# A NEW APPROACH TO ELLIPTICINE ANALOGUES; SYNTHESIS OF 11-HYDROXY-5,6-DIMETHYLPYRIDO[4,3-b]CARBAZOLE ☼

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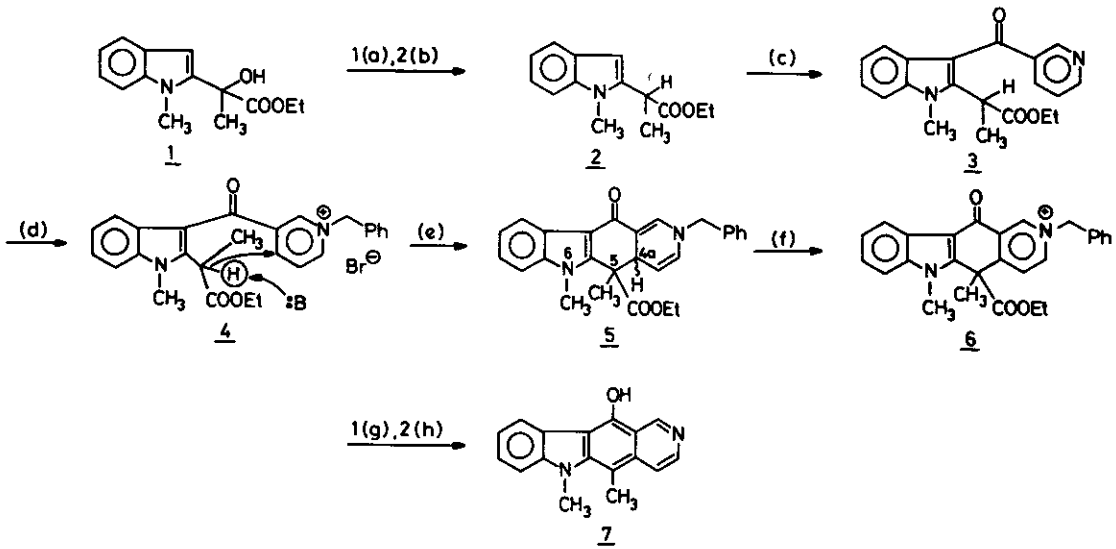
Abstract—2-(2'-Indolyl)propionic ester reacts with nicotinoyl chloride to give a pyridyl ketone which, following quaternization and treatment with base, cyclizes to the pyrido[4,3-b]carbazole skeleton.

Recently[1,2] we reported the stereoselective synthesis of the alkaloid sesbanine via a sequence of reactions in which the key step involved a nucleophilic addition of a suitably substituted anion to the C-4 position of N-benzyl-3-carbamoylpyridinium ion. The latter reaction constitutes a versatile synthetic operation, which has been applied in the construction of a number of heterocyclic systems in this laboratory[3]. In the present communication we report its application to the facile synthesis of the ellipticine skeleton.

Ellipticine and several of its derivatives are highly active antitumour agents. However, the practical utility of these compounds is restricted by their poor solubility characteristics. Although several synthetic approaches to ellipticine and its analogues have been reported in the literature[4-8], a practically convenient route to the pyrido[4,3-b]carbazole skeleton and to new ellipticine analogues would be an extremely valuable addition. The crucial steps of the synthetic scheme, developed in the present study, consist of acylation of a suitable 2-(2'-indolyl)-propionic acid derivative (2) with nicotinoylchloride, quaternization of the pyridine moiety in the acyl intermediate (3) and intramolecular nucleophilic addition of the ester α-carbon to the pyridinium cation.

Reaction of N-methylindole with butyllithium afforded the 2-lithio derivative[9], which reacted with ethyl pyruvate[10] to give 1 in 63% yield[11]. Elimination of water with $POCl_3$ in pyridine gave 1-methyl-2-(2'-carbomethoxyvinyl)indole which was reduced, without isolation, with sodium borohydride in ethanol, at room temperature, to the indolylpropionate 2[12] (58%). This indole derivative was acylated with nico-

☼ Dedicated to Prof.K.Tsuda, Tokyo Univ., on the occasion of his 75th birthday.




