

## PYRIDOCARBAZOLE ALKALOIDS. SYNTHESIS OF OLIVACINE AND ELLIPTICINE ANALOGUES

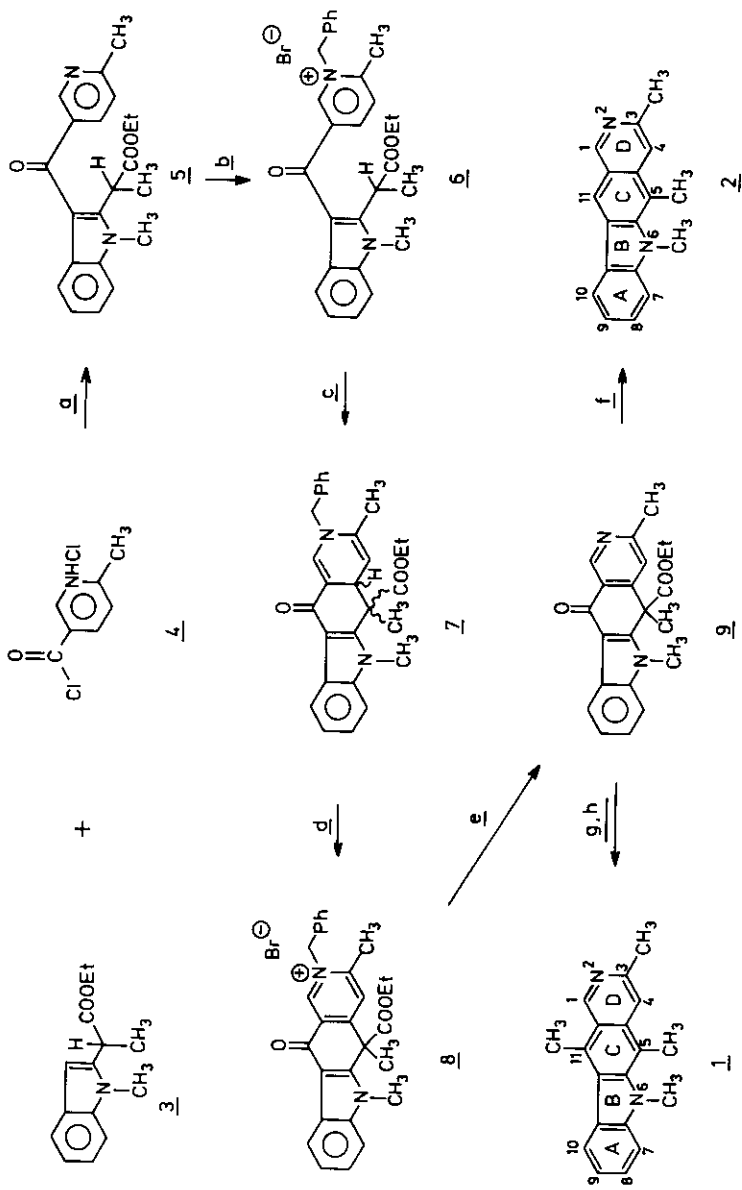
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Abstract - 3,6-Dimethylellipticine and 1-demethyl-3,6-dimethylolivacine have been synthesized via the common intermediate 5-ethoxycarbonyl-3,5,6-trimethyl-11-oxo-5,11-dihydropyrido[4,3-b]carbazole.

The reported antitumour activity of ellipticine and olivacine has generated a great deal of chemical interest in the synthesis of these pyridocarbazole alkaloids and their derivatives<sup>1a,b</sup>. Recently, we reported an approach to the construction of the pyridocarbazole skeleton<sup>2</sup>, which is capable of general application to a wide variety of analogues of the natural alkaloids. We now describe the convenient synthesis of two new compounds which represent peripherally ring D modified 6-methylellipticine (1) and 6-methylolivacine (2).

The synthetic scheme employs, as starting material, the AB ring synthon 3, described by us previously<sup>2</sup>. Acylation of the indole moiety of 3 by 6-methylnicotinoyl chloride hydrochloride 4<sup>3</sup> in sulfolane led to formation of the expected ketone 5<sup>4</sup> in 74% yield<sup>5</sup>. Formation of the pyridocarbazole skeleton (7a,b) was completed by N-benylation of 5 and subsequent base-catalyzed cyclization of the resulting salt 6, which was not isolated. The cyclization product consisted of a mixture of two diastereomers<sup>6</sup>, the oxidation of which yielded the N-benzyliated salt 8 (95%; mp 209-217° C). When 8 was reductively debenzylated (H<sub>2</sub>/Pd-C 10%), the central intermediate for the preparation of new pyridocarbazole alkaloids, namely 9<sup>7</sup>, mp 156-159° C, was produced in modest yield (41%). Conversion of 9 to 3,6-dimethylellipticine (1)<sup>8</sup> was carried out in one practical step by reaction with an excess of MeMgI/THF, followed by basic elimination (KOH/HOCH<sub>2</sub>CH<sub>2</sub>OH, 50%) of the elements of COOEt and OMgBr<sup>2</sup>. The driving force of the last step is derived from aromatization of ring C. Reduction of 9 with Red-Al<sup>2</sup> gave the analogue of olivacine 2<sup>9</sup> in 39% yield. Biological evaluation of 1 and 2 and development of methods for their hydroxylation at C(9) are in progress.



