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 activity1a-d. Although a number of syntheses for these alkaloids have been reported to date2a-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 earlier3.

As a part of a broader study of the application of the reaction of ester a-anions with N-alkylated nicotinic acid derivatives to the synthesis of polynuclear heterocycles, we have recently reported the syntheses of d,l-sesbanine4 and the pyridocarbazole derivative 3a3. 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 CH3MgI (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 $^6$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) Ph₃P=CH₂, THF, 20°; (b) KOH, EtOH/H₂O, Δ; (c) MeMgI (excess), THF, Δ; (d) REDAL, THF, r.t.

Scheme A
Scheme B

(e) Sulfolane, 160-170°C, 20 min; (f) PhCH₂Br, 110°C, 30 min; (g) Et₃N, r.t. 1 h; (h) N-Benzyllacridinium bromide; CH₃CN; (i) H₂/Pd
The second route involved the treatment of 3a with Ph$_3$P=CH$_2$ (2 eq.), whereupon the exo-methylene derivative 5 was obtained in good yield (65%). Hydrolysis of 5 (KOH/EtOH/H$_2$O, reflux) cleanly yielded 1 as a crystalline compound, m.p. 211-212$^\circ$ (60%). Relevant spectral data on 5 and 1 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-methylolivaceine 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 $\rightarrow$ 7 $\rightarrow$ 8 $\rightarrow$ 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$^\circ$), were assigned on the basis of their spectral data. 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$^\circ$, which exhibited $^1$H NMR spectral data consistent with the assigned structure.

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


5. 5: Unstable oil (65%); IR (CHCl₃): 1725, 1615, 1590 cm⁻¹. ¹H NMR (CDCl₃): δ 1.08 (t, J=7, CH₃); 1.90 (s, CH₃); 3.67 (s, N-CH₃); 4.12 (m, CH₂); 5.98 (s, =CH); 6.02 (s, =CH); 7.3-7.5 (m, C₄,7,8 and 2-H); 8.08 (d, J=8, C₁₀-H); 8.53 (d, J=6, C₃-H).

6. 2: M.p.: 211-212° (60%); IR (CHCl₃): 1595, 1470 cm⁻¹. ¹H NMR (CDCl₃): δ 3.00 (s, 5-CH₃); 3.14 (s, 11-CH₃); 4.08 (s, N-CH₃); 7.30 (t, J=8, C₈-H/C₉-H); 7.38 (d, J=8, C₇-H); 7.58 (t, J=8, C₆-H/C₉-H); 7.86 (d, J=7, C₄-H); 8.32 (d, J=8, C₁₀-H); 8.46 (d, J=7, C₃-H); 9.64 (s, C₁-H). MS (M⁺) 260.1307; Calcd. for C₁₈N₁₆N₂:

7. 7: Oil (30%); IR (CHCl₃): 1725, 1620, 1580 cm⁻¹. ¹H NMR (CDCl₃): δ 1.25 (t, J=7, CH₃); 1.66 (d, J=7, CH₃); 2.53 (s, CH₃); 3.76 (s, N-CH₃); 4.25 (q, J=7, CH₂); 5.05 (q, J=7, CH); 6.5-7.5 (m, arylprotons + pyridine C₅-H); 7.70 (d x d, J=7, J=1.5, pyridine C₄-H); 8.66 (d x d, J=5, J=1.5, pyridine C₆-H).

8. 8: M.p.: 174-177° (60%); IR (CHCl₃): 1740, 1655, 1615 cm⁻¹. ¹H NMR (CDCl₃): δ 1.16 (t, J=7, CH₂); 2.10 (s, CH₃); 3.50 (s, CH₃); 3.86 (s, N-CH₃); 4.28 (q, J=7, CH₂); 6.32 (s, O-CH₂); 7.3-7.5 (m, 8H-Ar); 8.22 (d, J=7, C₄-H); 8.41 (m, C₁₀-H); 9.98 (d, J=7, C₃-H).

9. 9: M.p.: 165-176° (81%); IR (CHCl₃): 1730, 1640, 1570 cm⁻¹. ¹H NMR (CDCl₃): δ 1.06 (t, J=7, CH₂); 1.95 (s, CH₃); 3.22 (s, CH₃); 3.78 (s, N-CH₃); 4.17 (q, J=7, CH₂); 7.35 (d, J=6, C₄-H); 7.45 (m, 3H-Ar); 8.45 (m, C₁₀-H); 8.63 (d, J=6, C₃-H).

10. 2: M.p.: 228-229° (57%); IR (CHCl₃): 1625 (sh), 1600 cm⁻¹. ¹H NMR (CDCl₃):
δ 2.81 (s, 1-CH₃); 2.98 (s, 5-CH₃); 3.86 (s, N-CH₃); 7.15-7.35 (m, C₈ and 9-H);
7.49 (d, J=8, C₇-H); 7.63 (d, J=6.5, C₄-H); 8.06 (d, J=8, C₁₀-H); 8.32 (d, J=6.5,
C₃-H); 8.39 (s, C₁₁-H). Ms. (M⁺) 260.1302; Calcd. for C₁₈H₁₆N₂: 260.1301.

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