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Synthesis of 2-Substituted Indolo Pyridin-4-ones.

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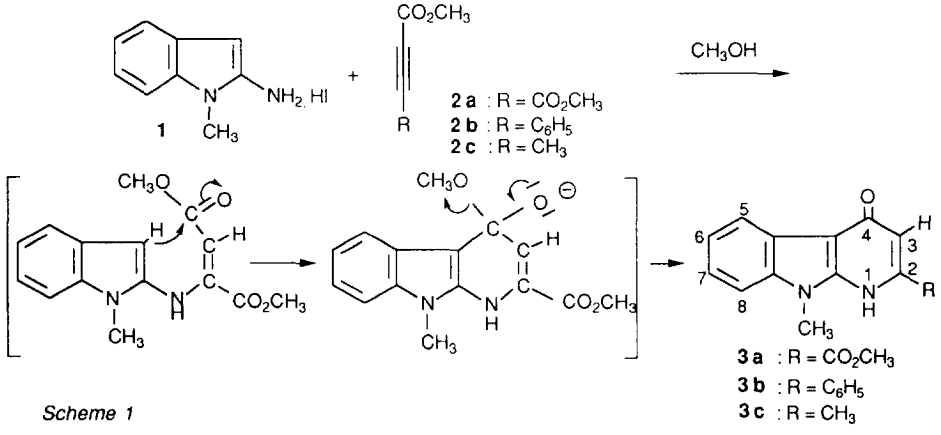
Summary. *The synthesis of 2-substituted indolo-pyridin-4-ones was achieved in good yields by a one-pot reaction between N-Me amino-2-indole (as hydriodide) with acetylenic esters.*

In the course of a programme devoted to the search of bioactive compounds from marine invertebrates, two α-carbolines, the cytotoxic grossularines-I and -II, isolated from the tunicate *Dendrodoa grossularia* [1] as the first naturally occuring α-carbolines, are likely to act on DNA [2]. This prompted us to undertake efforts towards the synthesis of these natural compounds and analogues. Several syntheses of α-carbolines are described and recently a new approach to α-carbolines bearing a dimethyl-amino-imidazole ring was proposed [3,4].

The synthesis of α-carbolines in the grossularine series can be envisaged starting from indolo-pyridin-4-ones **3**. As previously reported, the condensation of N-methyl amino-2 indole (as hydriodide), with β-diketones [5] or with diketenes yielded indolopyridin-2-ones accompanied, in this latter case, by minor amounts (16%) of indolopyridin-4-ones [6], caracterized on the basis of differences in the UV absorbance in respect to indolopyridin-2-ones. Hence another method to obtain indolo-pyridin-4-ones was desirable.

A general route to quinolone heterocycle synthesis was investigated, namely the Michael addition of a nucleophile moiety to an acetylenic carbonyl compound [7]. According to this scheme, condensation of anilines with acetylenic esters [8], allenic esters [9] or acetylenic derivatives devoid of carboxylate groups using Pd(0) catalyzed carbonylation [10] led to useful methods for syntheses of 2-substituted quinolones. Hence we investigated the possibility of condensing N-substituted amino-2 indole with suitable acetylenic derivatives to obtain indolo-pyridinones. In this paper we describe the first unambiguous synthesis of indolo-pyridin-4-ones.



Scheme 1

N-methyl amino-2 indole hydriodide **1** was chosen as the starting material, which was easily prepared according to [11]. Condensation of **1** with dicarbomethoxy-2-acetylene **2a** was achieved by heating (reflux) during 5 hours a methanolic solution of **1** (1mM) with **2a** (1.2 mM). Workup furnished the indolo-pyridin-4-one **3a** in a 65% yield after purification on preparative t.l.c. (chlororform/acetone 7/3), (m.p. 264° C, M.S. M^+ 256, IR: 3400, 1730, 1680 cm^{-1}). Direct (HMQC[12]) and long range (HMBC[13]) 2D ^1H-^{13}C NMR

