A New Synthesis of β-Carbolines by Metal Ion-catalysed Reduction of N-Imidotryptamines.

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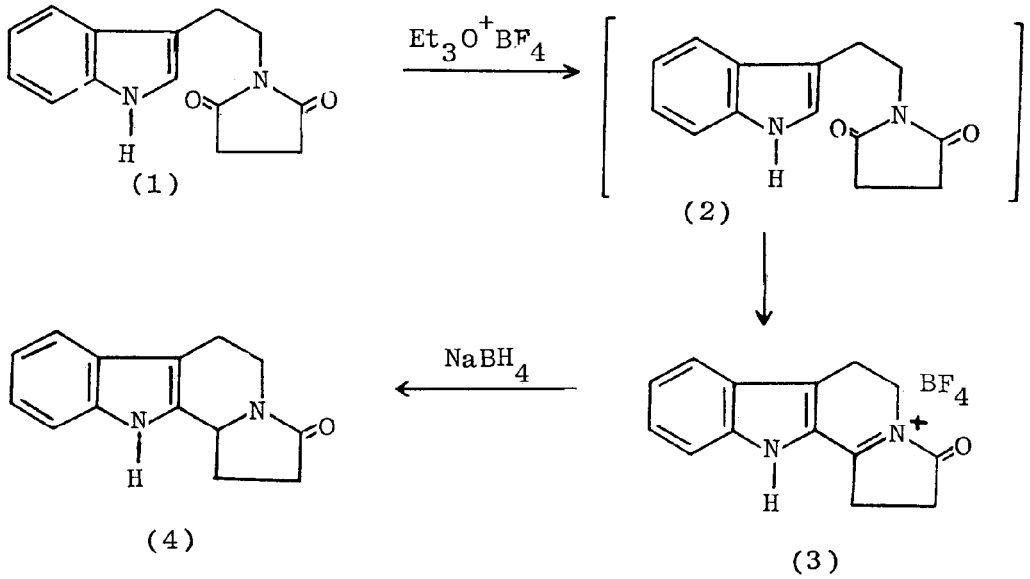
Summary: N-imidotryptamines may be converted in high yields to the corresponding hydroxylactams. Acid induced cyclization of the hydroxylactams affords β carbolines in quantitative yields.

The β-carboline system forms an integral part of the skeleton of many physiologically important indole alkaloids such as reserpine and ajmaline. Our interest in developing new synthetic methods[1-4] has led us to develop new syntheses of β- carbolines from N-imidotryptamines.[5-9] We now report a metal-ion catalysed procedure for the reduction of N-imidotryptamines to the corresponding α-hydroxylactams in high yields. The α-hydroxylactams could then be cyclized quantitatively to the corresponding β-carbolines in the presence of acid.

Our earlier apporach to the β-carboline system involved activation of the imide (1) carbonyl by alkylation with Meerweins reagent[7] which spontaneously cyclized to the corresponding β-carboline (3) (Scheme 1). While this procedure was found to be very effective for 5-membered imides (N-succinimidotryptamine), it failed with 6-membered imides. Our earlier finding that indole imides could be cleaved to the corresponding amide alcohols in high yields[5] led us to develop an alternative procedure for the synthesis of β-carbolines involving the generation of Vilsmeir complexes of N-imidotryptamines by treatment with $POCl_3$, which were found to afford the corresponding β- carboline lactams on treatment with zinc dust.[5-9] Although this procedure was found to be applicable to both 5-membered as well as 6-membered imides, the yields obtained were moderate. A different approach involved the reductive cyclization of N-imidotryptamines with $NaBH_4 - HCl$ in one step to the corresponding β- carbolines.[6] A similar procedure was independently developed by Speckamp and coworkers.[10]

