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

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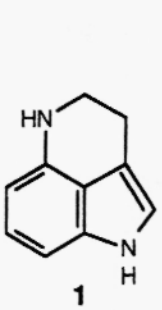
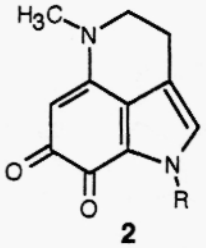
Abstract : The oxidation of some indolines into indoles with palladium in the presence of ammonium formate is studied with the aim to obtain precursors of indoloquinoline alkaloids.

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

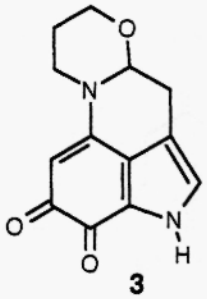


1



2

R = CH_3 : damirone A
R = H : damirone B



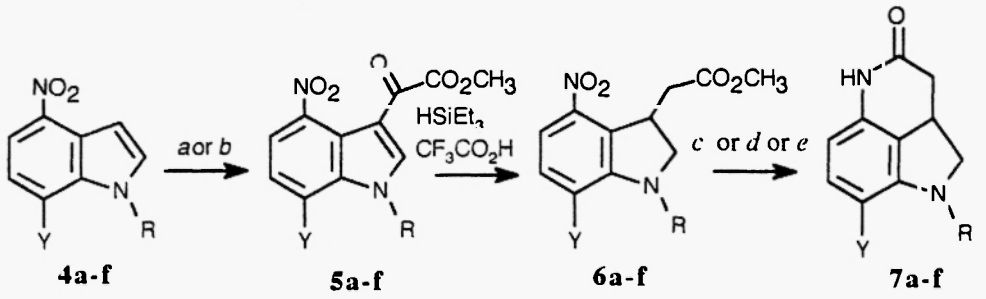
3

haematopodin

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 procedure[4]. 4-Nitro-7-methoxyindoles **4d-f** were synthesized by nitration of methoxyindoles as we have previously described[5]. **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 trifluroacetic acid. Lactams **7a-f** were obtained by reduction of nitro function (Pd-C 10%-H_2, 5 bars or PtO_2-H_2, atmospheric pressure or $SnCl_2$-12 N HCl, reflux temperature, 3 hours) and heating at reflux temperature in toluene (Scheme 2, table 1).



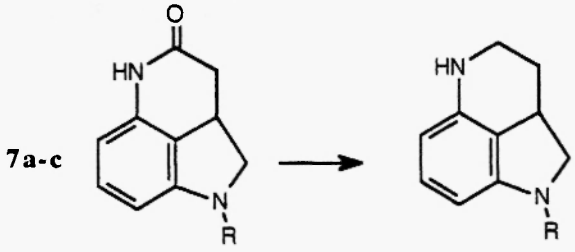
Scheme 2

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: $(COCl)_2$, Et_2O, then MeOH; *b* : $P_2O_3Cl_4$, methyl pyrrolidinylglyoxylate, room temperature, 2h, then MeOH ; *c* : $SnCl_2$-12N HCl, 110°C, 3 h; *d* : Pd-C, H_2, 5 bars , then toluene, 110°C, 12h ; *e* : PtO_2, H_2, atm. pressure , then toluene, 110°C, 12h.

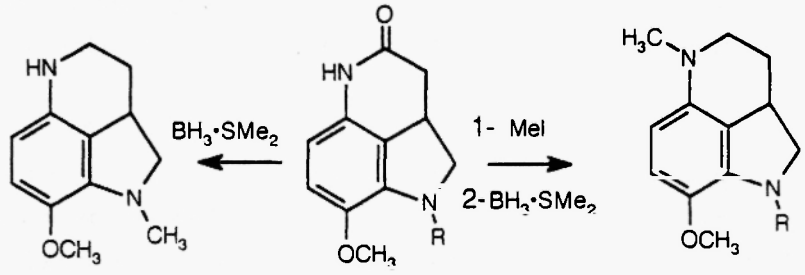
The lactams **7a-c** were reduced in good yields into amines **9a-c** by BH_3-SMe_2 in THF (Scheme 3).



