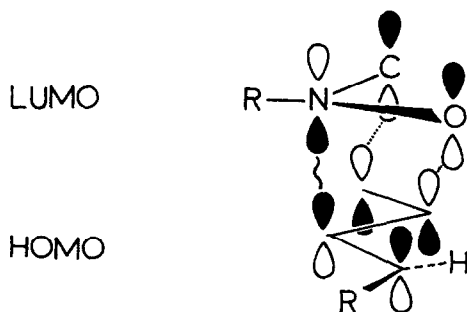


THE STEREOCHEMISTRY OF NITRONE-DIENE CYCLOADDITIONS. SYNTHESIS OF THE ALKALOIDS  
OF DARLINGIA DARLINGIANA

J. J. Tufariello and J. M. Puglis  
Department of Chemistry, State University of New York at Buffalo  
Buffalo, New York 14214

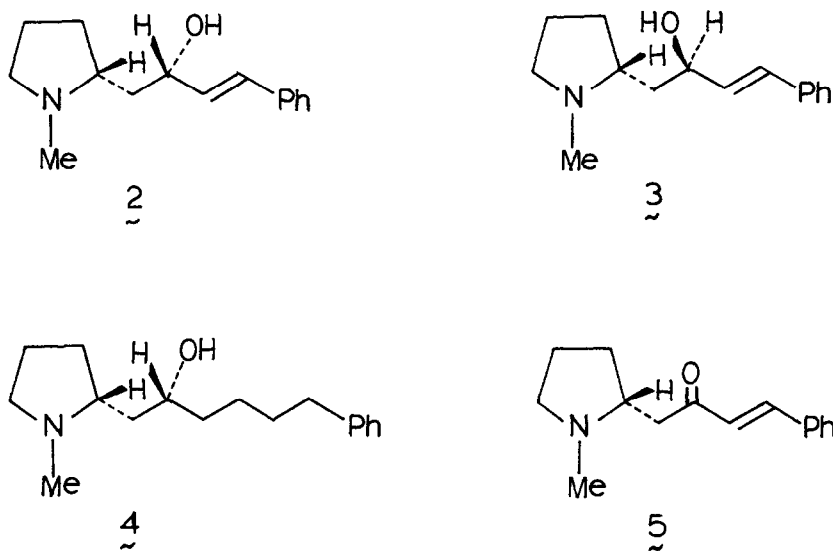
Summary: The stereochemical outcome of the reactions of cyclic nitrones with (E)-1-phenyl-1,3-butadiene has been explored. The syntheses of darlinine, epidarlinine, tetrahydrodarlingianine, and dehydrodarlinine have been accomplished.

The stereochemistry of nitrono cycloaddition reactions has been the subject of several recent studies.<sup>1-4</sup> A generally accepted view of these reactions involves an approach of the addends in two parallel planes.<sup>1,5</sup> Thus, like the Diels-Alder reaction, such processes may proceed through either exo- or endo-transition states. Examinations of the transition states involving certain electron deficient dipolarophiles (e.g. acrylates) from the perspective of frontier molecular orbital (FMO) theory suggest that an endo transition state should be favored over its exo-counterpart by a favorable secondary orbital involvement.<sup>2,3,6,7</sup> Indeed, the

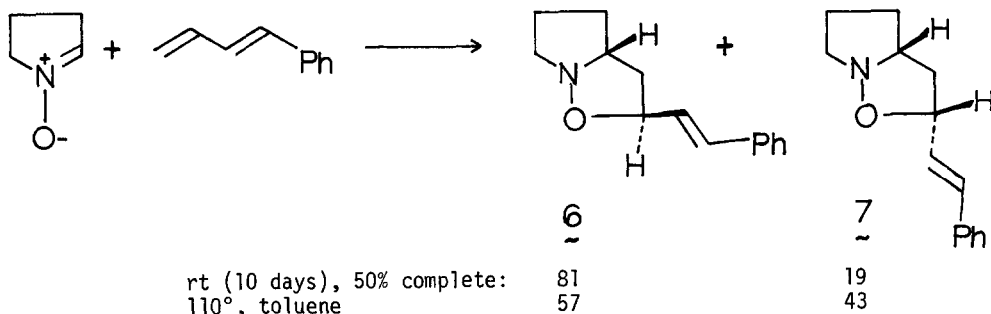


reactions of acyclic nitrones with dimethyl maleate do proceed with substantial stereoselectivity to afford the adducts expected from the endo-addition process;<sup>2,3,6</sup> however, additions of such nitrones to monosubstituted dipolarophiles such as methyl acrylate,<sup>8</sup>  $\alpha$ -methylstyrene,<sup>9</sup> and styrene<sup>10</sup> result in poor stereoselectivity.