An attractive alternative to the use of Meerwein's



Seheme I

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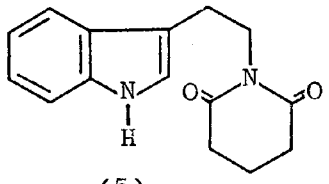
reagent for activation of the imide carbonyl group appeared to be the use of transition metal halides. These would be expected to complex with the imide carbonyl group and/or the N_b -nitrogen and thus increase the electrophilicity of the carbonyl carbon atom. We now report improved methods for β- carboline synthesis, involving the facile conversion of N-imidotryptamines to the corresponding α- hydroxy lactams with sodium borohydride in the presence of various metal halides, hydrochloric acid being unnecessary in this first step. The hydroxy lactams were then cyclized to the corresponding β-carboline lactams in the presence of acid. A typical reaction involved treatment of N-glutarimidotryptamine (5) with one equivalent of sodium borohydride in the presence of one equivalent of an appropriate metal halide in ethanol, in a freezing mixture. Reaction aliquots were drawn at regular intervals and checked by t.l.c. Examination of the chromatographic plates under U.V. light or iodine showed the gradual formation of one main product, which was found to be different on t.l.c. from the corresponding authentic amide alcohol (6), amide ester (7) or the cyclized β- carboline lactam (8) (Scheme 2). The product obtained was separated by preparative t.l.c. and identified to be the corresponding hydroxy lactam (9).

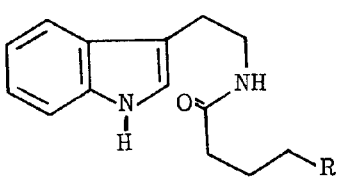
The mass spectrum of (9) showed the molecular ion peak at m/e 258 in agreement with the mass expected for the hydroxy lactam (9) or the cleaved aldehyde (10). However the formation of the aldehyde could be excluded by n.m.r. studies, which showed no signal of aldehydic proton. The signal of the hydroxyl proton appeared as a broad peak at δ 4.74. The *N-CH*$_2$ protons appeared as a triplet at δ 3.57 while the other two aliphatic protons (-CH_2 - CH_2 -N) resonated as a triplet at δ 3.52. The aromatic protons appeared as a multiplet in the region δ 6.9 - 7.86. The indolic nature of the product was apparent from its u.v. spectrum.

It was observed that the presence of certain metal halides produced a significant increase in the yield and rate of formation of the hydroxy lactam, as compared to a parallel blank reaction conducted in identical conditions without the metal halides. $SnCl_2$ and $SrCl_2$ showed a 60-65% conversion to the hydroxy lactam after two hours. Reactions in the presence of $CoCl_2$, $CrCl_3.6H_2O$, $FeCl_3$, $SbCl_3$ and $NiCl_2.6H_2O$ indicated a moderate catalytic effect. The blank reaction and the ones with $CuCl_2$. $2H_2O$, $HgCl_2$, $MnCl_2.4H_2O$, $CeCl_3$ and $BaCl_2$ afforded

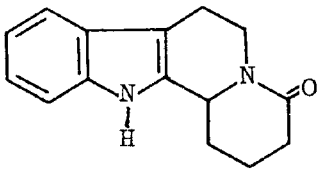


(5)

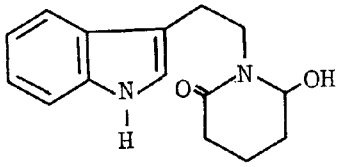
$NaBH_4$
metal halide



(6) R=CH_2OH
(7) R=CO_2Et



(8)



