

## A CONVENIENT SYNTHESIS OF 6-METHYLELLIPTICINE AND 6-METHYLOLIVACINE

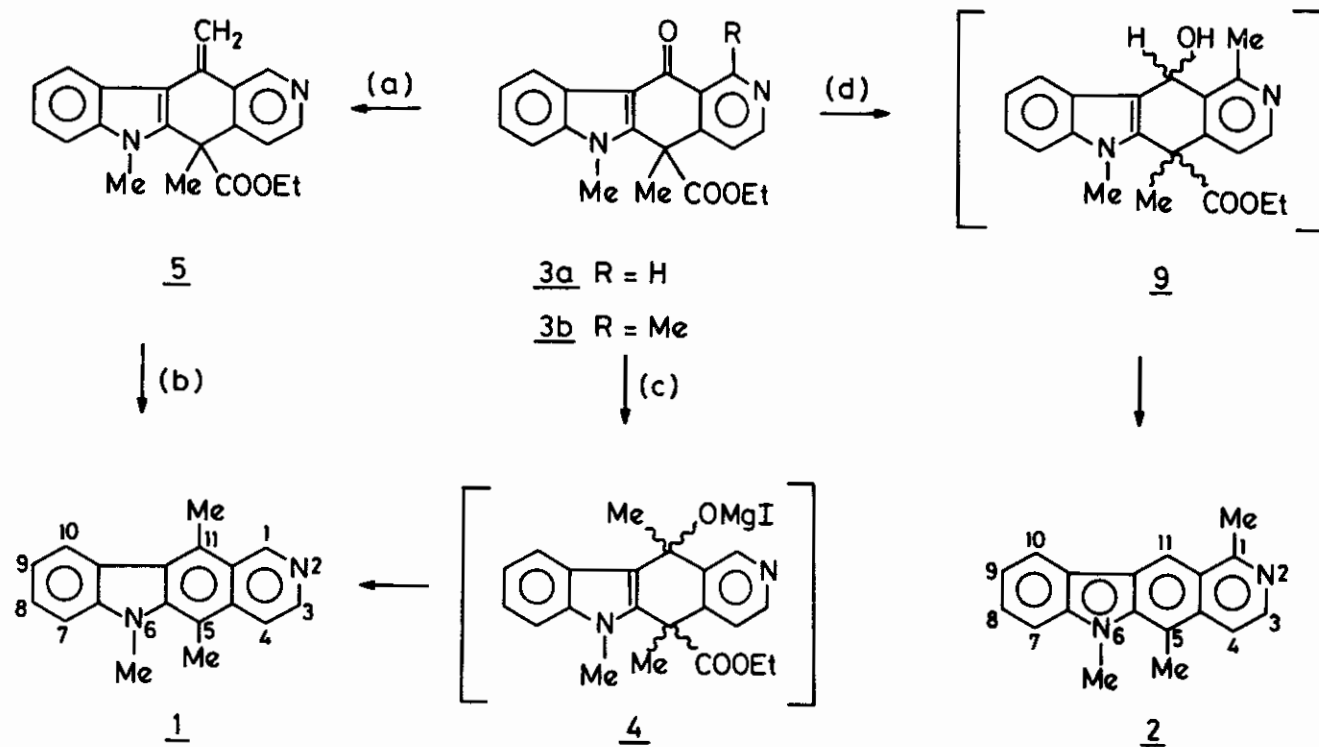
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Abstract — Readily accessible 11-ketopyrido[4,3-b]carbazole derivatives 3a,b have been used as central intermediates for the synthesis of 6-methylellipticine and 6-methylolivacine.

Considerable interest centres around the pyridocarbazole alkaloids ellipticine and olivacine, in view of their reported antitumour activity<sup>1a-d</sup>. Although a number of syntheses for these alkaloids have been reported to date<sup>2a-e</sup>, 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<sup>3</sup>.

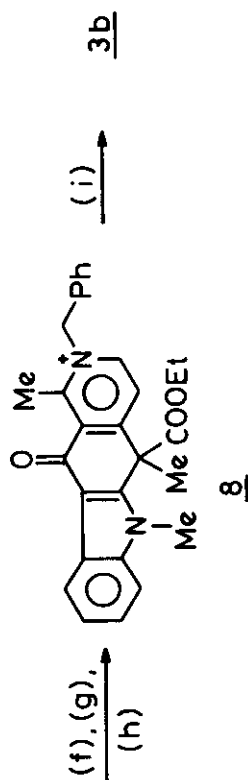
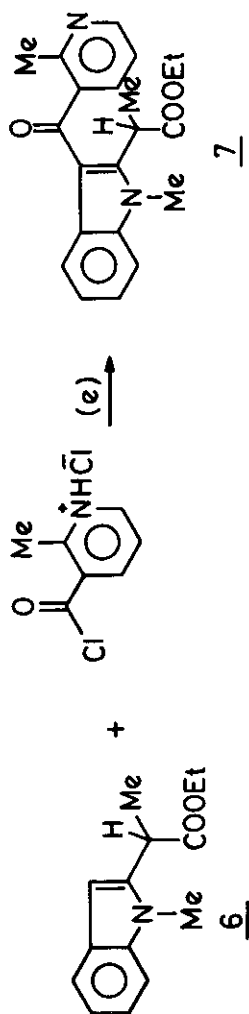
As a part of a broader study of the application of the reaction of ester  $\alpha$ -anions with N-alkylated nicotinic acid derivatives to the synthesis of polynuclear heterocycles, we have recently reported the syntheses of d,l-sesbanine<sup>4</sup> and the pyridocarbazole derivative 3a<sup>3</sup>. 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  $\text{CH}_3\text{MgI}$  (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  $^{\ominus}\text{OMgI}$ , 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)  $\text{Ph}_3\text{P}=\text{CH}_2$ , THF,  $20^\circ$ ; (b) KOH, EtOH /  $\text{H}_2\text{O}$ ,  $\Delta$ ; (c) MeMgI, (excess), THF,  $\Delta$ ;  
 (d) REDAL, THF, r.t.