The possibility of E/Z isomerization of the starting acyclic nitrones concomitant with cycloaddition suggested that cyclic nitrones, incapable of this complication, might be better vehicles with which to explore this phenomenon. Moreover, we were specifically interested in the cycloaddition of 1-pyrroline 1-oxide (1) with certain dienes as a means of synthesizing the major alkaloids (e.g., darlinine (2), epidarlinine (3), tetrahydrodarlingianine (4), and dehydrodarlinine (5)) derived from Darlingia darlingiana, tall trees found in the rain forest area of northern Queensland, Australia.<sup>11,12</sup>



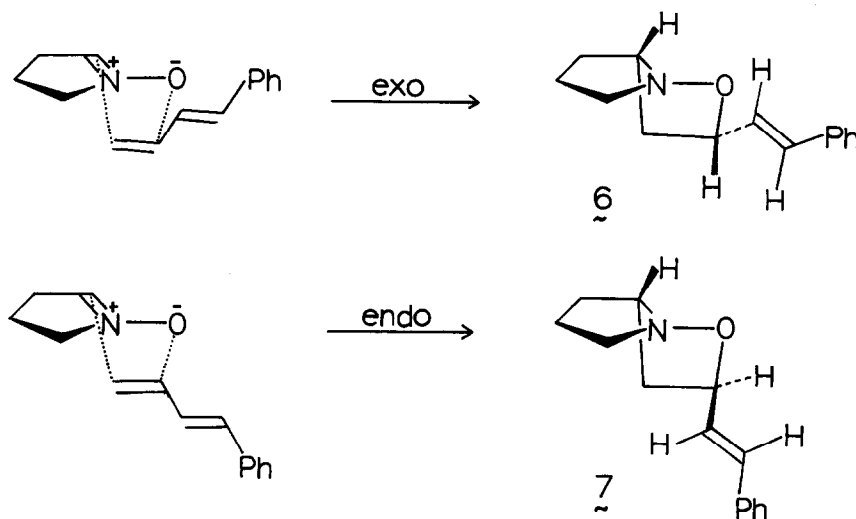
The cycloaddition of 1-pyrroline 1-oxide (1) with (E)-1-phenyl-1,3-butadiene in refluxing toluene affords a stereoisomeric mixture of cycloadducts, 6 and 7 (57:43 ratio, respectively), in 91% yield. The adduct 6 displays a characteristically sharp triplet at  $\delta$  3.2 ppm in its pmr spectrum, assignable to the C-6 protons adjacent to the nitrogen. These protons appear as two



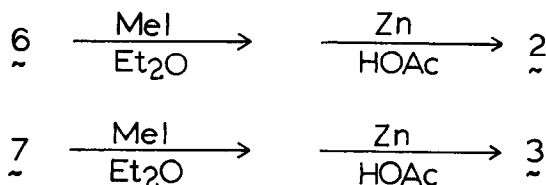
multiplets at approximately  $\delta$  3.0 and 3.5 ppm for the slower eluting (tlc: silica gel; ethyl acetate) isomer 7. That the isomer distribution obtained reflected thermodynamic factors was demonstrated by taking each pure cycloadduct and exposing it to 110°. In each case, the same ratio of 6 and 7 (i.e. 55:45) was obtained.

