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Synthesis of Novel Hydroxyellipticines

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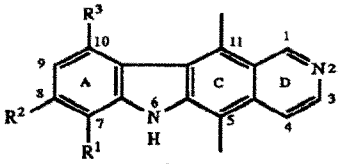
Abstract: 7-Methoxy-8-hydroxy and 10-hydroxyellipticines have been synthesised using Pivaloyl esters for regioselective deactivation and steric protection of reactive ring-A positions; the final cyclisation sequence has been analysed by ^{1}H-NMR.

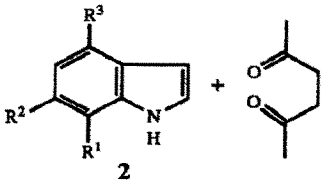
A multiplicity of synthetic routes to ellipticine **1a** exist[1,2,3], but considerably fewer to its derivatives and hardly any have been described to hydroxyellipticines. This is remarkable in view of the fact that 9-hydroxyellipticine is the basis of an anti-tumour drug, and that 9-hydroxy and 7-hydroxyellipticine are known to be metabolites of the parent anti-tumour compound **1a**[4].

One of the most successful strategies for the synthesis of ring-A substituted ellipticines has begun with the condensation of the appropriate indole **2** with hexane-2,5-dione to give the corresponding 1,4-dimethylcarbazole **3**[2]. When ring A of the carbazole contains oxygen substituents other than at solely position 6, the necessary step of



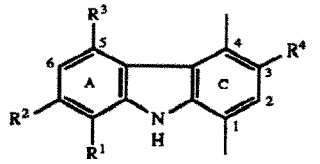
1

a) $R^1 = R^2 = R^3 = H$
b) $R^1 = OMe$; $R^2 = OCOCMe_3$; $R^3 = H$
c) $R^1 = OMe$; $R^2 = OH$; $R^3 = H$
d) $R^1 = R^2 = H$; $R^3 = OCOCMe_3$
e) $R^1 = R^2 = H$; $R^3 = OH$



2

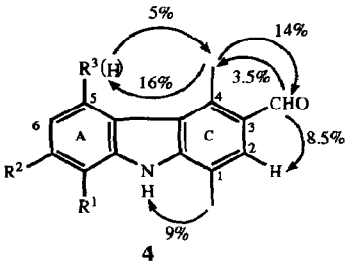
a) $R^1 = OMe$; $R^2 = OH$; $R^3 = H$



3

a) $R^1 = OMe$; $R^2 = OCOCMe_3$; $R^3 = R^4 = H$
b) $R^1 = R^2 = H$; $R^3 = OCOCMe_3$; $R^4 = H$
c) $R^1 = OMe$; $R^2 = OH$; $R^3 = R^4 = H$
d) $R^1 = OMe$; $R^2 = OAc$; $R^3 = R^4 = H$
e) $R^1 = R^2 = R^4 = H$; $R^3 = OH$
f) $R^3 = OCOCMe_3$; $R^1 = R^2 = R^4 = H$
g) $R^3 = OCOCMe_3$; $R^4 = CHO$; $R^1 = R^2 = H$
h) $R^1 = CHO$; $R^3 = OCOCMe_3$; $R^2 = R^4 = H$

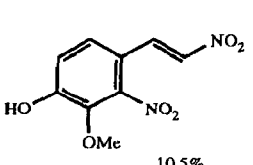
formylation occurs at ring A, rather than at the desired position 3 for the aldehydes **4**, necessary for annelation of ring D of the ellipticine **1**.