a) $POCl_3$ ; (b) $NaBH_4$ ;(c) Nicotinoyl chloride.HCl / sulfolane , 120° ; (d) $PhCH_2Br$ , R.T. ;

e) $Et_3N$ / EtOAc , R.T. ; (f) N-Benzylacridinium Bromide , RT , (g) $H_2$ / Pd 1 atm ;

h) NaOEt / EtOH

tinyl chloride (hydrochloride) by heating the reactants in sulfolane at 120°C whereupon, after 45 minutes, the product 3[13] could be isolated in 55% yield. While this ketone gave satisfactory spectral data[13], the NMR spectrum showed that it was associated with 1 equiv. of the solvent. The pyridyl ketone 3 was converted into the corresponding pyridinium salt 4, by treatment with benzyl bromide (R.T. 20 h) and the product was directly used for the critical ring closure step. Cyclization of 4 to dihydropyridine 5 proceeded smoothly, in ethyl acetate, upon reaction with triethylamine at room temperature (1 hour). The overall yield of the last two steps was 81%. It should be pointed out in this connection that attempts to cyclize 2-ethyl-3-nicotinylindole or the corresponding salt have been reported to be unseccessful[14]. Product 5 consisted, not unexpectedly, of a mixture of the cis- and trans isomers, whose structures and composition (1:1) was attested by the NMR-data[15]. Without separation the mixture was oxidized to the salt 6[16], in 90% yield, by treatment with 1 equiv. of N-benzylacridinium bromide ($CH_3CN$). The latter reagent is particularly suitable for this oxidation, since under the conditions the reaction is driven to completion in one hour at room temperature. Reductive debenzylation ($H_2$/Pd, 1 atm.) and removal of the carbethoxy group by treatment with 2 equiv. of sodium ethoxide in ethanol (30 min, reflux) afforded the title compound 7 in 45% yield, as an orange-red crystalline product[17]. Results of the in vivo anti-leukemia screening of 7 and some of its precursors, as well as the preparation of other pyrido[4,3-b]carbazole derivatives will be reported elsewhere.

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11. 1: M.p.: 53-54°C. IR($CHCl_3$): 3530, 1730 and 1460 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.14 (t, J=6, $CH_3$), 1.87 (s, $CH_3$), 3.62 (s, N-$CH_3$), 3.68 (s, OH), 4.20 (q, J=6, $CH_2$), 6.47 (s, indole $C_3$-H), 7.0-7.7 (m, aryl protons).

12. 2: B.p.: 125-130°C (0.01 mm), IR($CHCl_3$): 1730, 1475 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.18 (t, J=7, $CH_3$), 1.60 (d, J=7, $CH_3$), 3.62 (s, N-$CH_3$), 3.88 (q, J=7, C-H), 4.10 (q, J=7, $CH_2$), 6.37 (s, indole $C_3$-H), 7.0-7.7 (m, aryl protons).

13. 3: Oil. IR($CHCl_3$): 1725, 1620, 1590 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): δ 1.13 (t, J=7, $CH_3$), 1.60 (d, J=7, $CH_3$), 3.70 (s, N-$CH_3$), 4.11 (q, J=7, $CH_2$), 4.77 (q, J=7, C-H), 7.0-7.6 (aryl protons + pyridine $C_5$,-H), 8.12, (d x d x d, J=8, J=2, J=2, $C_4$,-H), 8.80 (d x d, J=5, J=2, $C_6$,-H), 8.99 (d, J=2, $C_2$,-H).

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15. 5: Oil. $^1H$ NMR ($CDCl_3$): δ 1.55, 1.71 (2 x s, $C_5$-$CH_3$), 3.50, 3.65 (2 x s, $N_6$-$CH_3$), 4.30 (s, N-$CH_2$), 4.4 - 4.9 (2 x d x d, J=8, J=2.5, $C_{4a}$-H), 5.92 m ($C_3$-H), 7-7.5 (m, aryl protons + $C_1$-H), 8.40 (m, $C_7$-H).

16. 6: M.p.: 178-180°C. IR($CHCl_3$): 1740, 1665 and 1620 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 1.08 (t, J=7, $CH_3$), 2.10 (s, $CH_3$), 3.90 (s, N-$CH_3$), 4.23 (m, $OCH_2$), 6.10 (AB-system, J=13, $CH_2Ø$), 7.50 (m, aryl protons), 7.65 (m, $C_8$-H + $C_9$-H), 7.85 (d, J=8, $C_{10}$-H), 8.33 (d, J=7, $C_7$-H), 8.45 (d, J=7, $C_4$-H), 9.40 (d, J=7, $C_3$-H), 9.92 (s, $C_1$-H).

17. 7: M.p.: 220-225°C. IR(KBr): 1640, 1605, 1540 and 1460 $cm^{-1}$. $^1H$ NMR (DMSO-$d_6$): δ 2.93 (s, $CH_3$), 4.20 (s, N-$CH_3$), 7.26 (t, J=8, $C_8$-H/$C_9$-H), 7.47 (t, J=8, $C_8$-H/$C_9$-H), 7.59 (d, J=8, $C_{10}$-H), 7.86 (d, J=7, $C_4$-H), 8.13 (d, J=8, $C_7$-H), 8.48 (d, J=7, $C_3$-H), 9.45 (s, $C_1$-H). UV ($C_2H_5OH$): 294, 323, 400 and 470 nm. $M^+$(F.D): m/e = 262.

Received, 11th July, 1981