

## Reductive Cyclization of Indolic Imides

A New  $\beta$ -Carboline Synthesis\*.

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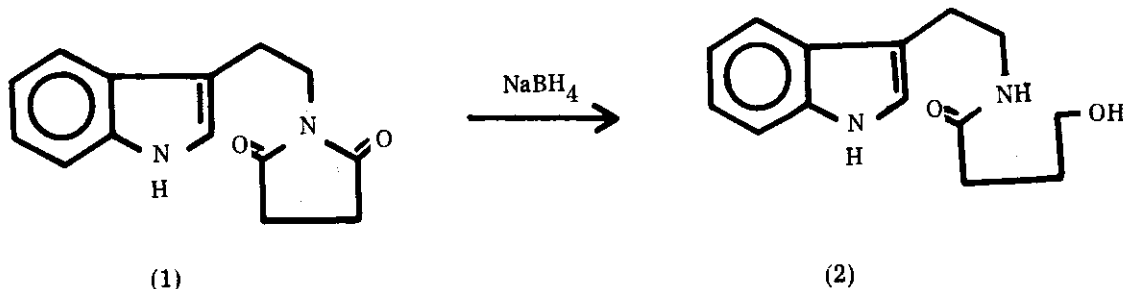
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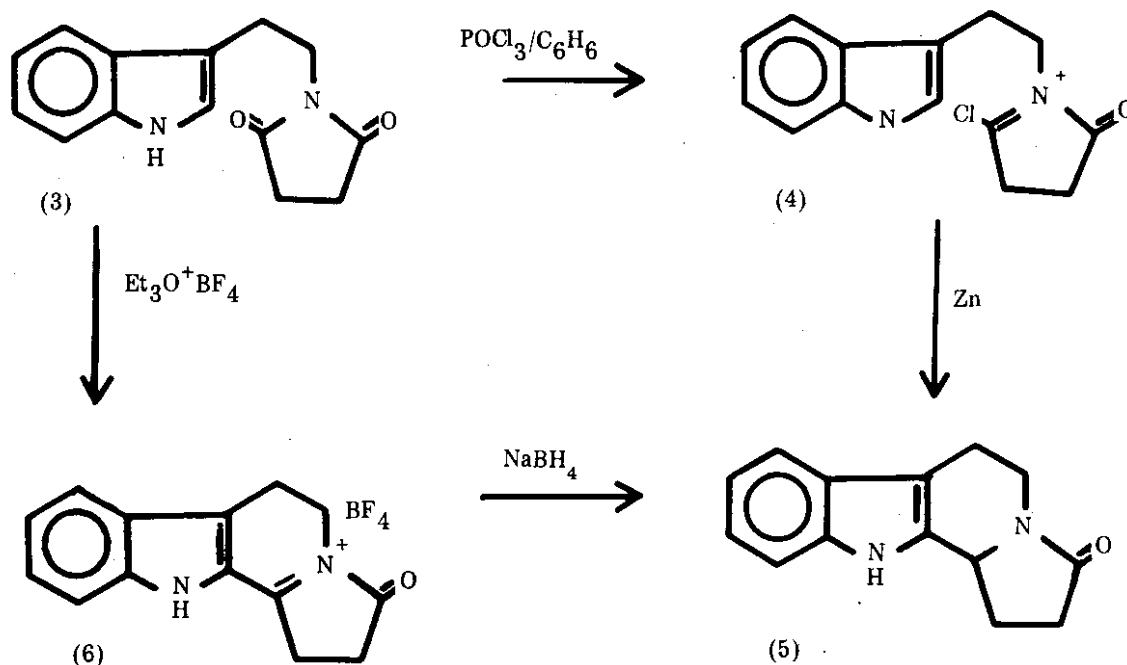
**Summary:** A new method is described for the synthesis of  $\beta$ -carboline from indolic imides by reaction of the intermediate vilsmeier complexes with zinc.

We have previously described novel methods using Vilsmeier complexes as intermediates for the reduction of amides to amines with sodium borohydride<sup>1</sup> or zinc/ethanol<sup>2</sup>. These complexes have also been used by us for developing new routes for the functionalization of amides<sup>3</sup>, and for the formation of aldehydes from tertiary amides in high yields<sup>4</sup>.

