SIDE-CHAIN SUBSTITUTION OF 6-METHYLELLIPTICINE

APPROACH TO A NEW CLASS OF ELLIPTICINE DERIVATIVES

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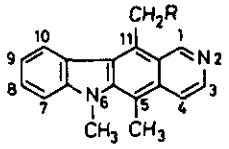
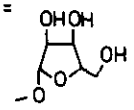
Abstract - Reaction of 6-methylellipticine with lithium diisopropylamide results in deprotonation of the C_{11}-CH_3 group, generating an anion which reacts with formaldehyde to give the corresponding hydroxymethyl derivative. The latter has been converted into its riboside, glucoside and galactoside.

Great interest centres around the derivatization of ellipticine[1] in view of the recognition that although the alkaloid possesses valuable anticancer activity, its application as an anticancer drug suffers from accompanying toxicity and practical problems of formulation owing to extremely limited solubility. The clinical use of 9-hydroxy-2-methylellipticinium acetate despite the aforementioned disadvantages, emphasizes the need to develop new water soluble ellipticine derivatives with lower toxicity. In order to achieve this objective ellipticine derivatives bearing a wide variety of substituents will have to be synthesized and subjected to biological activity evaluation. Since the ellipticine molecule is readily accessible by total synthesis[1,2] it is necessary to evolve synthetic methodology which would allow its direct and specific functionalization. In this communication we present an approach for introducing functional substituents at the C_{11}-methyl group of 6-methylellipticine. This approach has been utilized for the synthesis of several sugar derivatives.

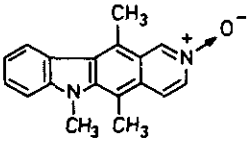
We have previously described[3] the total synthesis of 6-methylellipticine (1a) and its C_{11}-chloromethyl (1b) and C_{11}-hydroxymethyl (1c) derivatives. Compounds 1b and 1c have been converted into a variety of new ellipticines[4], amongst which the ribosyl compound (1d) was found to exhibit a significantly high water solubility and a favourable dose/toxicity profile. In an effort to functionalize the C_{11}-methyl group of ellipticine directly, we considered the possibility of applying the known chemistry of pyridine-N-oxide to the pyridocarbazole system. The transformation of 2-methylpyridine-N-oxide to 2-acetoxymethylpyridine, via reaction with acetic anhydride, is well documented[5]. Since the C_{11}-methyl of ellipticine is conjugatively analogous to the methyl group of 2-methylpyridine, it was tempting to speculate if the reaction of 6-methylellipticine-2-oxide with acetic anhydride would lead to the formation of 11-acetoxymethyl-6-methylellipticine (1e).



1a R = H
1b R = Cl
1c R = OH
1d R =



1e R = OAc



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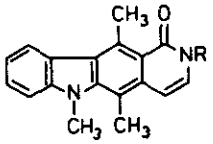
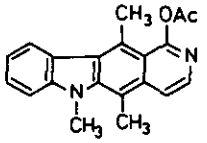


3a R = H, 3b = Ac



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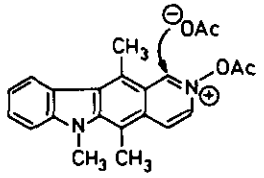

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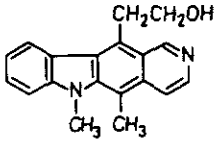

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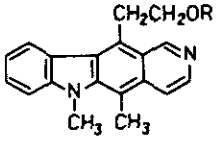
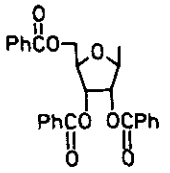
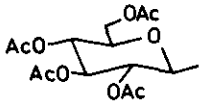


