Synthesis of 5-Hydroxy-2,6-dimethyl-6*H*-pyrido[4,3-*b*]carbazole

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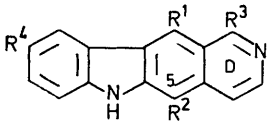
Summary The synthesis of the 5-hydroxy-5,11-didemethyl-2,6-dimethyl-1,2,3,4-tetrahydro-derivative of ellipticine is described.

CONSIDERABLE interest[1] in synthesis of the pyrido[4,3-*b*]-carbazole nucleus contained in such alkaloids as ellipticine (**1**), olivacine (**2**), and various naturally occurring ring-D-

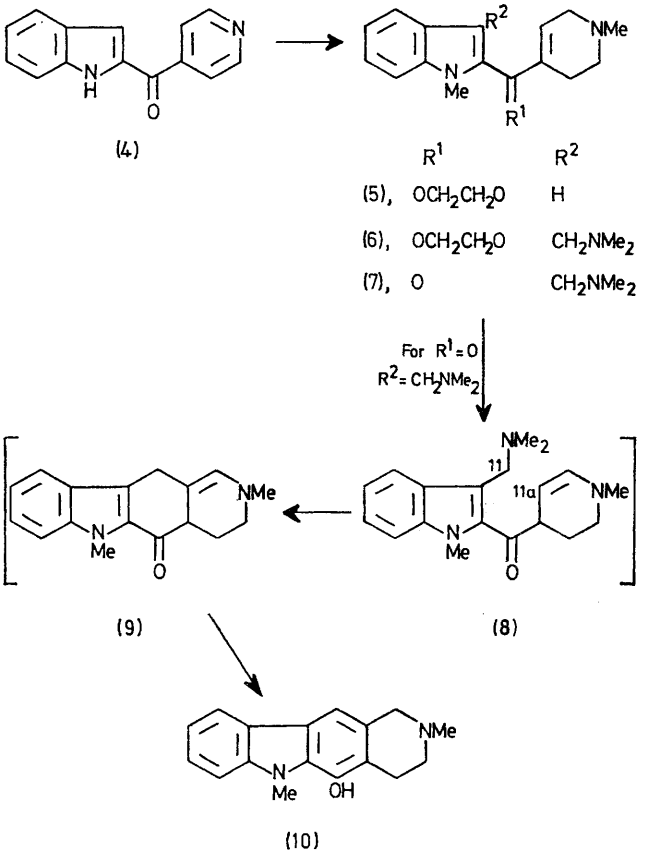
reduced derivatives, has arisen from the reported[2] antitumour and antileukemic activity of olivacine, ellipticine and especially the phenol, 9-hydroxy-ellipticine[2b] (**3**). Several groups have published successful approaches.[1] We report here a method for the construction of the tetracyclic ring system, the central theme for which is based on our earlier work[3,4] on γ-amino-enones. This method is novel in allowing the formation of a phenolic carbazole having the oxygen at C-5.



	R^1	R^2	R^3	R^4
(1),	Me	Me	H	H
(2),	H	Me	Me	H
(3),	Me	Me	H	OH

Protection of the carbonyl group by acetalisation of the ketone[4] (**4**) with $(CH_2OH)_2$–PhH–MeC_6H_4-*p*-SO_3H followed by indole then pyridine *N*-methylation with MeI–NaH–dimethylformamide and MeI–PhMe respectively and $NaBH_4$ reduction, gave the masked enone (**5**) (70% for 4 steps) [oil, $C_{18}H_{22}N_2O_2$, *m/e* 298·1684 (19%, M^+), 202(100), 167(54), 158(32), and 132(21); τ ($CDCl_3$) 3·35 (1H, s, indole-C-3-H), 4·31 (1H, m, C=CH), and 6·27 and 7·62 (6H, 2×s, NMe)]. Mannich reaction on this indole gave the desired indole-C-3-substituted product (**6**) (73%) [oil, $C_{21}H_{29}N_3O_2$, *m/e* 355·2264 (41%, M^+), 310(100), 267(35), 265(35), 239(62), 237(50), 166(64), and 94(44), τ ($CDCl_3$) 4·52 (1H, m, C=CH), 6·19 (2H, s, Me_2NCH_2), 7·72 (6H, s, CH_2NMe_2), no indole-C-3-H], which could be easily hydrolysed with 5N HCl at room temperature to the somewhat unstable conjugated ketone (**7**) (77%) [oil, $C_{19}H_{25}N_3O$, *m/e* 311·1992 (1·5%, M^+), 310(2·5), 267(26), 249(43), 224(74), 209(21), 144(26), 96(26), 94(30), and 58(100); λ_{max} (EtOH) 313 nm (log ε 3·84), λ_{infl} 243 and 350 nm (log ε 3·89 and 3·60); ν_{max} ($CHCl_3$) 1675 cm^{-1}].

This key intermediate was designed to have the necessary potential for closure of the c-ring, in that it has both a potential leaving group at the future C-11 and a 4-acyl-1,2,3,6-tetrahydropyridine system[3] which, it was anticipated, would be transformable into a non-conjugated 1,2,3,4-tetrahydropyridine (**8**) having the necessary nucleophilic centre at C-11a. These predictions were verified for when (**7**) was heated to reflux in degassed 50% aq AcOH under N_2, the phenol (**10**), m.p. 67—70 °C, was produced (25%), presumably *via* (**8**) and (**9**) as intermediates. The tetracyclic phenol had u.v. absorption very similar, in neutral and basic solution, to that of 1-hydroxycarbazole and n.m.r.



signals and mass spectral fragmentation entirely consistent with structure (**10**) [$C_{17}H_{18}N_2O$, *m/e* 266·1421 (78%, M^+), 265(83), 249(24), and 223(100), τ ($CDCl_3$) 2·05 (1H, d, ArH), 2·5—2·93 (4H, m, ArH), 5·88 (3H, s, CH_3), 6·26 (2H, s, $ArCH_2N$), 6·95—7·3 (4H, m, $ArCH_2CH_2N$), and 7·3 (3H, s, NMe).

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