PYRIDOCARBAZOLE ALKALOIDS. SYNTHESIS OF OLIVACINE AND ELLIPTICINE ANALOGUES

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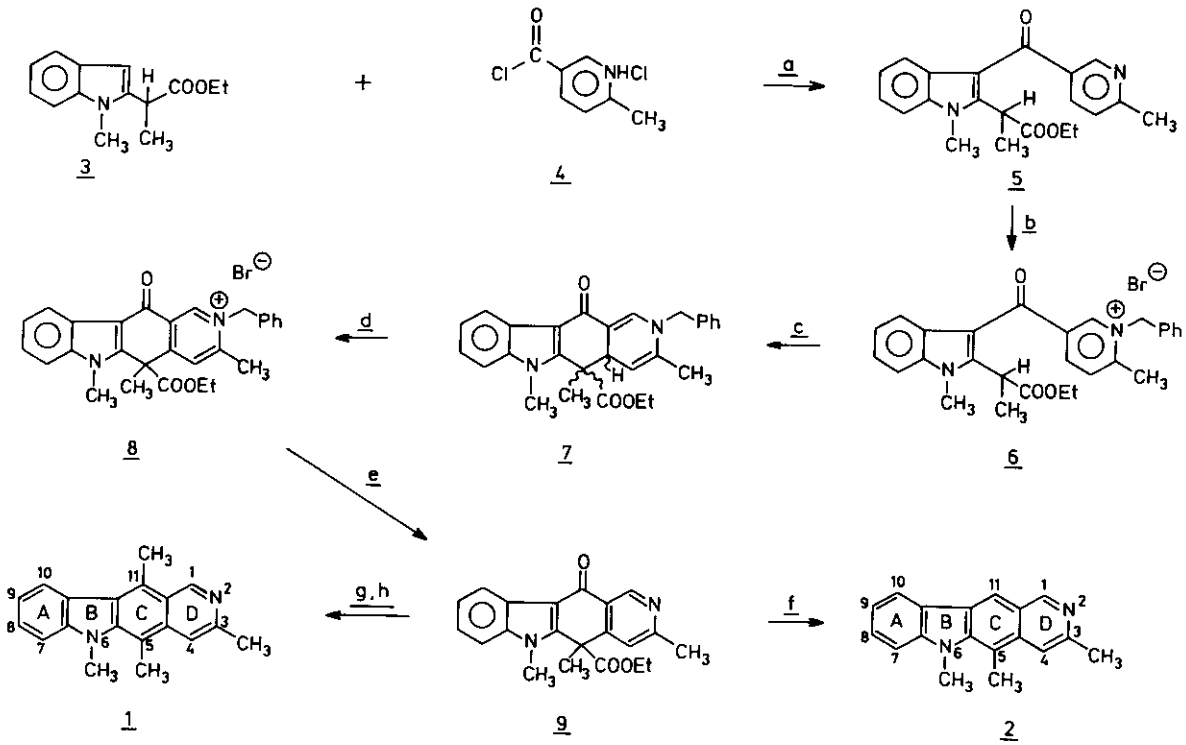
Abstract - 3,6-Dimethylellipticine and 1-demethyl-3,6-dimethylolivacine have been synthesized via the common intermediate 5-ethoxycarbonyl-3,5,6-trimethyl-11-oxo-5,11-dihydropyrido[4,3-b]carbazole.

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[1a,b]. Recently, we reported an approach to the construction of the pyridocarbazole skeleton[2], 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[2]. Acylation of the indole moiety of 3 by 6-methylnicotinoyl chloride hydrochloride 4[3] in sulfolane led to formation of the expected ketone 5[4] in 74% yield[5]. Formation of the pyridocarbazole skeleton (7a,b) was completed by N-benzylation 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[6], the oxidation of which yielded the N-benzylated salt 8 (95%; mp 209-217° C). When 8 was reductively debenzylated (H_2/Pd-C 10%), the central intermediate for the preparation of new pyridocarbazole alkaloids, namely 9[7], mp 156-159° C, was produced in modest yield (41%). Conversion of 9 to 3,6-dimethylellipticine (1)[8] was carried out in one practical step by reaction with an excess of MeMgI/THF, followed by basic elimination (*KOH/$HOCH_2CH_2OH$, 50%*) of the elements of COOEt and OMgBr[2]. The driving force of the last step is derived from aromatization of ring C. Reduction of 9 with Red-Al[2] gave the analogue of olivacine 2[9] 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 $PhCH_2Br$, 90°C , 30 min. ; c NEt_3 / EtOAc , r.t. ;

d N-benzylacridinium bromide , MeCN , r.t. ; e H_2 / 10% Pd-C , EtOH ; f Red-Al , THF ;

g MeMgI , THF , Δ ; h KOH / $HOCH_2CH_2OH$ (50%) , 160°C .

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4. 5, light yellow crystals, mp 133-136° C (74%); 1725, 1620, 1590; PMR ($CDCl_3$): 1.15 (t, 3H, J=7, $COOCH_2\underline{CH_3}$), 2.65 (s, 3H, Pyr-CH_3), 3.75 (s, 3H, N-CH_3), 4.15 (q, 2H, J=7, $COO\underline{CH_2}CH_3$), 4.84 (q, 1H, J=7, -$\underline{CH}(CH_3)$), 7.05-7.37 (m, 5H, Ar-H + 1 Pyr-H), 7.97 (dd, 1H, J=2, J=8, Pyr-H_4), 8.87 (d, 1H, J=2, Pyr-H_6); MS: 350.1615, Calc. for $C_{21}H_{22}N_2O_3$ 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* ($CDCl_3$): δ 1.61 (s, 0.6 H, 20% C(5)-CH_3), 1.77 (s, 2.4H, 80% C(5)-CH_3) + C(3)-CH_3), 3.72 (s, 3H, N-CH_3), 4.53 (s, 2H, Ph-CH_2), 4.70 (s, 1H, C(4)-H).

7. 9, mp 156-159° C, yield 41%; PMR* ($CDCl_3$): δ 1.95 (s, 3H, C(5)-CH_3), 2.68 (s, 3H, C(3)-CH_3), 3.79 (s, 3H, N-NH_3), 9.48 (s, 1H, C(1)-H); MS: 348.1462, Calc. for $C_{21}H_{20}N_2O_3$ 348.1451.

8. 1, mp 229-231° C, yield 52%; PMR ($CDCl_3$): δ 2.74 (s, 3H, C(3)-CH_3), 2.96 (s, 3H, C(5)-CH_3), 3.18 (s, 3H, C(11)-CH_3), 4.06 (s, 3H, N-CH_3), 7.68 (s, 1H, C(4)-H), 9.56 (s, 1H, C(1)-H); MS: 274.1458, Calc. for $C_{19}H_{18}N_2$ 274.1446.

9. 2, yellow crystals, mp 149-151° C, yield 39%; PMR* ($CDCl_3$): δ 2.77 (s, 3H, C(3)-CH_3), 3.06 (s, 3H, C(5)-CH_3), 4.16 (s, 3H, N-CH_3), 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 $C_{18}H_{16}N_2$ 260.1322.

* selected chemical shifts.

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