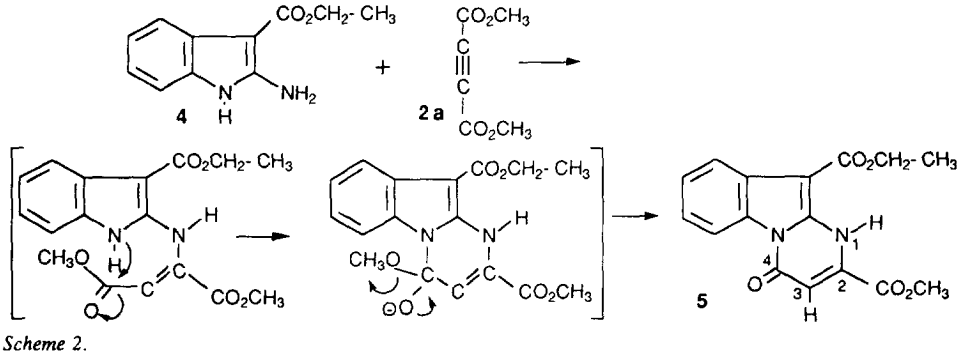
heteronuclear correlations confirmed the pyridin-4-one structure and led to assign all the proton and the carbon chemical shifts (Table). The reaction may proceeed through an enamine adduct formed via a Michael addition, which undergoes cyclization to indolo-pyridinone **3a**. Other easily available acetylenic substrates were condensed with **1** by the same procedure to obtain the indolopyridinones : **3b** (R= C_6H_5)(65 %), m.p. 172°C, M.S. (C.I.) : $[M+H]^+$ 275; **3c** (R= CH_3), 60%, m.p.178-180°C, M.S. (E.I.) M^+ 212. (Scheme 1).

Table . ^1H (300 MHz) and ^{13}C (75 MHz) NMR data of compounds ***3a, 3b, 3c*** *(δ ppm)*

Compounds	**3a** (DMSO d-6)(i)		**3b** ($CDCl_3$)(ii)		**3c** ($CDCl_3$)(iii)	
Assignment	^1H	^{13}C	^1H	^{13}C	^1H	^{13}C
1a		151.4		150.9		154.2
2		134.7		147.0		147.5
3	6.91 (s)	102.0	6.40 (s)	100.3	6.98 (s)	109.3
4		162.3		160.2		160.2
4a		104.2		104.7		105.3
5a		119.2		119.2		123.7
5	8.45 (d,1H, *J* = 8)	123.4	7.62 (dd)	124.1	7.52 (d)	126.8
6	7.24 (dd, 1H, *J* = 8,8)	119.4	7.62 (m, 1H)	120.3	7.33 (dd)	120.8
7	7.47 (dd, 1H, *J* = 8,8)	125.4	7.40	120.7	7.35 (dd)	122.4
8	7.58 (d, *J*=8)	109.3	7.0 (d)	108.9	7.05 (s)	111.7
8a		139.4		138.7		141.7
N-CH_3	3.84 (s, 3H)	27.7	4.0	28.7	4.0	30.2

i) $COOCH_3$ δ 4.01 (52.7, 166.4. ii) C_6H_5 δ 7.52 (d, 2H), 7.35 (m, 3H), (126.4 (2C), 118.6 (2C), 128.7, 139.5. iii) CH_3 δ 2.4 (23.2).

When the starting material was a 3-substituted amino-2 indole such as the amino-2 carbethoxy-3 indole **4**, the condensation with **2a** afforded a pyrimido [3,2-a] indole-3-carboxylate **5**[14]*via* the expected intramolecular cyclization occuring on the indolic NH (68%).



Scheme 2.

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14. ^1H NMR ($CDCl_3$, δ ppm): 8.62 (d) H-8; 7.78 (d) H-5; 7.42 (dd) H-7; 7.23 (dd) H-6; 6.52 (s) H-3; 4.42 (q) $O\underline{CH_2}$-CH_3; 4.01 (s) COOMe; 1.42 (t) OCH_2-$\underline{CH_3}$. M.S. M^+ 312.

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