4

a) R^1 = OMe; R^2 = OH; R^3 = H
b) R^1 = OMe; R^2 = OAc; R^3 = H
c) R^1 = OMe; R^2 = $OCOCMe_3$; R^3 = H

NOE figures for compd. 4c



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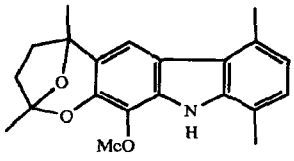

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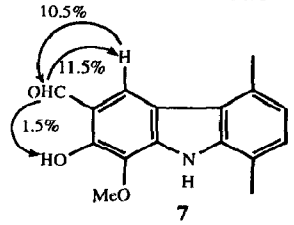
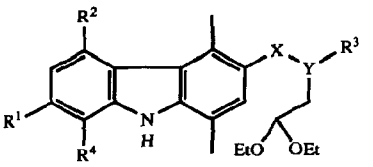


7

For various ellipticines we have overcome this problem in different ways[5]- but for the 7-methoxy-8-hydroxy and 10-hydroxy ellipticines **1c** and **1e** we decided to use the corresponding pivaloyloxycarbazole intermediates **3a** and **b** respectively, which would have less nucleophilic activity in ring A and high steric protection for the most reactive position 6.

The dinitrostyrene **5** (m.p. 188-191°C, lit[6] 188-189°C), on reduction with activated iron powder, gave the indole **2a**[7] which, with hexane-2,5-dione in the presence of toluene-p-sulfonic acid, gave the hydroxycarbazole **3c** m.p. 137-140°C (40%) and a 1.5% yield of the tetrahydrooxepine **6**, m.p. 170-175°C. Vilsmeier formylation of carbazole **3c** gave mainly the aldehyde **7**, (36%) m.p. 199-202°C whose structure was confirmed by the NOE enhancements shown.



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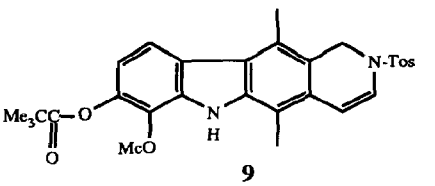
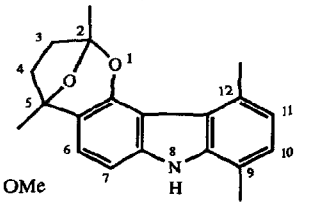


9

a) X-Y = CH=N; R^1 = OAc; R^2 = H; R^4 = OMe
b) X-Y = CH_2-N; R^1 = OAc; R^2 = R^3 = H; R^4 = OMe
c) X-Y = CH_2-N; R^1 = OH; R^2 = R^3 = H; R^4 = OMe
d) X-Y = CH=N; R^1 = $OCOCMe_3$; R^2 = H; R^4 = OMe
e) X-Y = CH_2-N; R^1 = $OCOCMe_3$; R^2 = R^3 = H; R^4 = OMe
f) X-Y = CH_2-N; R^1 = $OCOCMe_3$; R^2 = H; R^3 = p-$SO_2C_6H_4Me$; R^4 = OMe
g) X-Y = CH=N; R^2 = $OCOCMe_3$; R^1 = R^4 = H
h) X-Y = CH_2-N; R^2 = $OCOCMe_3$; R^1 = R^3 = R^4 = H
i) X-Y = CH_2-N; R^2 = $OCOCMe_3$; R^1 = R^4 = H; R^3 = p-$SO_2C_6H_4Me$



10

Acetylation of the hydroxycarbazole **3c** gave the derivative **3d** m.p. 172-175°C (73%) and Vilsmeier formylation of this gave the aldehyde **4b** m.p. 196-199°C (61%) m.p., which showed in its ^{1}H-NMR spectrum the expected replacement of the AB quartet of ring C of the starting material by a singlet at δ 7.77. Small amounts of the N-formyl (4%) and 6-formyl (4%) isomers were also formed and isolated.

