A CONVENIENT SYNTHESIS OF 6-METHYLELLIPTICINE AND 6-METHYLOLIVACINE

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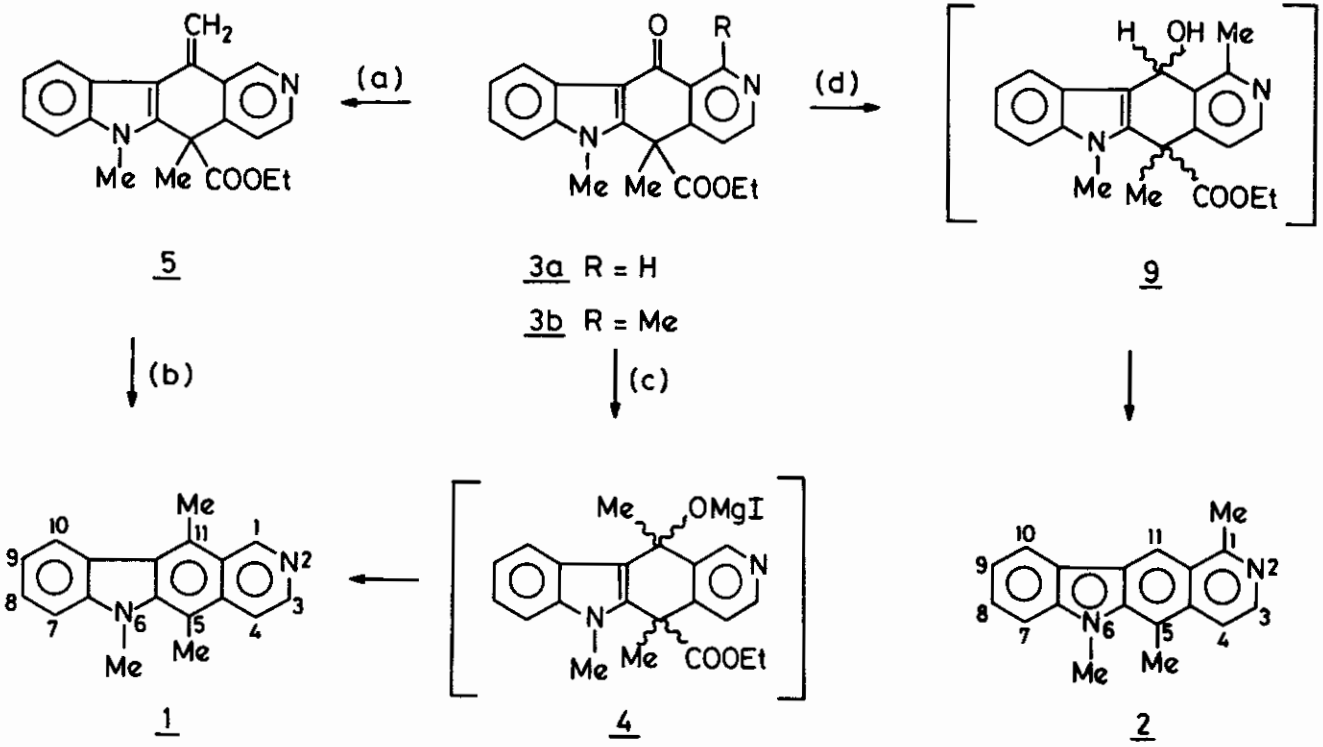
Abstract — Readily accessible 11-ketopyrido[4,3-b]carbazole derivatives 3a,b have been used as central intermediates for the synthesis of 6-methylellipticine and 6-methylolivacine.

Considerable interest centres around the pyridocarbazole alkaloids ellipticine and olivacine, in view of their reported antitumour activity[1a-d]. Although a number of syntheses for these alkaloids have been reported to date[2a-e], a convenient approach to the parent compounds and their derivatives, starting from readily available materials, has been lacking. In this communication we present the synthesis of both 6-methylellipticine (1) and 6-methylolivacine (2) via a general synthesis of the pyridocarbazole skeleton which has been reported by us earlier[3].

