APPROACH OF PYRROLO[4,3,2-*de*] QUINOLINE ALKALOID STRUCTURE

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Abstract : The oxidation of some indolines into indoles with palladium in the presence of ammonium formate is studied with the aim to obtain precursors of indoloquinoline alkaloids.

The tetrahydropyrrolo-[4,3,2-*de*]quinoline **1** structure is found in several alkaloids such as damirone A and B **2**, isolated from sponges¹, and haematopodin **3**, isolated from fungi².

Scheme 1

Recently we have described the synthesis of 1,3,4,5-tetrahydropyrrolo-[4,3,2-*de*]quinoline **1**³ from 4-nitroindole. Thus, in this Short Communication, we used this strategy to obtain methoxy synthetic precursors of **2** and **3**, and we described our first tries to obtain the oxazine cycle of **3**.

4-Nitroindoles **4a-c** were synthesized by Bergman procedure⁴. 4-Nitro-7-methoxyindoles **4d-f** were synthesized by nitration of methoxyindoles as we have previously described⁵. **5a-f** were obtained by condensation of oxalyl chloride and then treatment with methanol or by modified Vilsmeier reaction^{3,6}; **5a-f** were reduced into indolines **6a-f** by HSiEt_3 (3 equivalents) in trifluoroacetic acid. Lactams **7a-f** were obtained by reduction of nitro function ($\text{Pd-C } 10\%-\text{H}_2$, 5 bars or PtO_2-H_2 , atmospheric pressure or $\text{SnCl}_2-12 \text{ N HCl}$, reflux temperature, 3 hours) and heating at reflux temperature in toluene (Scheme 2, table 1).

Scheme 2

Table 1 : Synthesis of lactam-indolines 7a-f

4a-f			5a-f		6a-f	7a-f		
Y	R		a (%)	b (%)	%	c (%)	d (%)	e (%)
a	H	H	2	65	94	70	92	-
b	H	Me	63	83	85	75	75	-
c	H	Bn	-	43	80	80	-	-
d	OMe	H	-	74	73	0	-	-
e	OMe	Me	96	54	81	14	-	87
f	OMe	Bn	78	0	86	-	-	70

a : (COCl)₂, Et₂O, then MeOH; b : P₂O₃Cl₄, methyl pyrrolidinylglyoxylate, room temperature, 2h, then MeOH; c : SnCl₂-12N HCl, 110°C, 3 h; d : Pd-C, H₂, 5 bars, then toluene, 110°C, 12h; e : PtO₂, H₂, atm. pressure, then toluene, 110°C, 12h.

The lactams 7a-c were reduced in good yields into amines 9a-c by BH₃-SMe₂ in THF (Scheme 3).

Scheme 3

7e-f was methylated by CH₃I to give 10e-f (81% and 90% respectively) which were reduced with BH₃-SMe₂ into 11e-f (88% and 81%). 11g was formed from 7e (81%) (Scheme 4).

Scheme 4

The oxidation of indoline structure is a well-documented reaction. In our hands, the classical reagents (DDQ⁷, CuCl₂-O₂⁸, cinnamic acid⁸, PIFA⁹) did not give result. Manganese dioxide¹⁰ gave only oxidation of **7e** at room temperature to lead to the keto-amide **12a** (42%). This compound was not reduced into **12b** with LiAlH₄. After having successfully used palladium in the presence of ammonium formate^{3,11} to oxidize indolines into indoles this reaction was applied for the synthesis of **7e**, **9a-b** and **11f**. Thus, indoles **13a-b** were obtained with high yields, whereas **11f** led to the debenzylated indole **13f** with moderate yield. **7e** was not oxidized (Table 2).

Table 2 : Oxidation of indolines into indoles

indolin	indole	yield
9a	13a : R ₁ =R ₂ =H, Y=H	90% ⁵
9b	13b : R ₁ =H, R ₂ =Me, Y=H	98%
11f	13f : R ₁ =Me, R ₂ =H, Y=OMe	67%
7e		no reaction

Indoline **14a** was obtained from **7f** by alkylation with 1-iodo-3-(tetrahydropyran-2-yloxy)propane (I-(CH₂)₃-OTHP) (98%), but this compound did not give indole even after long reaction time, only debenzylation into indoline **15** was observed (97%). The corresponding indole **16a** was obtained by oxidation of **15** by the use of Barton reagent (diphenylselenic anhydride)¹² (41%) (Scheme 5).

Scheme 5

14a and **16a** were hydrolyzed in acidic medium into alcohol **14b**, **16b** (98%, 90%). The treatment of **14b** with LiAlH₄ did not give cyclization, only reduction of the carbonyl group was observed to form **18** (32%) (Scheme 6). Under these conditions **16b** was not reduced by LiAlH₄ and

Red-Al®. The oxazine **19** was obtained by the use of Red-Al® from **14b** (20%). Unfortunately we have never obtained indole from **19**.

Scheme 6

In conclusion, in this work we obtained the precursors of both damirones and haematopodin and now we study the oxidation of these compounds to obtain the natural products.

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- Physical data of some products : **10f**: F: 107-110°C; HRMS: calculated for $\text{C}_{19}\text{H}_{20}\text{N}_2\text{O}_2$: 308.1524, found: 308.1522; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): 2.45 (1H, t, $J = 15$ Hz) 2.85 (2H, m), 3.27 (3H, s) 3.59 (1H, t, $J = 8$ Hz) 3.81 (3H, s) 4.16 (1H, d, $J = 14$ Hz) 5.07 (1H, d, $J = 14$ Hz) 6.29 (1H, d, $J = 9$ Hz) 6.71 (1H, d, $J = 9$ Hz) 7.29-7.31 (3H, m). **11f**: HRMS: calculated for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$: 294.1731, found: 294.1732; $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): 1.71 (1H, m) 2.06 (1H, m) 2.64 (1H, dd, $H = 8$ and 12 Hz) 2.84 (3H, s) 3.17 (2H, m) 3.41 (1H, t, $J = 8$ Hz) 3.74 (3H, s) 3.98 (1H, d, $J = 14$ Hz) 5.14 (1H, d, $J = 14$ Hz) 6.03 (1H, d, $J = 9$ Hz) 6.65 (1H, d, $J = 9$ Hz) 7.30-7.35 (5H, m). **19**: $^1\text{H-NMR}$ (CDCl_3 , 300 MHz): 1.60 (2H, m) 1.92 (2H, m) 2.66 (1H, m) 3.29 (1H, m) 3.41 (2H, m) 3.75 (3H, s) 3.92 (2H, m) 4.07 (2H, m) 6.15 (1H, d, $J = 8$ Hz) 6.68 (1H, d, $J = 8$ Hz) 7.29-7.31 (5H, m); $^{13}\text{C-NMR}$: 31.1, 31.9, 46.9, 54.9, 57.9, 61.7, 68.3, 85.4, 103.1, 114.5, 115.0, 126.2, 128.3, 130.1, 135.7, 139.0, 139.6.

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