The aldehyde **4b** condensed with aminoacetaldehyde diethylacetal to give the crude Schiff's base **8a** but the ^{1}H-NMR spectrum showed evidence of some hydrolysis of the acetal group and ammonolysis of the acetate group. In support of the latter, substantial amounts of N-acetylaminoacetaldehyde diethylacetal was observed after hydrogenation of the Schiff's base over Adams' catalyst. This resulted in even greater lability of the acetyl group - giving predominantly a mixture of the amines **8b** and **8c** in the ratio 1:2 respectively. It was clear that the acetyl group, although directing the formylation appropriately, was too unstable to the conditions for ring D annelation to give purifiable products in good yields. Treatment of the hydroxycarbazole **3c** with pivaloyl chloride in pyridine, however, gave the pivaloyloxy carbazole **3a** (81%) and Vilsmeier formylation of this with N-methylformanilide and phosphorus oxychloride in trichloroethylene gave the 3-formylcarbazole **4c** m.p. 216-219°C (78%). The position of formylation was confirmed by ^{1}H-NMR [new singlet signal (1H, δ7.76)] and the NOE enhancements shown. The N-formyl isomer was also isolated (7%).

Condensation of the aldehyde **4c** with aminoacetaldehyde diethylacetal gave the stable Schiff's base **8d**, m.p. 113-116°C, (100%) which was hydrogenated over Adams' catalyst to the crude amine **8e** in quantitative yield. Treatment with toluene-p-sulfonyl chloride in pyridine gave the sulfonamide **8f** m.p. 93-96°C (74%) after chromatography. In a small scale preview of its cyclisation, the sulfonamide **8f** was treated in DMSO-d_6 (0.5 ml) with DCl in D_2O (0.084 ml of a 20% solution). The ^{1}H-NMR spectrum was recorded initially at ambient temperature, then, periodically, at 64°C for 3 h. and finally at 74°C for a further 60 h. The progress of the reaction was followed quantitatively and the results are shown in the Figure. It can be seen that during the first three hours there was a relatively rapid cyclisation of the sulfonamide **8f** to the tosyldihydropyridocarbazole **9**. After three hours, none of the starting sulfonamide **8f**

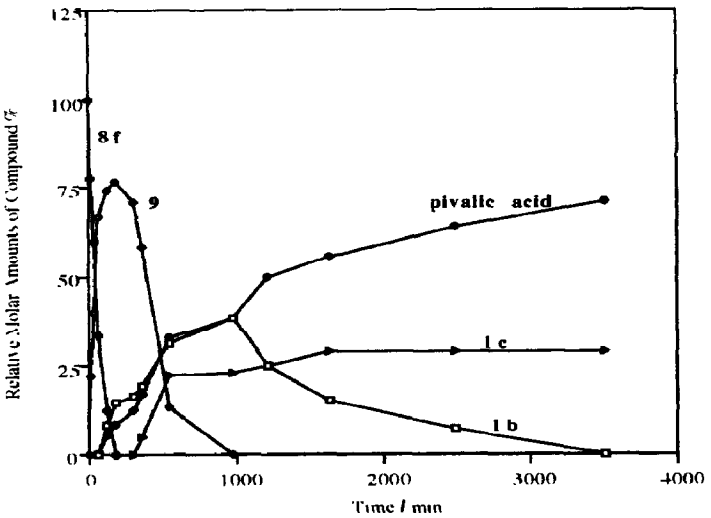


Figure: Cyclisation of the Sulfonamide **8f**

remained and the mixture contained the intermediate **9** (77%), the pivaloylated hydroxyellipticine **1b** (15%) and pivalic acid (8%). From three to nine hours the intermediate **9** declined in concentration and both the protected (**1b**) and deprotected (**1c**) ellipticines increased until, after 20 hours there was a 1:1 mixture of **1b** and **1c** and no intermediate. Thereafter the protected ellipticine **1b** slowly hydrolysed to the target 6-hydroxy-7-methoxyellipticine **1c**[8]. On the basis of this ^{1}H-NMR experiment, preparative scale cyclisations