Scheme A



(e) Sulfolane, 160-170°, 20 min ; (f) PhCH<sub>2</sub>Br, 110°, 30 min ; (g) Et<sub>3</sub>N, r.t. 1 h ; (h) N-Benzylacridinium bromide ; CH<sub>3</sub>CN ; (i) H<sub>2</sub> / Pd

Scheme B

The second route involved the treatment of 3a with  $\text{Ph}_3\text{P}=\text{CH}_2$  (2 eq.), whereupon the exo-methylene derivative 5 was obtained in good yield (65%). Hydrolysis of 5 (KOH/EtOH/H<sub>2</sub>O, reflux) cleanly yielded 1 as a crystalline compound, m.p. 211-212° (60%). Relevant spectral data on 5<sup>5</sup> and 1<sup>6</sup> 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<sup>7</sup>. 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 <sup>1</sup>H NMR spectral data<sup>8</sup> 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<sub>3</sub>): 1725, 1615, 1590 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.08 (t, J=7, CH<sub>3</sub>); 1.90 (s, CH<sub>3</sub>); 3.67 (s, N-CH<sub>3</sub>); 4.12 (m, CH<sub>2</sub>); 5.98 (s, =CH); 6.02 (s, =CH); 7.3-7.5 (m, C<sub>4,7,8</sub> and 9-H); 8.08 (d, J=8, C<sub>10</sub>-H); 8.53 (d, J=6, C<sub>3</sub>-H); 9.32 (s, C, -H).
6. 1: M.p.: 211-212° (60%); IR (CHCl<sub>3</sub>): 1595, 1470 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 3.00 (s, 5-CH<sub>3</sub>); 3.14 (s, 11-CH<sub>3</sub>); 4.08 (s, N-CH<sub>3</sub>); 7.30 (t, J=8, C<sub>8</sub>-H/C<sub>9</sub>-H); 7.38 (d, J=8, C<sub>7</sub>-H); 7.58 (t, J=8, C<sub>8</sub>-H/C<sub>9</sub>-H); 7.86 (d, J=7, C<sub>4</sub>-H); 8.32 (d, J=8, C<sub>10</sub>-H); 8.46 (d, J=7, C<sub>3</sub>-H); 9.64 (s, C<sub>1</sub>-H). MS (M<sup>+</sup>) 260.1307; Calcd. for C<sub>18</sub>N<sub>16</sub>N<sub>2</sub>: 260.1301.
7. (a) 7: Oil (30%); IR (CHCl<sub>3</sub>): 1730, 1620, 1580 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.25 (t, J=7, CH<sub>3</sub>); 1.66 (d, J=7, CH<sub>3</sub>); 2.53 (s, CH<sub>3</sub>); 3.76 (s, N-CH<sub>3</sub>); 4.25 (q, J=7, CH<sub>2</sub>); 5.05 (q, J=7, CH); 6.5-7.5 (m, arylprotons + pyridine C<sub>5</sub>-H); 7.70 (d x d, J=7, J=1.5, pyridine C<sub>4</sub>-H); 8.66 (d x d, J=5, J=1.5, pyridine C<sub>6</sub>-H).
- (b) 8: M.p.: 174-177° (60%); IR (CHCl<sub>3</sub>): 1740, 1655, 1615 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.16 (t, J=7, CH<sub>3</sub>); 2.10 (s, CH<sub>3</sub>); 3.50 (s, CH<sub>3</sub>); 3.86 (s, N-CH<sub>3</sub>); 4.28 (q, J=7, CH<sub>2</sub>); 6.32 (s,  $\phi$ -CH<sub>2</sub>); 7.3-7.5 (m, 8H-Ar); 8.22 (d, J=7, C<sub>4</sub>-H); 8.41 (m, C<sub>10</sub>-H); 9.98 (d, J=7, C<sub>3</sub>-H).
- (c) 3b: M.p.: 165-176° (81%). IR (CHCl<sub>3</sub>): 1730, 1640, 1570 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ 1.06 (t, J=7, CH<sub>3</sub>); 1.95 (s, CH<sub>3</sub>); 3.22 (s, CH<sub>3</sub>); 3.78 (s, N-CH<sub>3</sub>); 4.17 (q, J=7, CH<sub>2</sub>); 7.35 (d, J=6, C<sub>4</sub>-H); 7.40 (m, 3H-Ar); 8.45 (m, C<sub>10</sub>-H); 8.63 (d, J=6, C<sub>3</sub>-H).
8. 2: M.p.: 228-229° (57%). IR (CHCl<sub>3</sub>): 1625 (sh), 1600 cm<sup>-1</sup>. <sup>1</sup>H NMR (CDCl<sub>3</sub>):

$\delta$  2.81 (s, 1-CH<sub>3</sub>); 2.98 (s, 5-CH<sub>3</sub>); 3.86 (s, N-CH<sub>3</sub>); 7.15-7.35 (m, C<sub>8</sub> and 9-H); 7.49 (d, J=8, C<sub>7</sub>-H); 7.63 (d, J=6.5, C<sub>4</sub>-H); 8.06 (d, J=8, C<sub>10</sub>-H); 8.32 (d, J=6.5, C<sub>3</sub>-H); 8.39 (s, C<sub>11</sub>-H). Ms. (M<sup>+</sup>) 260.1302; Calcd. for C<sub>18</sub>H<sub>16</sub>N<sub>2</sub>: 260.1301.

Received, 23rd August, 1982