Our finding<sup>5</sup> that cyclic imides (1) can be reduced to the corresponding cleaved amide alcohols (2) in good yields has led us to examine the possibility of developing a new  $\beta$ -carboline synthesis by the reductive cyclization of indolic imides. We report here a new method for the synthesis of  $\beta$ -carboline involving the generation of Vilsmeier complexes as intermediates. These complexes are formed by refluxing imides with  $\text{POCl}_3$  in dry benzene for one hour, and treatment of the resulting complexes with zinc-dust affords the corresponding  $\beta$ -carboline lactams in moderate to good yields. The reaction proceeds via uncyclized chloroimmonium intermediates rather than cyclized enamides. This was established by the aqueous treatment of aliquots of complexes prior to zinc-dust addition, when only starting material was

recovered and no cyclized enamide was detectable. Thus N-succinimidotryptamine (3) afforded the corresponding complex (4) on refluxing with  $\text{POCl}_3/\text{C}_6\text{H}_6$  for one hour. The reaction mixture was then cooled to  $0^\circ\text{C}$ , excess of zinc-dust was added and the reaction mixture was warmed to  $60^\circ\text{C}$  for 1-2 minutes. As t.l.c. revealed the formation of three spots with some unreacted imide, the reaction mixture was refluxed at  $85^\circ\text{C}$  for a further 1 hour. Aqueous work up and extraction into ethyl acetate afforded the  $\beta$ -carboline lactam (5) in 50% to 70% yields. The substance was found to possess a normal indolic chromophore and the amide carbonyl absorption appeared at  $1662\text{ cm}^{-1}$ . The mass spectrum afforded the molecular ion at  $m/e = 226$  with other prominent peaks at  $m/e = 225, 182, 170$  and  $169$ . The NMR spectrum showed the lack of olefinic protons  $\alpha$ -to the indole nitrogen atom. Wenkert and co-workers had earlier reported<sup>6</sup> the failure of the imide (3) to cyclize under Bischler-Napieralski conditions and we had therefore developed<sup>7</sup> a new procedure for the cyclization by the treatment of the imide (3) with triethyl-oxonium tetrafluoroborate to afford (6). The reduction of (6) with sodium borohydride afforded a substance chromato-





graphically and spectroscopically identical with the products of zinc dust treatment of the Vilsmeier complex, thus confirming the structure (5) assigned.

N-glutarimidotryptamine (7) when similarly refluxed with  $\text{POCl}_3$  in dry benzene followed by treatment with zinc dust afforded the lactam (9) in 60% yield. The product possessed an indolic chromophore and the mass spectrum afforded the molecular ion at  $m/e = 240$  with other major peaks at  $m/e = 239, 225, 196, 184, 170$  and 169.

N-Phthalimidotryptamine (10) on identical treatment with  $\text{POCl}_3/\text{C}_6\text{H}_6$  and zinc dust afforded the lactam (12) in 90% yield. The product was found to have a normal indolic u.v. spectrum. The amide carbonyl absorption appeared at  $1672\text{ cm}^{-1}$  and the mass spectrum afforded the molecular ion at  $m/e = 274$  with other major peaks at 273, 245, 243, 217 and 130. The NMR spectrum was also in agreement with structure (12) assigned to the product.

The above procedure offers an attractive new method of preparing  $\beta$ -carbolines from N-imidotryptamines. Wenkert<sup>6</sup> and others<sup>7,8</sup> have previously reported difficulties in synthesising  $\beta$ -carboline lactams from N-imidotryptamines due to the instability of the intermediate cyclized enamides. The method reported here avoids the intermediacy of these unstable conjugated enamides and offers a direct synthesis of  $\beta$ -carbolines from the readily prepared N-imidotryptamines.

## Experimental

The infra-red spectra were recorded on a Unicam SP-200 I.R. spectrometer. The ultra-violet spectra were recorded on a Unicam SP-800 U.V. spectrometer. The N.M.R. spectra were recorded on a JEOL PMX-60 spectrometer. The mass spectra were recorded on a VG-Micromass MM-12 mass spectrometer.