When the cycloaddition of nitrone 1 with (E)-1-phenyl-1,3-butadiene was performed under non-equilibrating conditions (room temperature, 10 days), adducts 6 and 7 were produced in an 81:19 ratio, respectively. This ratio is similar to that reported<sup>4</sup> for the addition of styrene to the related cyclic nitrone 3,4,5,6-tetrahydropyridine 1-oxide. Thus, we anticipated that

the major stereoisomer (i.e. 6) was derived by an exo-mode of addition, while 7 was produced via



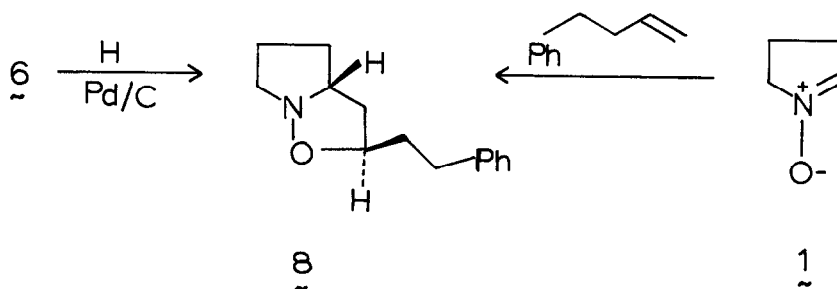
an endo-transition state. The structural assignments were confirmed by conversion of each isomer into the respective Darlingia alkaloid. Toward this end, both 6 and 7 were independently converted into their respective methiodide salts by treatment with methyl iodide in ether at room



temperature. Nitrogen-oxygen bond cleavage in the methiodide salt derived from 6 afforded darlinine (2), while like treatment of the methiodide salt derived from 7 afforded epidarlinine (3). The spectral characteristics of the synthetic alkaloids correspond to those of the authentic alkaloids.<sup>13,14</sup>

A manganese dioxide induced oxidation of either darlinine or epidarlinine in dry methylene chloride gave dehydrodarlinine (5) in 60% yield.

With the knowledge that diene-nitron cycloadditions proceed to afford both stereoisomeric adducts, we chose to compare these findings with those obtained by the cycloaddition of a related terminal alkene. When nitron 1 was added to 4-phenyl-1-butene in refluxing toluene, only a single adduct (i.e. 8) was obtained in 73% yield. That this cycloaddition proceeded through an



exo-transition state was confirmed by a positive spectral comparison of this adduct (i.e. 8) with that product obtained (86%) upon hydrogenation (Pd/C; ethanol) of the exo-adduct 6. In contrast, hydrogenation of 7 afforded an adduct (70%) spectrally distinct from 8. Thus, as anticipated,<sup>4</sup> alkene-nitronium cycloadditions proceed via exo-transition states exclusively. Tetradehydrodarlingianine (4) was prepared by the addition of 6-phenyl-1-hexene to nitronium 1 in refluxing toluene, followed by methiodide formation and subsequent zinc induced hydrogenolytic cleavage of the N-O bond.

#### References and Notes

- (a) Huisgen, R. *J. Org. Chem.* 1976, 41, 403;  
(b) Huisgen, R.; Grashey, R.; Hauck, H.; Seidl, H. *Chem. Ber.* 1968, 101, 2043.
- Grée, R.; Carrié, R. *Tetrahedron Lett.* 1971, 4117.
- Joucla, M.; Gree, D.; Hamelin, J. *Tetrahedron* 1973, 29, 2315.
- Tufariello, J. J.; Ali, Sk. A. *Tetrahedron Lett.* 1978, 4647.
- Leroy, G.; Nguyen, M. T.; Sana, M. *Tetrahedron* 1978, 34, 2459.
- Grée, R.; Tonnard, F.; Carrié, R. *Bull. Chim. Soc. Fr.* 1975, 1325.
- Houk, K. N.; Sims, J.; Watts, C. R.; Luskas, L. J. *J. Am. Chem. Soc.* 1973, 95, 7301.
- Joucla, M.; Hamelin, J. *J. Chem. Res. (S)* 1978, 276.
- Huisgen, R.; Grashey, R.; Seidl, H.; Hauck, H. *Chem. Ber.* 1968, 101, 2559.
- Huisgen, R.; Grashey, R.; Hauck, H.; Seidl, H. *Chem. Ber.* 1968, 101, 2548.
- Bick, I. R.; Gillard, J.; Leow, H. *Aust. J. Chem.* 1979, 37, 2523.
- Anderson, B.; Robertson, G.; Bick, I. R.; Gillard, J.; Leow, H. *Chem. and Ind. (London)* 1977, 764.
- Leow, H. Ph.D. Dissertation, University of Tasmania (Australia), 1979.
- We thank Professor Bick for sending us the spectral information relating to the Darlingia alkaloids.

(Received in USA 19 November 1985)