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

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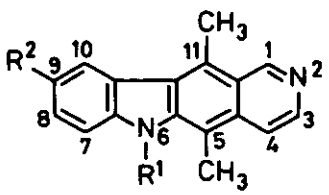
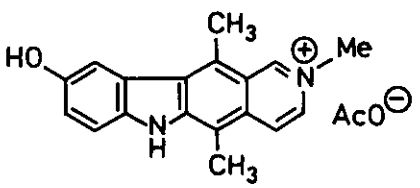
Abstract - 6-Methylellipticine is converted to the corresponding 9-hydroxy derivative via a reaction sequence involving selective C-9 formylation followed by a Baeyer-Villiger rearrangement.

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 activity[2] 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
1a	H	H
1b	H	OH
1c	CH_3	H
1d	CH_3	CHO
1e	CH_3	OH



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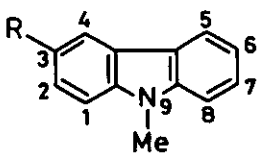

3a R = H
3b R = CHO
3c R = OH

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 feasability of this procedure, a model study was carried out using N(9)-methylcarbazole (3a). The formylation of 3a, employing Vilsmeyer conditions (DMF, $POCl_3$, 100-110°C) resulted in a selective reaction at C-3 and formation of 3b[6] in practical yields (∿ 60%). The latter compound could be conveniently converted into the corresponding hydroxy derivative 3c[7] (90%) by treatment with H_2O_2 (aq. 35%) in the presence of acid[8].

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 reagents[10]. In the context of the present study, the formylation of 1c, by reaction with $ClCH_2OCHCl_2$ ($AlCl_3$, CH_2Cl_2, 0°), followed by hydrolysis, proceeded in excellent overall yield (> 90%). The structure of 9-formyl-6-methylellipticine 1d followed from its spectral data[11]. The rearrangement of 1d to 9-hydroxy-6-methylellipticine 1e[12] proceeded smoothly (> 90%) upon reaction with hydrogen peroxide (aq. H_2O_2, 35%, H_2SO_4, 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.

ACKNOWLEDGEMENTS

The financial support by The Netherlands Foundation for Cancer Research (Koningin Wilhelmina Fonds) is gratefully acknowledged. We are indebted to Dr. M. Suffness, National Cancer Institute, N.I.H. Bethesda, U.S.A. for a generous supply of ellipticine.

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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 ($CHCl_3$): 1685, 1620, 1590. NMR ($CDCl_3$)*: δ 3.7 (s, N-CH_3), 10.0 (s, -CHO).

7. 3c.: mp 145°C, NMR (DMSO-d_6): δ 3.75 (s, N-CH_3), 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 (HNO_3/AC_2O) and acetylation (CH_3COCl, $AlCl_3$, CH_2Cl_2, 0°C) of 1c gave the corresponding 9-substituted derivatives.

11. 1d: mp 215°C (91%); IR ($CHCl_3$): 1677, 1590; NMR ($CDCl_3$)*: δ 2.96 (s, 5-CH_3), 3.14 (s, 11-CH_3), 4.06 (s, N-CH_3), 10.07 (s, -CHO).

12. 1e: mp > 350°C, (93%), IR (KBr): 1590, 1390, 1475. NMR (DMSO-d_6)*: δ 3.00 (s, 5-CH_3), 3.14 (s, 11-CH_3), 4.11 (s, N-CH_3), 9.49 (s, -OH).

* selected chemical shifts

Received, 6th October, 1986