

## Heteroatom Directed Photoarylation; an Approach to the Synthesis of *Aspidosperma* Alkaloids

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**Summary** The photochemical synthesis of the indolines (6) and (8) is described.

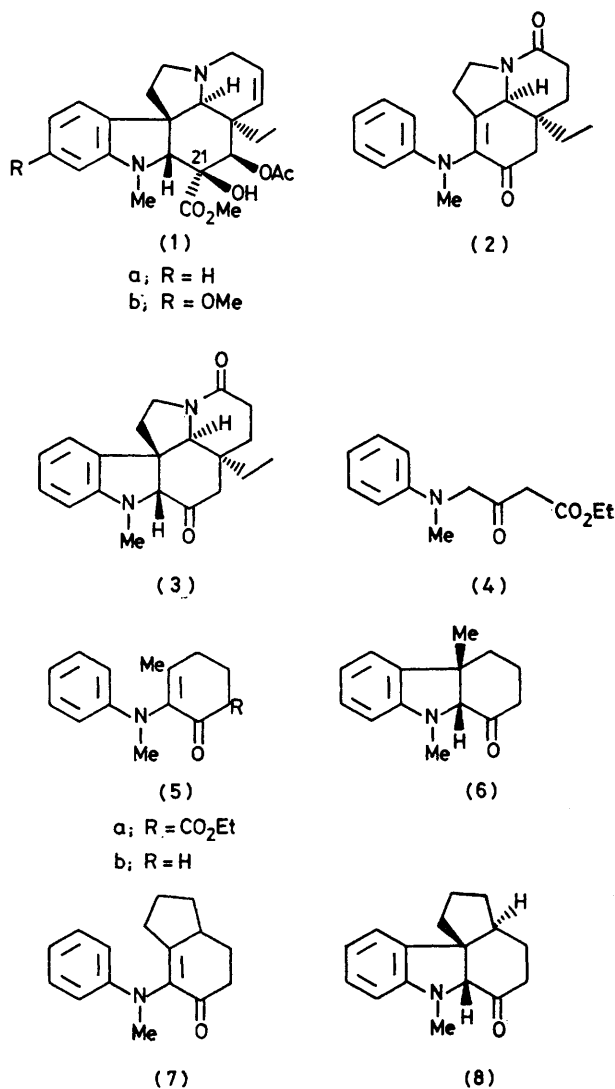
CONSTRUCTION of the indoline portion of the *Aspidosperma* alkaloids has been accomplished by either annelation of preformed indole<sup>1</sup> and oxindole<sup>2</sup> rings, or incorporation of the Fisher indole synthesis late in the synthetic plan.<sup>3</sup> We report a conceptually new approach to the synthesis of the medicinally important *Aspidosperma* alkaloids vindorosine (1a) and vindoline (1b). The method is demonstrated here by photocyclization-rearrangement (heteroatom directed photoarylation) of the 2-anilincyclohex-2-enones (5b) and (7), which serve as models for the projected conversion (2)→(3).<sup>4</sup>

The stereochemical consequences of photoarylation,<sup>4,5</sup> together with the structural features at C(21) in (1), suggest that a ketone group at C(21) would be highly desirable. Consequently, we have devised a convergent approach to (2), which features the 'three-carbon' annelation reagent (4).<sup>6</sup>

Reaction of (4) and methyl vinyl ketone (1 equiv.) at room temperature with sodium hydride (0.1 equiv.) in benzene gives the expected Michael adduct (70%, b.p. 170 °C at 0.07 mmHg),† which is cyclized to (5a) (76%, b.p. 129 °C at 0.003 mmHg) with potassium hydride (0.1 equiv.) in benzene at reflux temperature. Saponification (KOH in EtOH) and acid-catalysed decarboxylation gives the anilincyclohexenone (5b) [b.p. 147 °C at 0.1 mmHg; λ<sub>max</sub> (MeOH) 370 (ε 232) and 295 nm (ε 1935) with tailing into the visible region].

Pyrex-filtered irradiation of (5b) in degassed benzene solution (0.05M) for 3 h gives the *cis*-fused indoline (6) (90%, b.p. 126 °C at 0.15 mmHg; <sup>1</sup>H n.m.r.: 3H singlets at δ 1.39 and 2.71, and 1H singlet at δ 3.15), together with the *trans*-fused isomer (7%, m.p. 120–122 °C; <sup>1</sup>H n.m.r. 1.03, 2.83, and 3.59). The two epimers are easily separated by silica gel chromatography (benzene solvent) and the *trans*-isomer is converted into the *cis*-isomer (6) by treatment with methanolic sodium carbonate.

Similarly, (4), with 2-methylenecyclopentanone, is converted into the enone (7) (b.p. 110 °C at 0.004 mmHg), and irradiation of (7) gives predominately the *cis*-fused indoline (8) (71%, b.p. 156 °C at 0.15 mmHg; <sup>1</sup>H n.m.r.: 3H singlet at δ 2.67 and 1H singlet at δ 3.23). The stereochemistry of the indoline ring fusion in (8) [and similarly in (6)] is assigned on the basis of n.m.r. data and the observed stability of (8) in sodium carbonate-methanol; the stereochemistry of the hydrindanone ring fusion is tentatively



assigned by analogy with that resulting from photocyclization-rearrangement of related fused-ring aryloxyenones.<sup>7</sup>

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† All reported yields are for isolated products.

<sup>1</sup> This approach has been elegantly demonstrated by the total synthesis of (±)-vindoline; M. Ando, G. Büchi, and T. Ohnuma, *J. Amer. Chem. Soc.*, 1975, **97**, 6880.

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<sup>3</sup> This kind of Fisher indole synthesis was first reported by V. Georgian, *Chem. and Ind.*, 1957, 1124, and has been applied to the synthesis of (±)-aspidospermine; G. Stork and J. E. Dolfini, *J. Amer. Chem. Soc.*, 1963, **85**, 2872.

<sup>4</sup> Photocyclization of *N*-aryl-enamines was first reported by O. L. Chapman, G. L. Eian, A. Bloom, and J. Clardy, *J. Amer. Chem. Soc.*, 1976, **98**, 3564.

<sup>5</sup> A. G. Schultz and W. K. Hagmann, *J.C.S. Chem. Comm.*, 1976, 726.

<sup>6</sup> M. E. Jung, *Tetrahedron*, 1976, **32**, 3.

<sup>7</sup> A. G. Schultz and W. Y. Fu, *J. Org. Chem.*, 1976, **41**, 1483.