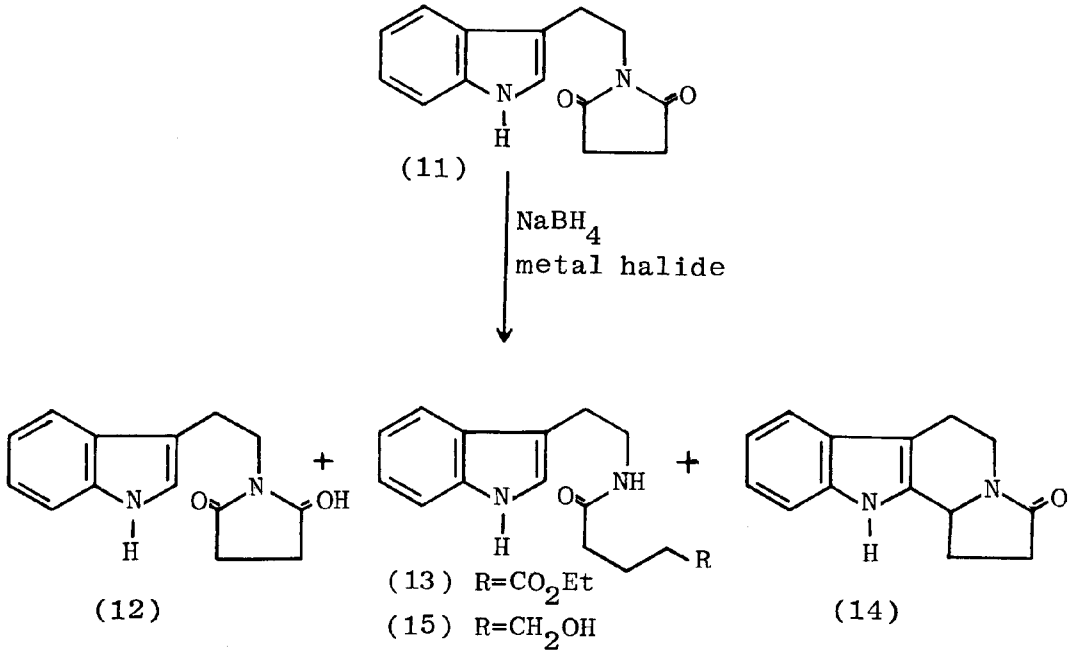
(9)

Scheme II

the hydroxy lactam in 20% yield. The presence of $CdCl_2$ was observed to retard the formation of the hydroxy lactam which was obtained only in traces. Some reactions were also accompanied by the formation of small amounts of the cleaved amide alcohol. The same set of reactions when repeated at room temperature (30°C), afforded the amide ester (7) in addition to the amide alcohol (6). No change was observed in the behaviour of $CdCl_2$.

An increase in the concentration of sodium borohydride used from one equivalent to five equivalents, and conducting the reaction in a freezing mixture of ice and salt, resulted in the formation of the hydroxylactam (9) in high yields. Reactions employing $CuCl_2.2H_2O$, $CrCl_3.6H_2O$, $FeCl_3$, $HgCl_2$, $SnCl_2$, $SbCl_3$ and $NiCl_2.6H_2O$, $MnCl_2.4H_2O$ and $CeCl_3$ gave yields of 70-85% of the hydroxy lactam. With $CuCl_2.2H_2O$ 60% yield of (9) was obtained. Addition of $BaCl_2$ appeared to have no effect on the course of the reaction as rate of formation and yield (45%) of the hydroxy lactam were similar to those of the blank reaction. When the reductions with five equivalents of sodium borohydride were repeated at 30°C, an increased formation of the undesired cleaved amide alcohol was observed after 2 hours on t.l.c. The hydroxy lactam was initially formed in moderate yields after an interval of ten minutes but as the reaction progressed it was converted to the corresponding amide alcohol. Only $MnCl_2.4H_2O$ increased the yield of hydroxy lactam (80%) after a reaction time of two hours at this temperature. Reactions with halides of Fe, Hg, Sn, Sr, Sb and Ce afforded 70-90% of the undesired amide alcohol. $CdCl_2$ was observed to give 15% of the hydroxy lactam. The results are tabulated in Table 1.

When the reductions were repeated with ten equivalents of sodium borohydride, initially at 0°C it was observed that complete conversion of the starting imide into the products took place. The low temperature, if carefully maintained, prevented the further reduction of the hydroxy lactam to the corresponding amide alcohol, while an increase in the reaction temperature resulted in increased formation of the cleaved amide alcohol. In these reactions the cyclized β carboline lactam (8) was also obtained in low yields (10-20%) in the most of the reactions. When the same set of reactions was repeated at 30°C, it was observed that it was again mainly the amide alcohol which was formed after 30 minutes. The only notable change observed was that in the presence of $CdCl_2$ the amide ester was formed in good yields



