out the possibility that the spectrum obtained from 1c is that of a mixture of monoradicals rather than a biradical spectrum. For although the two phenolic rings of 1c are oxidised with equal ease, thus statistically favouring the formation of a biradical; if the rate of intramolecular coupling, once a biradical is produced, greatly exceeds the rate of oxidation, the spectrum of the biradical would not be visible.

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References and Notes

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8. Satisfactory analyses and NMR spectra were obtained for all new compounds.

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