- a** sulfolane, 90–100°C, 24 h; **b** PhCH<sub>2</sub>Br, 90°C, 30 min.; **c** NEt<sub>3</sub> / EtOAc, r.t.;  
**d** N-benzylacridinium bromide, MeCN, r.t.; **e** H<sub>2</sub> / 10% Pd-C, EtOH; **f** Red-Al, THF;  
**g** MeMgI, THF, Δ; **h** KOH / HOCH<sub>2</sub>CH<sub>2</sub>OH (50%), 160°C.

## REFERENCES

1. For reviews see: (a) M. Suffness and G.A. Cordell, 'The Alkaloids' vol. XXV, Academic Press, New York, 1985, p. 89; (b) G.W. Gribble and M.A. Saulnier, *Heterocycles*, 1985, 23, 1277.
2. M.J. Wanner, G.J. Koomen and U.K. Pandit, *Tetrahedron*, 1983, 39, 3673.
3. (a) R. Graf, *J. Prakt. Chem.*, 1932, 133, 19; (b) R. Graf and F. Zettl, *ibid.*, 1936, 147, 188; (c) R.N. Castle and C.W. Whittle, *J. Org. Chem.*, 1959, 24, 1189.
4. 5, light yellow crystals, mp 133-136° C (74%); 1725, 1620, 1590; PMR (CDCl<sub>3</sub>): 1.15 (t, 3H, J=7, COOCH<sub>2</sub>CH<sub>3</sub>), 2.65 (s, 3H, Pyr-CH<sub>3</sub>), 3.75 (s, 3H, N-CH<sub>3</sub>), 4.15 (q, 2H, J=7, COOCH<sub>2</sub>CH<sub>3</sub>), 4.84 (q, 1H, J=7, -CH(CH<sub>3</sub>)), 7.05-7.37 (m, 5H, Ar-H + 1 Pyr-H), 7.97 (dd, 1H, J=2, J=8, Pyr-H<sub>4</sub>), 8.87 (d, 1H, J=2, Pyr-H<sub>6</sub>); MS: 350.1615, Calc. for C<sub>21</sub>H<sub>22</sub>N<sub>2</sub>O<sub>3</sub> 350.1601.
5. The yield of 5 is very sensitive to the temperature at which the reaction is carried out, due to instability of the acid chloride above 100° C.
6. 7 is a diastereomeric mixture of two compounds (4:1, 54%). The mp of the mixture shows two distinct ranges, 150-157° C and 167-173° C; PMR\* (CDCl<sub>3</sub>): δ 1.61 (s, 0.6 H, 20% C(5)-CH<sub>3</sub>), 1.77 (s, 2.4 H, 80% C(5)-CH<sub>3</sub>) + C(3)-CH<sub>3</sub>, 3.72 (s, 3H, N-CH<sub>3</sub>), 4.53 (s, 2H, Ph-CH<sub>2</sub>), 4.70 (s, 1H, C(4)-H).
7. 9, mp 156-159° C, yield 41%; PMR\* (CDCl<sub>3</sub>): δ 1.95 (s, 3H, C(5)-CH<sub>3</sub>), 2.68 (s, 3H, C(3)-CH<sub>3</sub>), 3.79 (s, 3H, N-NH<sub>3</sub>), 9.48 (s, 1H, C(1)-H); MS: 348.1462, Calc. for C<sub>21</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub> 348.1451.
8. 1, mp 229-231° C, yield 52%; PMR (CDCl<sub>3</sub>): δ 2.74 (s, 3H, C(3)-CH<sub>3</sub>), 2.96 (s, 3H, C(5)-CH<sub>3</sub>), 3.18 (s, 3H, C(11)-CH<sub>3</sub>), 4.06 (s, 3H, N-CH<sub>3</sub>), 7.68 (s, 1H, C(4)-H), 9.56 (s, 1H, C(1)-H); MS: 274.1458, Calc. for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub> 274.1446.
9. 2, yellow crystals, mp 149-151° C, yield 39%; PMR\* (CDCl<sub>3</sub>): δ 2.77 (s, 3H, C(3)-CH<sub>3</sub>), 3.06 (s, 3H, C(5)-CH<sub>3</sub>), 4.16 (s, 3H, N-CH<sub>3</sub>), 7.75 (s, 1H, C(4)-H), 8.51 (s, 1H, C(11)-H), 9.28 (s, 1H, C(1)-H); MS: 260.1318, Calc. for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub> 260.1322.

\* selected chemical shifts.

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