### *$\beta$ -Carboline lactam (5)*

N-Succinimidotryptamine (3) (500 mg., 0.002 mole) was dissolved in dry benzene (30 ml).  $\text{POCl}_3$  (0.96 ml., 0.01 mole) was added and the solution was refluxed at  $85^\circ\text{C}$  for one hour till a reddish brown complex was formed. An aliquot was checked by aqueous work up which showed complete reconversion of the complex to the starting imide. The reaction mixture was then cooled to  $0^\circ\text{C}$ , zinc dust (675 mg., 0.01 mole) was added and the reaction mixture was refluxed at  $85^\circ\text{C}$  for 1 hour. The reaction mixture was worked up and t.l.c. revealed the formation of three compounds with some unreacted imide. Undissolved zinc dust was filtered off and the filtrate was evaporated under reduced pressure. The residue was basified with 10% NaOH solution and then partitioned between water (60ml) and ethyl acetate (60ml). The ethyl acetate layer was dried with anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The crude mixture was then subjected to preparative t.l.c. The major band afforded the  $\beta$ -carboline lactam (5) (233 mg., 50% yield); U.V. spectrum: typically

indolic,  $\lambda$  max. = 225, 280, 290 n.m.,  $\lambda$  min. = 245, 285 n.m.; I.R. spectrum:  $1612\text{ cm}^{-1}$  (amide carbonyl); mass spectrum:  $m/e = 226 (M^+)$ , 225, 182, 170, 169; N.M.R. spectrum:  $\delta$  6.9-7.8 (4 H, aromatic), no olefinic protons or proton  $\alpha$ -to indole nitrogen visible.

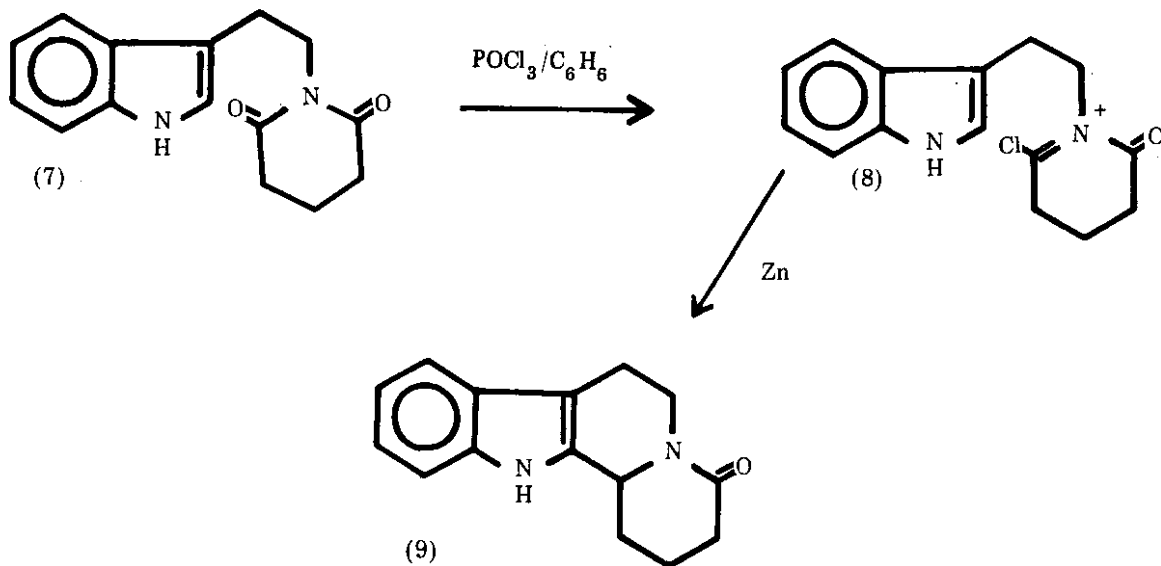
#### $\beta$ -Carboline lactam (9)