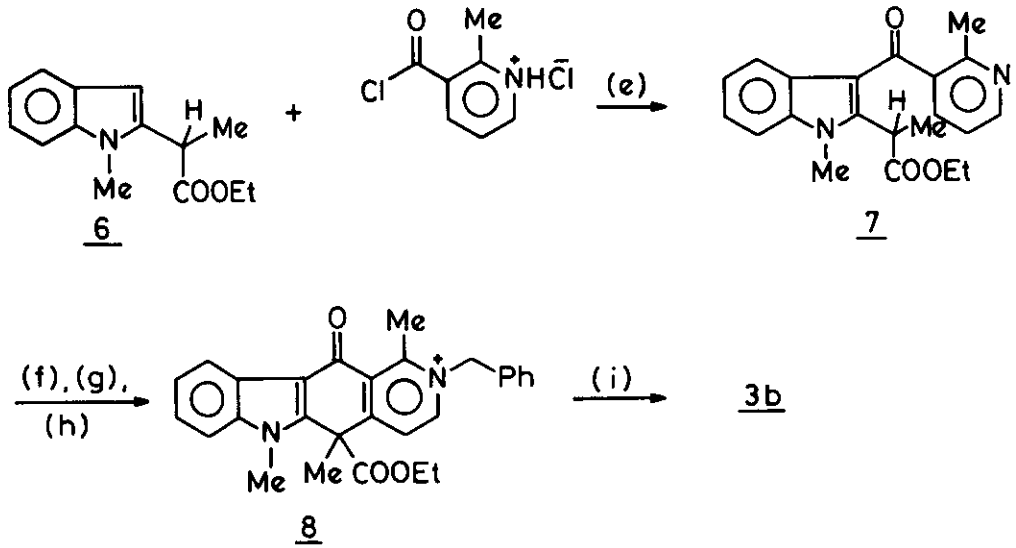
As a part of a broader study of the application of the reaction of ester α-anions with N-alkylated nicotinic acid derivatives to the synthesis of polynuclear heterocycles, we have recently reported the syntheses of d,l-sesbanine[4] and the pyridocarbazole derivative 3a[3]. The conversion of 3a to the corresponding ellipticine derivative 1 and the preparation of the analogous precursor (3b), and its transformation to the related olivacine system (2), constituted worthwhile synthetic targets.

The conversion of 3a to 1 could be achieved via two routes (Scheme A). Reaction of 3a with CH_3MgI (excess, THF, reflux) led directly to the formation of 6-methylellipticine (40%) in one practical step. The reaction presumably proceeds via intermediate 4, which undergoes a fragmentation, involving loss of $^{\ominus}OMgI$, mediated by attack of the Grignard reagent (excess) on the ester carbonyl. An alternate mechanism could involve an analogous fragmentation of a lactone, formed by intramolecular reaction between the incipient alkoxide anion - generated by initial Grignard attack - and the ester group.



(a) $Ph_3P{=}CH_2$, THF , 20°; (b) KOH , EtOH / H_2O , Δ ; (c) MeMgI , (excess) , THF , Δ ;
(d) REDAL , THF , r.t.

Scheme A



(e) Sulfolane, 160-170°, 20 min ; (f) $PhCH_2Br$, 110°, 30 min ; (g) Et_3N, r.t. 1h ; (h) N-Benzylacridinium bromide ; CH_3CN ; (i) H_2 / Pd

Scheme B

The second route involved the treatment of 3a with $Ph_3P=CH_2$ (2 eq.), whereupon the exo-methylene derivative 5 was obtained in good yield (65%). Hydrolysis of 5 (KOH/EtOH/H_2O, reflux) cleanly yielded 1 as a crystalline compound, m.p. 211-212° (60%). Relevant spectral data on 5[5] and 1[6] attested to their structures. It should be emphasized that both routes are capable of variation and that 3a can serve as a central intermediate for the synthesis of diverse ellipticine analogues.