were performed on the sulfonamide **8f** (a) using 5.3 molar hydrochloric acid in dimethylsulfoxide at 64°C in the dark, under nitrogen for 3.5 h. and (b) at 74°C for 7 h. Experiment (a) gave, after chromatography, the intermediate **9** m.p. 177-180°C (40%), the novel pivaloylated ellipticine **1b** m.p. 275-277°C (dec) and the 8-hydroxy-7-methoxyellipticine **1c**, m.p. 238-240°C (dec), (24%). The more extreme conditions (b) gave the same products **9**, **1b** and **1c** in the yields 8, 27 and 44% respectively. Variation in the reaction conditions can obviously be used to favour the intermediate **9** or the hydroxyellipticine **1c**.

Of the simple monohydroxyellipticines, there has been no report of the 10-hydroxy derivative. The corresponding intermediate carbazole **3e** would be expected to formylate at the most reactive 6 position, and the same strategy of deactivation and steric protection was used for **3e** to induce formylation at C-3. 4-Hydroxyindole condensed with hexane-2,5-dione in the presence of toluene-p-sulfonic acid to give the hydroxycarbazole **3e** m.p. 106-109°C (30%) and the tetrahydrooxepine **10** (6%). Formylation of carbazole **3e** gave a mixture (2:1) of the 6- and 8-formyl derivatives respectively, hence, the carbazole **3e** was converted quantitatively to the pivaloyl ester **3f**, using an excess of pivaloyl chloride. Vilsmeier formylation as above gave a mixture of the 3-formylcarbazole **3g** (37%) and the 8-formyl isomer **3h** (19%). The aldehyde **3g** was converted, as above, into the crude Schiff's base **8g** (85%), hydrogenation of which, as before, gave the amine **8h** (88%). Immediate treatment with toluene-p-sulfonyl chloride in pyridine in the dark for 4 days gave the sulfonamide **8i**, m.p. 165-168°C (70%). Treatment of the sulfonamide **8i** with 0.885 M-HCl in dimethylsulphoxide at 76°C for 12.5 h. gave, after chromatography, the ellipticine **1d** (55%) m.p. 150-153°C. Hydrolysis of **1d** with aqueous potassium hydroxide gave, after chromatography, the novel 10-hydroxyellipticine **1e**[9] m.p. 210-213°C (dec) (40%).

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8. δ_H (360 MHz) (DMSO-d_6) 11.04 (1H, br s, NH), 9.67 (1H, s, 1-H), 9.65 (1H, br s, OH), 8.41 (1H, d, J 5 Hz, 3-H), 7.91 (2H, m, 10, 4-H), 6.84 (1H, d, J 8 Hz, 9-H), 3.93 (3H, s, 7-OCH_3), 3.17 (3H, s, 11-CH_3) and 2.84 (3H, s, 5-CH_3); m/z (%) 292 (M^+, 100), 277 (67), 262 (3), 249 (18), 231 (11) and 219 (8); λ_{max} 386 (ε 1240), 350 (sh) (1870), 320 (sh) (3500), 299 (23 430), 286 (sh) (16 590) and 238 (9910) nm. (Found: M^+, 292.1212. $C_{18}H_{16}N_2O_2$ requires M, 292.1212).
9. δ_H (360 MHz) (Acetone-d_6) 10.43 (1H, br s, NH), 9.72 (1H, s, 1-H), 9.41 (1H, br s, OH), 8.43 (1H, d, J 5 Hz, 3-H), 7.91 (1H, d, J 5 Hz, 4-H), 7.33 (1H, t, J 8 Hz, 8-H), 7.06 (1H, d, J 8 Hz, 7-H), 6.76 (1H, d, J 8 Hz, 9-H), 3.65 (3H, s, 11-CH_3), 2.82 (3H, s, 5-CH_3); m/z (%) 262 (M^+, 100), 247 (23), 233 (5), 219 (7), 204 (3) and 190 (3). (Found: M^+ 262.1106. $C_{17}H_{14}N_2O$ requires M, 262.1106).

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