New Synthesis of Olivacine *via* a Heteroarylation Reaction

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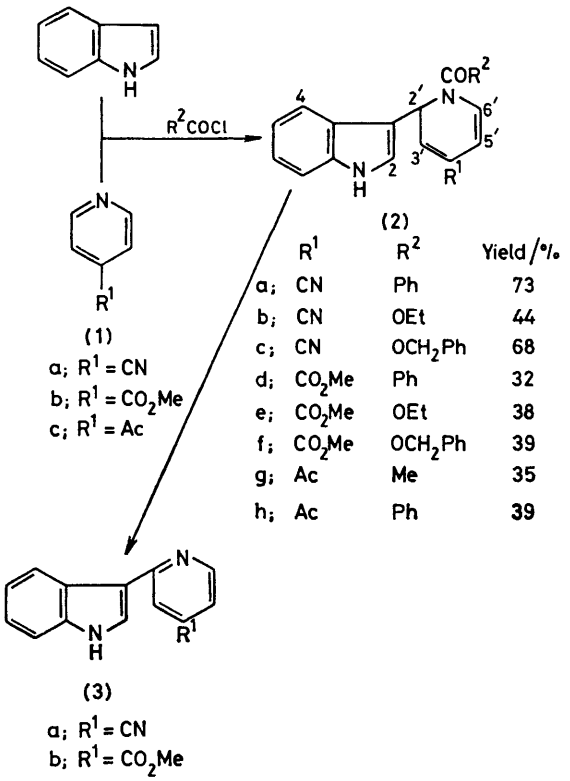
Summary The heteroarylation reaction between indole and 4-substituted pyridines under acylating conditions, followed by acidic cyclisation, provides a useful route to indole alkaloids, as exemplified by a new synthesis of olivacine.

WHILST studying[1] enamide cyclisation under acylating conditions, we found a simple preparation of the synthetically useful 3-(2-piperidyl)indoles, which form the skeleton of a large number of indole alkaloids, and a method for their conversion into the anti-tumour alkaloid, olivacine.[2]

Since only a few examples of heteroarylation reactions between indole and 4-substituted pyridines have been reported,[3] we examined the condensation of indole with pyridines, possessing an electron-attracting group at the 4-position, in the presence of an acylating agent.

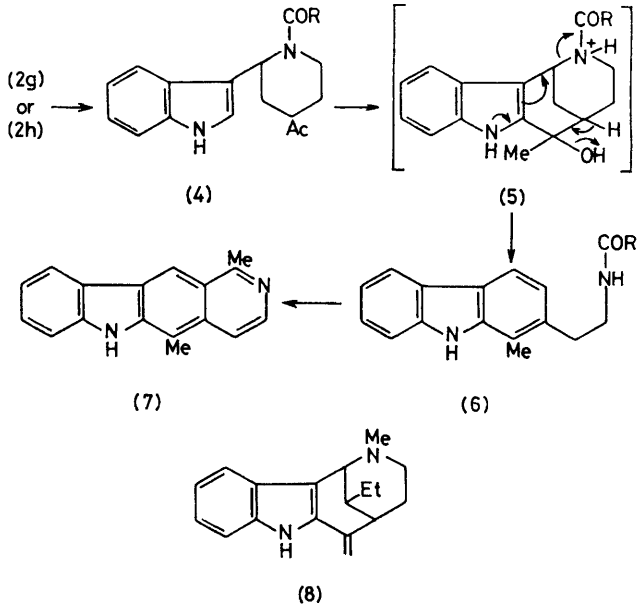


	R^1	R^2	Yield/%
a;	CN	Ph	73
b;	CN	OEt	44
c;	CN	OCH_2Ph	68
d;	CO_2Me	Ph	32
e;	CO_2Me	OEt	38
f;	CO_2Me	OCH_2Ph	39
g;	Ac	Me	35
h;	Ac	Ph	39

To a mixture of the 4-substituted pyridines (**1a**)—(**1c**) (3 equiv.) and acylating agent (3 equiv.) in dichloromethane, indole (2 equiv.) was added at temperatures ranging from 0 to 25 °C and the mixture was stirred for 1—8 h. Purification by preparative thin layer or column chromatography separated the condensation products (**2a**)—(**2h**).