The 6-methylolivacine precursor (3b) was prepared via the sequence of reactions described in Scheme B. This sequence starts with the known indolylpropionic ester 6 (Scheme B) and follows the steps 6 → 7 → 8 → 3b, in a manner analogous to that described previously for the synthesis of 3a. The only difference is represented by the use of 2-methylnicotinyl chloride hydrochloride, in place of the nicotinyl chloride hydrochloride salt. The structures of intermediates 7 and 8, and compound 3b (m.p. 165-167°), were assigned on the basis of their spectral data[7]. The keto ester 3b was converted to 2 (57%), in one practical step, by reaction with excess of RedAl. It is assumed that a hydroxy compound (9) is initially formed, which is further reduced and decomposed (perhaps via a lactone) to 2 under the reaction conditions. The product 2 is a crystalline compound, m.p. 228-229°, which exhibited ^1H NMR spectral data[8] consistent with the assigned structure.

The scope of the conversion of intermediates of type 3 to ellipticine and olivacine derivatives is being actively investigated.

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5. 5: Unstable oil (65%); IR ($CHCl_3$): 1725, 1615, 1590 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.08 (t, J=7, CH_3); 1.90 (s, CH_3); 3.67 (s, N-CH_3); 4.12 (m, CH_2); 5.98 (s,=CH); 6.02 (s, =CH); 7.3-7.5 (m, $C_{4,7,8}$ and $_9$-H); 8.08 (d, J=8, C_{10}-H); 8.53 (d, J=6, C_3-H); 9.32 (s, C, -H).

6. 1: M.p.: 211-212° (60%); IR ($CHCl_3$): 1595, 1470 cm^{-1}. ^1H NMR ($CDCl_3$): δ 3.00 (s, 5-CH_3); 3.14 (s, 11-CH_3); 4.08 (s, N-CH_3); 7.30 (t, J=8, C_8-H/C_9-H); 7.38 (d, J=8, C_7-H); 7.58 (t, J=8, C_8-H/C_9-H); 7.86 (d, J=7, C_4-H); 8.32 (d, J=8, C_{10}-H); 8.46 (d, J=7, C_3-H); 9.64 (s, C_1-H). MS (M^+) 260.1307; Calcd. for $C_{18}N_{16}N_2$: 260.1301.

7.(a) 7: Oil (30%); IR ($CHCl_3$): 1730, 1620, 1580 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.25 (t, J=7, CH_3); 1.66 (d, J=7, CH_3); 2.53 (s, CH_3); 3.76 (s, N-CH_3); 4.25 (q, J=7, CH_2); 5.05 (q, J=7, CH); 6.5-7.5 (m, arylprotons + pyridine C_5-H); 7.70 (d x d, J=7, J=1.5, pyridine C_4-H); 8.66 (d x d, J=5, J=1.5, pyridine C_6-H).

(b) 8: M.p.: 174-177° (60%); IR ($CHCl_3$): 1740, 1655, 1615 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.16 (t, J=7, CH_3); 2.10 (s, CH_3); 3.50 (s, CH_3); 3.86 (s, N-CH_3); 4.28 (q, J=7, CH_2); 6.32 (s, Ø-CH_2); 7.3-7.5 (m, 8H-Ar); 8.22 (d, J=7, C_4-H); 8.41 (m, C_{10}-H); 9.98 (d, J=7, C_3-H).

(c) 3b: M.p.: 165-176° (81%). IR ($CHCl_3$): 1730, 1640, 1570 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.06 (t, J=7, CH_3); 1.95 (s, CH_3); 3.22 (s, CH_3); 3.78 (s, N-CH_3); 4.17 (q, J=7, CH_2); 7.35 (d, J=6, C_4-H); 7.40 (m, 3H-Ar); 8.45 (m, C_{10}-H); 8.63 (d, J=6, C_3-H).

8. 2: M.p.: 228-229° (57%). IR ($CHCl_3$): 1625 (sh), 1600 cm^{-1}. ^1H NMR ($CDCl_3$):

δ 2.81 (s, 1-CH_3); 2.98 (s, 5-CH_3); 3.86 (s, N-CH_3); 7.15-7.35 (m, $C_{8 \text{ and } 9}$-H); 7.49 (d, J=8, C_7-H); 7.63 (d, J=6.5, C_4-H); 8.06 (d, J=8, C_{10}-H); 8.32 (d, J=6.5, C_3-H); 8.39 (s, C_{11}-H). Ms. (M^+) 260.1302; Calcd. for $C_{18}H_{16}N_2$: 260.1301.

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