PREPARATION OF 7-METHOXY-3,4-DIHYDRO-β-CARBOLINE

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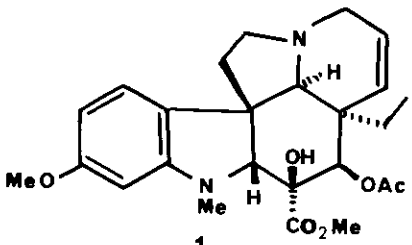
Abstract - 7-Methoxy-3,4-dihydro-β-carboline (4a), starting material in total synthesis of several indole alkaloids, has been prepared in a three-steps sequence from 3-methoxyaniline.

A total synthesis of dihydroindole alkaloid vindoline (1) has been recently performed in our laboratory.[1] An imino Diels-Alder reaction between 9-methyl-7-methoxy-3,4-dihydro-β-carboline (2) and methyl pentadienoate was one of the key steps of this synthesis. Compound (2) has been prepared from N_a-methyl-6-methoxytryptamine (3) by a modified Bischler-Napieralsky process.[1] However the preparation of the tryptamine derivative (3) from 3-methoxyaniline was rather tedious.[2] So we were interested in developing a shorter route to 7-methoxy-3,4-dihydro-β-carboline (4a), which could be of interest for both total syntheses of vindoline (1) and reserpine.

7-Methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4b]indol-1-one (5), which could be the direct precursor of 7-methoxy-3,4-dihydro-β-carboline (4a), has been prepared in the past in low yields from 4-chloro-3-nitroanisole[3] or from harmaline.[4] However the Japp-Klingemann reaction seems to be a more direct route to prepare compound (5).

Thus diazonium salt (6), obtained by classical diazotation ($NaNO_2$, HCl) of 3-methoxyaniline, was treated with 3-carboxy-2-piperidone (7).[5] The resulting arylhydrazone (8) was treated without purification with formic acid to lead with a rather good regioselectivity to a mixture of 7-methoxy-2,3,4,9-tetrahydro-1H-pyrido[3,4b]indol-1-one (5) (51%) and of the 5-methoxy corresponding isomer (9) (10%). It was interesting to note that in the case of the Fischer indole cyclisation of 3-arylhydrazones of 2,3-piperidine-diones,[5] bearing an electron-withdrawing group on the aryl moiety, nearly the same regioselectivity was observed.

The lactam (5) was reduced with an excess of lithium aluminium hydride (5 equiv.



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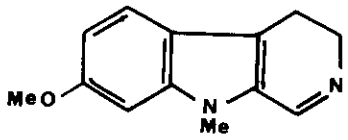

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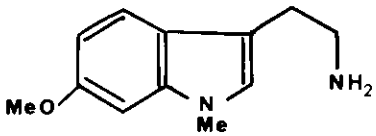

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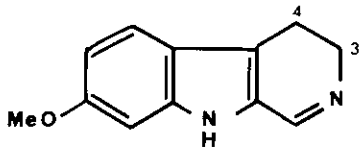
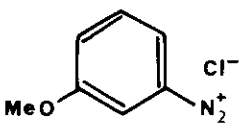


4a

4b : $\Delta^{3,4}$



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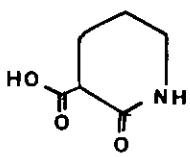

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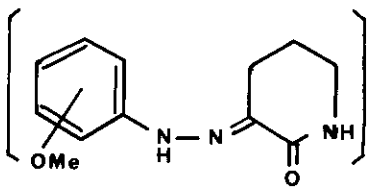

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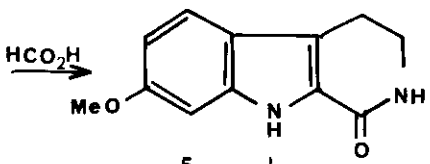

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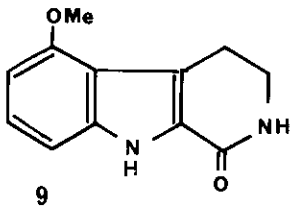

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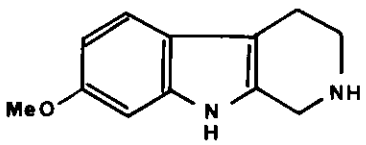

10

4a

in THF) to afford quantitatively 7-methoxy-1,2,3,4-tetrahydro-β-carboline (10). Several oxidative reagents such as potassium permanganate,[6] benzeneseleninic anhydride[7] and diphenyl selenium bis-trifluoro-acetate[8] have been tested on compound (10). The results are summarized in the table.

Table. Oxidation of tetrahydro-β-carboline (10)

Reagent	Equiv.	Solvent	Temp.	Time (h)	Products (%)
$KMnO_4$	1.4	Acetone	0°	1	(4a) : 38% (10) : 12%
$(PhSeO)_2O$	0.5	THF	20°	15	(4a) : 39% (4b) : 16%
	0.5 + 0.5 Indole	THF	20°	48	(4a) : 44% (4b) : 17%
	1 + 0.5 Indole	THF	20°	48	(4a) : 30% (4b) : 10%
$PhSe_2(OCOCF_3)_2$	1.2	DME	20°	48	(4a) : 26% (10) : 10%

The best yields were obtained with benzeneseleninic anhydride (0.5 equiv.) in the presence of indole (0.5 equiv.).

In summary 7-methoxy-3,4-dihydro-β-carboline (4a), starting material for various alkaloids syntheses, has been prepared in a straightforward three-steps sequence from commercially available compounds.

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