

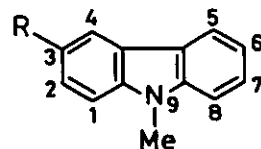
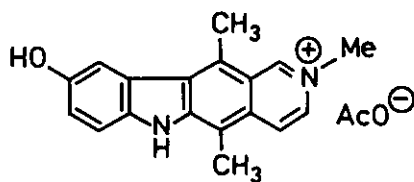
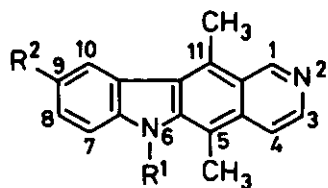
A NEW APPROACH TO C-9 HYDROXYLATION OF N(6)-SUBSTITUTED ELLIPTICINE

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Abstract - 6-Methylellipticine is converted to the corresponding 9-hydroxy derivative via a reaction sequence involving selective C-9 formylation followed by a Baeyer-Villiger rearrangement.

Several reports^{1a-e} suggest that the mechanism of antitumour activity of ellipticine (1a) is associated with an initial hydroxylation of the C-9 position of the pyridocarbazole nucleus. 9-Hydroxyellipticine (1b) is a metabolite which displays higher activity² than ellipticine. The clinically employed anticancer drug elliptinium^R is 9-hydroxy-N-2-methylellipticinium acetate (2)^{3a,b}. Many of the chemical syntheses of 9-hydroxyellipticine utilize an appropriately



	R ¹	R ²
<u>1a</u>	H	H
<u>1b</u>	H	OH
<u>1c</u>	CH ₃	H
<u>1d</u>	CH ₃	CHO
<u>1e</u>	CH ₃	OH

<u>3a</u>	R = H
<u>3b</u>	R = CHO
<u>3c</u>	R = OH

protected hydroxylated aromatic starting material^{4a-b}. To our knowledge there is only one report in the literature which describes the synthesis of 9-hydroxyellipticine (1b)⁵ from ellipticine (1a) itself, albeit in low overall yield. The development of a facile procedure for the introduction of a hydroxyl group at the C-9 position of ellipticine and its derivatives is of practical value in the synthesis of potentially active ellipticine derivatives. In this communication we describe such a method.

The strategy for introduction of the hydroxyl group in 1a recognized that the C-9 and possibly the C-7 positions of the molecule are potential sites of electrophilic attack. It was projected that a selective C-9 acylation of suitably protected 1a followed by a Baeyer-Villiger rearrangement, should constitute a simple sequence for an overall hydroxylation process. To test the feasibility of this procedure, a model study was carried out using N(9)-methycarbazole (3a). The formylation of 3a, employing Vilsmeier conditions (DMF, POCl₃, 100-110°C) resulted in a selective reaction at C-3 and formation of 3b⁶ in practical yields (~60%). The latter compound could be conveniently converted into the corresponding hydroxy derivative 3c⁷ (90%) by treatment with H₂O₂ (aq. 35%) in the presence of acid⁸.

Having achieved the hydroxylation of 3a we turned our attention to the ellipticine system and chose as the substrate 6-methylellipticine 1c, which has been described by us^{9a} and others^{9b,c}. Compound 1c underwent electrophilic substitution at C-9, exclusively, upon reaction with a variety of reagents¹⁰. In the context of the present study, the formylation of 1c, by reaction with ClCH₂OCHCl₂ (AlCl₃, CH₂Cl₂, 0°), followed by hydrolysis, proceeded in excellent overall yield (>90%). The structure of 9-formyl-6-methylellipticine 1d followed from its spectral data¹¹. The rearrangement of 1d to 9-hydroxy-6-methylellipticine 1e¹² proceeded smoothly (>90%) upon reaction with hydrogen peroxide (aq. H₂O₂, 35%, H₂SO₄, MeOH). It is noteworthy that under these conditions the pyridine nitrogen (N-2) is not oxidized.

The hydroxylation procedure described in this communication is potentially applicable to the synthesis of a variety of 9-hydroxyellipticine derivatives.

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6. 3b: mp 79-82°C, lit. 74°C, (Ng.Ph.Buu-Hoi and Ng.Hoan, J.Am.Chem.Soc., 1951, 73, 98).
 IR (CHCl₃): 1685, 1620, 1590. NMR (CDCl₃)*: δ 3.7 (s, N-CH₃), 10.0 (s, -CHO).

7. 3c: mp 145°C, NMR (DMSO-d₆): δ 3.75 (s, N-CH₃), 5.03 (dd, J_{1,2}=8.5, J_{2,4}=2, H-2), 5.66 (d, J_{2,4}=2, H-4). The compound, without its melting point, has been described in the literature, R.F. Novak, D.R. Koop and P.F. Hollenberg, Mol.Pharmacol., 1980, 17, 128.
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10. Nitration (HNO₃/AC₂O) and acetylation (CH₃COCl, AlCl₃, CH₂Cl₂, 0°C) of 1c gave the corresponding 9-substituted derivatives.
11. 1d: mp 215°C (91%); IR (CHCl₃): 1677, 1590; NMR (CDCl₃)*: δ 2.96 (s, 5-CH₃), 3.14 (s, 11-CH₃), 4.06 (s, N-CH₃), 10.07 (s, -CHO).
12. 1e: mp > 350°C, (93%), IR (KBr): 1590, 1390, 1475. NMR (DMSO-d₆)*: δ 3.00 (s, 5-CH₃), 3.14 (s, 11-CH₃), 4.11 (s, N-CH₃), 9.49 (s, -OH).

* selected chemical shifts

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