

## Uncarine C, D (Speciophylline), E, and F: C-3 and C-7 Epimeric Oxindoles related to Tetrahydroalstonine

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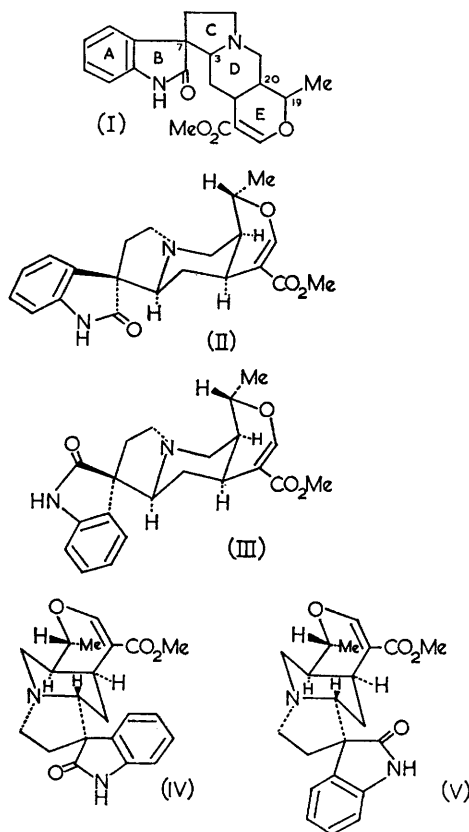
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UNCARINE C and uncarine D (speciophylline<sup>1</sup>), two oxindole alkaloids from *Uncaria bernaysii* and *U. ferrea*, have been shown to be stereoisomers of the general formula (I), and they have been assigned partial structures in which the ring D/E junction is *cis* and C-19-H,C-20-H *trans*.<sup>2</sup> An examination of the products of the equilibration reaction of both uncarine C and uncarine D in pyridine solution at reflux temperature now indicates the formation of four stereoisomeric oxindoles which are epimeric at both C-3 and C-7. The *cis*-D/E ring junction and *trans*-C-19-H,C-20-H configuration for these stereoisomers are now proved by the preparation of the same four stereoisomers from tetrahydroalstonine, an indole alkaloid of known stereochemistry.<sup>3</sup>

The equilibration of oxindole alkaloids is considered to occur by cleavage and re-formation of the C-3,C-7 bond,<sup>4</sup> and although epimerization at both C-3 and C-7 might be expected, it has been suggested<sup>4</sup> that because of the bulk of the spiro-oxindole substituent, epimerization would occur only at C-7 with retention of configuration at C-3. Uncarine C and D, however, are considered<sup>2</sup> to be epimeric at C-3 and the steric interaction of the axial spiro-oxindole substituent is relieved by a chair-to-chair inversion of the D-ring with consequent change of conformation at the *cis*-D/E ring junction. These conformational changes are reflected in the n.m.r. spectra by a large difference in the C-19-H,C-20-H vicinal coupling constants (uncarine C, 11 c./sec., *trans*-*pseudo*-diaxial; uncarine D, 1.5 c./sec., *trans*-*pseudo*-diequatorial). The n.m.r. spectra of the four stereoisomers (uncarine C, D, E, and F) show that uncarine C and uncarine E (II and III) have the same value for the C-19-H,C-20-H coupling constant (11 c./sec.), and consequently that they have the same stereochemistry at C-3, ring-D, and ring-E ( $3\alpha$ -H with C-19-H,C-20-H *trans*-*pseudo*-diaxial). Uncarine D and uncarine F (IV and V) therefore have the  $3\beta$ -H and C-19-H,C-20-H *trans*-*pseudo*-diequatorial conformation ( $J_{19,20}$  1.5 c./sec.).

It is more difficult to arrive at specific assignments of configuration at C-7 for the C-3 epimeric pairs. Uncarine D (IV) and uncarine F (V) can be distinguished by the chemical shifts of the CO<sub>2</sub>Me methyl groups ( $\delta$  3.32 and  $\delta$  3.60 respectively) and the relative upfield shift in the spectrum of uncarine D is attributed to the shielding of the methyl group

by the oxindole benzenoid ring. Insufficient evidence is available for specific assignments of structures (II) and (III) to uncarine C and uncarine E.



Our results clearly establish that epimerization can occur at both C-3 and C-7 in D/E-*cis*-oxindole alkaloids, and they are in accord with the C-3/C-7 epimeric structures proposed for the alkaloids rauvoxine, rauvoxinine, and carapanaubine.<sup>5</sup> It was not demonstrated, however, that the epimerization at C-3 in these alkaloids was accompanied by conformational inversion of ring-D.

The stereoisomeric uncarines C, D, E, and F from both the equilibration reactions and from the oxidation of tetrahydroalstonine with lead tetraacetate under the conditions used for the similar oxidation of isoreserpinine,<sup>5,6</sup> were isolated by preparative thin-layer chromatography. When

uncarine D was heated for a short time (1—2 hr.) in pyridine solution, uncarine F was a major constituent of the reaction mixture, but longer heating

(10—15 hr.) gave mainly uncarine C and uncarine E, and not, as previously reported,<sup>2</sup> only uncarine C. Relevant physical data are tabulated.

	M.p.	$[\alpha]_D(\text{CHCl}_3)$	$J_{19,20}$	$\delta(\text{CO}_2\text{Me})$
Uncarine C	212—213°	-109°	11 c./sec	3·55
Uncarine E	205—206°	-96°	11	3·60
Uncarine D	183—184°	+74°	1·5	3·32
Uncarine F	glass	+85°	1·5	3·60

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<sup>1</sup> Uncarine D has been shown by direct comparison to be identical with the alkaloid speciophylline from *Mitragyna speciosa*: A. H. Beckett, E. J. Shellard, J. D. Phillipson, and C. M. Lee, *Planta Medica*, 1966, **14**, 266.

<sup>2</sup> S. R. Johns and J. A. Lamberton, *Tetrahedron Letters*, 1966, 4883.

<sup>3</sup> E. Wenkert, B. Wickberg, and C. L. Leicht, *J. Amer. Chem. Soc.*, 1961, **83**, 5037.

<sup>4</sup> E. Wenkert, B. Wickberg, and C. L. Leicht, *Tetrahedron Letters*, 1961, 822.

<sup>5</sup> J.-L. Pousset and J. Poisson, *Compt. rend.*, 1964, **259**, 597.

<sup>6</sup> N. Finch, C. W. Gemenden, I. H.-C. Hsu, and W. I. Taylor, *J. Amer. Chem. Soc.*, 1963, **85**, 1520.