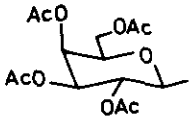
7a R =



7b R =



7c R =



Starting with 6-methylellipticine[6], the corresponding 2-oxide (2) was conveniently obtained by oxidation with m-chloroperbenzoic acid (CH_2Cl_2, 0°C, 75%). Reaction of 2[7] with acetic anhydride (reflux, 1.5 h, 0.25 eq NaOAc) yielded a mixture of two products 3a[8] and 3b[9] in a ratio dependent upon conditions of the reaction mixture workup. Structures of 3a and 3b were established by their spectral data. It would appear from the structures of 3a and 3b that they presumably arise via 4 and that the latter is formed by attack of acetate ion on C_1-position of intermediate 5, followed by elimination of acetic acid. Apparently, addition of acetate ion to the proximate carbon of the positively charged nitrogen, in 5, is favoured compared to deprotonation of the C_{11}-methyl group by the same ion, acting as a base. In view of these results we turned our attention to base catalyzed functionalization of the C_{11}-methyl group of 1a. As an example of this approach for derivatization, we have studied the reaction of the anion of 1a (LDA, THF, -78°C) with formaldehyde. Although the conditions of the condensation reaction have not yet been optimized, the hydroxymethylation product 6[10] was obtained in over 50% yield. The site of hydroxymethylation i.e. at the C_{11}--methyl, in 6 was established by Differential Nuclear Overhauser experiments involving amongst others irradiation of the 6-methyl substituent, whereupon an enhancement of the signals for the C_5-methyl and for H-7 was observed. The hydroxyl group in 6 provides a convenient function for coupling the ellipticine system to diverse reagents. In view of the observed properties of riboside 1d, special attention has been directed to the synthesis of sugar derivatives. The glycosidation step was carried out by reaction of 6 with the appropriately derivatized sugar using $SnCl_4$ as a catalyst (CH_3CN, RT). Employing the tribenzoate 1-β-acetate of ribose and the pentaacetates of glucose and galactose, the ellipticine derivatives 7a[11], 7b[12] and 7c[13], respectively were obtained. The stereochemistry of the glycosidic linkage in 7a-c was established by NMR spectroscopic analysis[14].

The synthetic opportunities for derivatization of ellipticine starting with 6 and other C_{11}-functional derivatives as central intermediates, derived via the anion of 1a are being investigated.

ACKNOWLEDGEMENT

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(b) M.J.E. Hewlins, A.M. Oliveira-Campos and P.V.R. Shannon, Synthesis, 1984, 289.

3. M.J. Wanner, G.J. Koomen and U.K. Pandit, Tetrahedron, 1983, 39, 3673.

4. Amino, amino acid, ester and bis-ellipticine derivatives have been prepared and tested. Unpublished results.

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6. The 6-methylellipticine was prepared from ellipticine supplied to us by the National Cancer Institute through the courtesy of Dr. M. Suffness.

7. 2: mp 185-192°C. IR (KBr): 1585, 1470, 1385, 1235, NMR ($CDCl_3$): δ 3.03, 3.06 (2 x s, 5-CH_3 and 11-CH_3), 7.9 (d, J=7.3, H-4), 8.12 (d, J=7.3, H-3), 9.18 (s, H-1).

8. 3a: NMR ($CDCl_3$): partial spectra δ 2.85 (s, 5-CH_3), 3.47 (s, 11-CH_3), 6.74 (d, J=7.6, H-4), 6.97 (d, J=7.6, H-3).

9. 3b: IR ($CHCl_3$): 1710, 1670, 1570, 1245. NMR ($CDCl_3$): δ 2.81 (s, $COCH_3$), 2.85 (s, 5-CH_3), 3.36 (s, 11-CH_3), 6.72 (d, J=8.5, H-4), 7.84 (d, J=8.5, H-3).