The structure of the condensation product (**2a**) was established from spectral data [*m/z* 325 (M^+); ν 3475, 2225, 1655, and 1565 cm^{-1}; δ 8·69 (1 H, br, NH), 7·93 (1 H, m, 4-H), 7·13 (1 H, d, *J* 3 Hz, 2-H), 6·72 (1 H, d, *J* 6 Hz, 2′-H), 6·53 (1 H, d, *J* 8 Hz, 6′-H), 6·52 (1 H, dd, *J* 6 and 1·6 Hz, 3′-H), and 5·45 (1 H, dd, *J* 8 and 1·6 Hz, 5′-H)] and the following chemical conversion of (**2a**) into the known compound (**3b**). Deacylation of (**2a**) under mild alkaline conditions (1% KOH–MeOH, at 50 °C for 5 min), followed by methanolysis of the resulting nitrile (**3a**), afforded the ester (**3b**) which was found to be identical with the known key intermediate for the synthesis of deethyldasycarpidone,[4] from a comparison of their spectral data. The other condensation products (**2b**)—(**2h**) showed mass and i.r. spectra corresponding to their structures, which were also established from their n.m.r. spectra (see the Table).

The synthetic utility of the condensation products (**2g**) and (**2h**) was also demonstrated by the following new synthesis of olivacine.[2] Catalytic hydrogenation of (**2g**) and (**2h**) on platinum oxide afforded the piperidines (**4a**) and (**4b**) [*m/z* 346 (M^+); ν 3480, 1705, and 1620 cm^{-1}; δ 5·80 (1 H, t, *J* 5 Hz, 2′-H) and 1·80 (3 H, s, Ac)] in 55 and 52% yields, respectively. Treatment of (**4a**) and (**4b**) with toluene-*p*-sulphonic acid or $BF_3.Et_2O$ in chloroform yielded the carbazoles (**6a**) and (**6b**) in 62 and 56% yields, respectively, presumably *via* the route involving cyclisation into the intermediates[5] (**5a**) and (**5b**), followed by spontaneous ring-opening (see the Scheme). The carbazole (**6a**) was also



SCHEME

prepared from (**6b**) upon hydrolysis and acetylation and is a potential key intermediate for the synthesis of olivacine.[2] The subsequent steps to olivacine (**7**), that is, cyclisation with phosphoryl chloride and dehydrogenation with palladium on charcoal, proceeded smoothly according to known procedures[2] and so completes a new synthesis of the alkaloid.

TABLE. ^1H N.m.r. δ ($CDCl_3$) for (**2b**)—(**2h**).

Compounds	4-H	2′-H	3′-H	6′-H	5′-H	4′-R^1
(**2b**)	7·90(m)	6·47(s)	6·47(s)	7·00(d, *J* 8 Hz)	5·60(d, *J* 8 Hz)	—
(**2c**)	7·83(m)	6·40(s)	6·40(s)	7·00(d, *J* 8 Hz)	5·57(d, *J* 8 Hz)	—
(**2d**)	8·07(m)	6·80(d, *J* 6 Hz)	6·93(dd, *J* 6 and 1·6 Hz)	6·57(d, *J* 8 Hz)	5·93(dd, *J* 8 and 1·6 Hz)	3·93(3 H, s)
(**2e**)	—	6·35 and 6·73 (each 1 H, br d, *J* 6 Hz)		6·77(br d, *J* 8 Hz)	5·90(dd, *J* 8 and 1·6 Hz)	3·77(3 H, s)
(**2f**)	—	6·57(3 H, m)			5·90(dd, *J* 8 and 1·6 Hz)	3·77(3 H, s)
(**2g**)	7·87(m)	6·70(3 H, m)			6·10(d, *J* 8 Hz)	2·33(3 H, s)
(**2h**)	8·03(m)	6·67(s)	6·67(s)	6·47(d, *J* 8 Hz)	5·97(d, *J* 8 Hz)	2·33(3 H, s)

Since the acidic cyclisation of the *N*-alkyl congeners of (**4a**) and (**4b**) into other indole alkaloids, such as uleine (**8**), has been reported,[6] the work herein suggests that either the carbazole-type or the uleine-type alkaloid could be synthesised, depending on the choice of substituent on the nitrogen of the piperidine ring of (**4**).

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