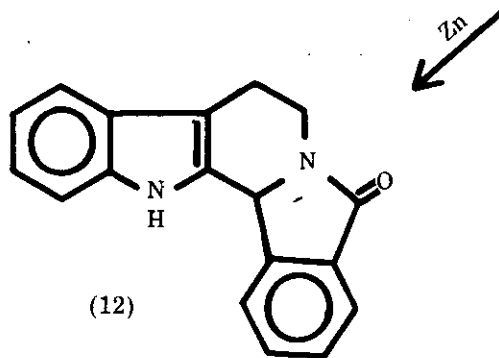
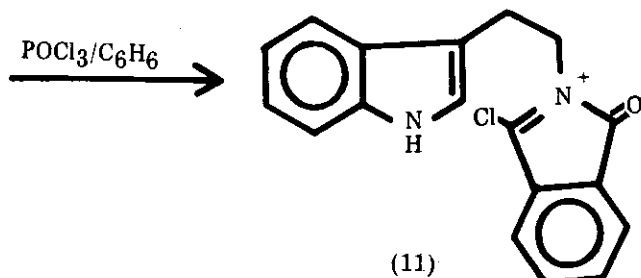
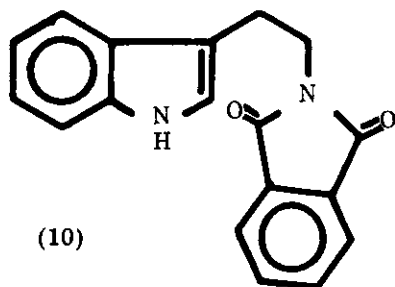
N-glutarimidotryptamine (7) (500 mg., 0.002 mole) was dissolved in dry benzene (30 ml).  $\text{POCl}_3$  (0.92 ml., 0.0099 mole) was added to the solution and refluxed at  $85^\circ\text{C}$  for one hour till a reddish brown complex was formed. The reaction mixture was cooled to  $0^\circ\text{C}$ , zinc-dust (640 mg., 0.0097 mole) was added and the reaction mixture was refluxed at  $85^\circ\text{C}$  for 1 hour. After work-up t.l.c. revealed the formation of three compounds with some unreacted imide. Undissolved zinc-dust was filtered off and the filtrate was evaporated under vacuum. The residue was basified with 10% NaOH and partitioned between ethyl acetate (60ml) and water (60ml). The ethyl acetate layer was dried with sodium sulphate (anhydrous), filtered and evaporated under reduced pressure. The crude mixture was subjected to preparative t.l.c. to afford as the major product the  $\beta$ -carboline lactam (9) (280 mg., 60% yield); U.V. spectrum: typically indolic,  $\lambda$  max = 225, 280, 290nm.,  $\lambda$  min = 245 and 285nm.; I.R. spectrum:  $1612\text{ cm}^{-1}$  (amide carbonyl); mass spectrum:  $m/e = 240 (M^+)$ , 239, 224, 196, 184,

170 and 169; N.M.R. spectrum:  $\delta$  6.86-7.33 (4H, aromatic), no olefinic protons or proton  $\alpha$ -to indole nitrogen visible.

#### $\beta$ -Carboline lactam (12)

N-Phthalimidotryptamine (10) (500 mg., 0.0017 mole) and  $\text{POCl}_3$  (0.80 ml., 0.0086 mole) were refluxed in dry benzene (30ml) for one hour at  $85^\circ\text{C}$  till a reddish brown complex was formed. After the formation of the complex the reaction mixture was cooled to  $0^\circ\text{C}$ . Then zinc dust 560 mg., 0.0085 mole) was added and the reaction mixture was warmed at  $85^\circ\text{C}$  for 1 hour. After work up t.l.c. revealed the formation of three new compounds with some unreacted imide. The undissolved zinc-dust was filtered off. The filtrate was evaporated under vacuum. The residue was basified with 10% NaOH and then partitioned between water (60ml) and ethyl acetate (60ml). The ethyl acetate layer was dried with anhydrous sodium sulphate, filtered and evaporated under reduced pressure. The crude mixture was then subjected to preparative t.l.c. The major product separated was the  $\beta$ -carboline lactam (12) (425 mg., 90% yield); U.V. spectrum: typically indolic,  $\lambda$  max = 225, 280 and 290nm.,  $\lambda$  min = 245, 285nm.; I.R. spectrum:  $1672\text{ cm}^{-1}$  (amide carbonyl); mass spectrum:  $m/e = 274 (M^+)$ , 273, 245, 243, 217 and 130; N.M.R. spectrum:  $\delta$  6.93-7.83 (8H, aromatic), no olefinic protons or protons  $\alpha$ -to indole nitrogen visible.





### References

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