9a : R = H 90%
9b : R = Me 70%
9c : R = Bn 97%

Scheme 3

7e-f was methylated by CH_3I to give **10e-f** (81% and 90% respectively) which were reduced with BH_3-SMe_2 into **11e-f** (88% and 81%). **11g** was formed from **7e** (81%) (Scheme 4).



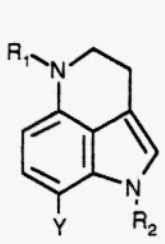
11g

7e : R = Me
7f : R = Bn

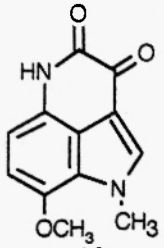
11e : R = Me
11f : R = Bn

Scheme 4

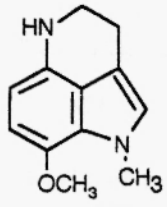
The oxidation of indoline structure is a well-documented reaction. In our hands, the classical reagents (DDQ[7], $CuCl_2$-O_2[8], cinnamic acid[8], PIFA[9]) did not give result. Manganese dioxide[10] gave only oxidation of **7e** at room temperature to lead to the keto-amide **12a** (42%). This compound was not reduced into **12b** with $LiAlH_4$. After having successfully used palladium in the presence of ammonium formate[3,11] to oxidize indolines into indoles this reaction was appliedfor 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).



13a,b,f



12a

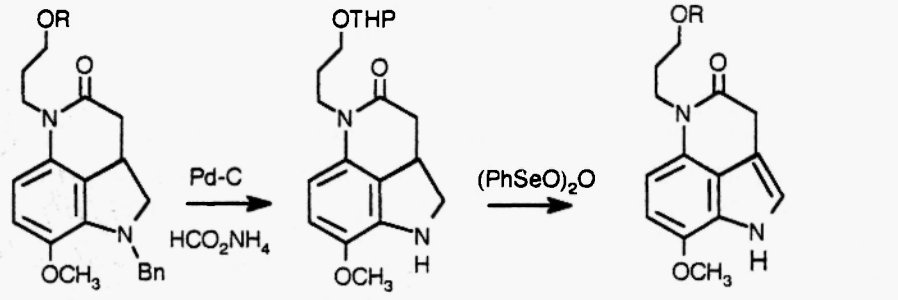


12b

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-$(CH_2)_3$-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).



14a : R = THP
14b : R = H

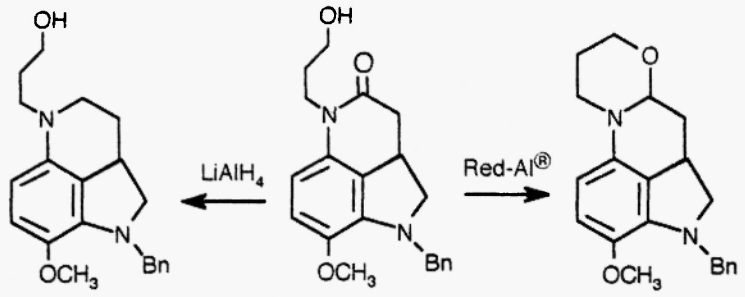
15

16a : R = THP
16b : R = H

Scheme 5

14a and **16a** were hydrolyzed in acidic medium into alcohol **14b**, **16b** (98%, 90%). The treatment of **14b** with $LiAlH_4$ 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 $LiAlH_4$ 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**.



18 **14b** **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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13 Physical data of some products : **10f** : F : 107-110°C; HRMS : calculated for $C_{19}H_{20}N_2O_2$: 308.1524, found : 308.1522; ^{1}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 $C_{19}H_{22}N_2O$: 294.1731, found : 294.1732; ^{1}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}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}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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