10. 6: IR (KBr): 3200, 2960, 2920, 2850, 1590, 1475, 1440, 1390, 1240. NMR (DMSO-d_6, 250 MHz): 3.07 (5, 3H, C-(5)-CH_3), 3.90 (dt, 4H, C-(11)-CH_2-CH_2), 4.17 (s, 3H, N-CH_3), 5.08 (t, 1H, J=5.2, OH), 7.34, 7.66 (2t, 2H, J=8.0, H-8 + H-9), 7.65 (d, 1H, J=8.0, H-7), 8.02 (d, 1H, J=6.0, H-4), 8.37 (d, 1H, J=7.9, H-10), 8.46 (d, 1H, J=5.8, H-3), 9.71 (s, 1H, H-1). MS: m/c=290.1402 (Calc. for $C_{19}H_{18}N_2O$ 290.1419). NOE experiments were carried out in pyridine-d_5. Irradiation of the methyl group at 3.07 ppm gave an enhancement for the methyl group and the H-4. Irradiation of N-methyl group gave an enhancement for the methyl group at 3.07 ppm and for H-7.

11. 7a: IR ($CHCl_3$): 2970, 1725, 1600, 1470, 1450, 1280, 1110. NMR ($CDCl_3$): 3.02 (s, 3H, C-(5)--CH_3), 3.95-4.32 (m, 4H, C-(11)-CH_2CH_2), 4.07 (s, 3H, N-CH_3), 4.18 (dd, 1H, J=5.8, J=11.6, $H_{5',A}$), 4.55 (dd, 1H, J=4.4, J=11.5, $H_{5',B}$), 4.63 (m, 1H, $H_{4'}$), 5.30 (s, 1H, $H_{1'}$), 5.65 (d, 1H, J=5.0, $H_{2'}$), 5.69 (dd, 1H, J=5.0, J=6.2, $H_{3'}$), 7.25-7.57 (m, 12H), 7.82-7.99 (m, 7H), 8.30 (d, 1H, J=7.8, H-10), 8.48 (d, 1H, J=6.2, H-3), 9.68 (s, 1H, H-1).

12. 7b: IR ($CHCl_3$): 2950, 1740, 1590, 1460, 1230, 1030. NMR ($CDCl_3$): 2.00-2.07 (4s, 12H, 4 x $COCH_3$), 3.04 (s, 3H, C-(5)-CH_3), 3.65 (m, 1H, H-5'), 3.89-4.34 (m, 6H, $H_{6'A}$, $H_{6'B}$, CH_2-CH_2), 4.54 (d, 1H, J=7.8, H-1'), 4.98-5.18 (m, 3H, H-2', H-3', H-4'), 7.28 (t, 1H, J= 7.9, H-8 or H-9), 7.40 (d, 1H, J=8.1, H-7), 7.57 (t, 1H, J=7.4, H-8 or H-9), 7.88 (d, 1H, J= 5.5, H-4), 8.24 (d, 1H, J=7.9, H-10), 8.47 (d, 1H, H-4), 9.65 (s, 1H, H-1).
13. 7c: IR ($CHCl_3$): 1745, 1590. NMR ($CDCl_3$): 2.02-2.12 (4s, 13H, $COCH_3$), 2.99 (s, C-(5)-CH_3), 3.88 (dd, 1H, J=6.4, J=6,7, H-5'), 4.06 (s, 3H, N-CH_3), 4.00-4.31 (m, 6H, $H_{6A'}$, $H_{6B'}$ + CH_2-CH_2), 4.56 (d, 1H, J=8.0, H-1'), 4.96 (dd, 1H, J=10.4, J=3.4, H-3'), 5.22 (dd, 1H, J=10.4, J=8.0, H-2'), 5.34 (d, 1H, J=3.5, H-4'), 7.29 (t, 1H, J=7.6, H-8 or H-9), 7.36 (d, 1H, J=8.1, H-7), 7.57 (t, 1H, J=7.6, H-8 or H-9), 7.87 (d, 1H, J=6.2, H-4), 8.22 (d, 1H, J=7.8, H-10), 8.46 (d, 1H, J=6.0, H-3), 9.64 (s, 1H, H-1).
14. Details of these will be described elsewhere.

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