Scheme III

Table. 1. Reduction of N-Gultarimidotryptamine 5 equivalent $NaBH_4$

		% Product (0°C)				% Product (30°C)			
METAL-HALIDE	TIME min.	(9)	(8)	(6)	(5)	(9)	(8)	(6)	(5)
Blank	10	5			95	10	T	T	90
reaction	30	30	70		70	25	20	25	30
	60	45		5	50	10	20	45	25
	120	45		5	50	T	20	60	20
$CuCl_2$	10	T			M	10		T	90
	30	60			40	25		T	75
$2H_2O$	60	60			40	35		10	55
	120	80			20	55		30	15
$CoCl_2$	10	5			95	40		T	60
	30	50			50	40		20	40
	60	50			50	10	5	40	20
	120	60		10	30	20	5	20	15
$CrCl_3$	10	20			80	55		5	40
	30	60		T	40	60		10	30
	60	80			20	55		15	30
	120	85		T	15	45		45	10
$FeCl_3$	10	40			60	55		5	40
	30	70		T	30	20	T	60	20
	60	75		T	25	15	T	85	T
	120	80		10	10		T	M	
$HgCl_2$	10	50		50	50	75		5	20
	30	70			30	50		50	T
	60	70			30	50		90	T
	120	80			20	10		90	
$SnCl_2$	10	30			70	60		T	40
	30	70			30	50		40	10
	60	70		T	30	30	T	60	10
	120	75		10	15	20	T	70	10
$SrCl_2$	10	50			50	50		25	25
	30	70			30	10	10	60	20
	60	70		T	30		20	60	15
	120	75			25	T	30	70	
$CdCl_2$	10	5			95	T			M
	30	5			95	T			M

	60	10			90	10	T	T	90
	120	10		5	85	15	T	5	80
$SbCl_3$	10	20			80	60		T	40
	30	20			80	40	T	35	25
	60	50		T	50	10	T	70	20
	120	70		5	25	T	10	70	20
$NiCl_2$.	10	60			40	60			40
	30	60			40	30	T	40	30
$6H_2O$	60	70		T	30		20	60	20
	120	70		5	25		30	50	20
$MnCl_2$.	10	45			55	50			50
	30	70			30	50			50
$4H_2O$	60	70		T	30	70		10	20
	120	75		15	10	80		10	10
$CeCl_3$	10	60			40	50		10	40
	30	70			30	40	T	30	30
	60	80			20	5	5	90	T
	120	80	T	T	20		10	90	
$BaCl_2$	10	T			M	10	T	T	90
	30	25			75	25	20	25	30
	60	45		5	50	10	20	55	15
	120	45		5	50	T	10	60	30

T = Trace formation of the products.

M = Major formation of the products (above 95% estimated yield).

after the completion of two hours.

Similar reductions were carried out with N-succinimidotryptamine in the presence of various metal halides. Five equivalents of sodium borohydride and a reaction temperature of 0° afforded optimum yields. The reductions resulted in the formation of a product which was slower moving than the ester (13) and β- carboline (14) but faster moving than ide alcohol (15) on a t.l.c. plate. The product was olated from the reaction mixture by preparative t.l.c. The mass spectrum of the compound afforded the molecular ion peak at m/e 244. The n.m.r. spectrum showed the -OH signal at δ-5.5 (CHO*H*) and the indolic -NH appeared at δ-10.9. The u.v. spectrum in methanol indicated the indolic nature of the product. The i.r. spectrum showed the presence of the amide carbonyl stretching vibrations at 1680 cm^{-1}. The product was identified as the hydroxy lactam (12) on the basis of these spectral data.

It was observed that the presence of $CuCl_2$. $2H_2O$, $CoCl_2$, $CrCl_3$. $6H_2O$, $FeCl_3$, $SnCl_2$. $SrCl_2$, $SbCl_3$, $NiCl_2$. $6H_2O$ or $CeCl_3$, assisted the conversion to the hydroxyl lactam (12) which was obtained in 85-98% yields with only trace formation of the amide alcohol. The use of $CdCl_2$ (as in the earlier reductions with N-glutarimidotryptamine) produced an overall retarding effect. The same reductions, when repeated at 30°C instead of 0°C, resulted in a quicker reduction to the hydroxy lactam but an increased formation of the undesired cleaved amide alcohol (15) was observed except in the presence of $MnCl_2$. $4H_2O$ which exclusively promoted the formation of the hydroxy lactam (Table 11).

N-Phthalimidotryptamine on reduction with so-

Table. 2. Recution of N-succinimidotryptamine
5 equivalent $NaBH_4$

METAL-HALIDE	TIME min.	% Product (0°C) (12)	(14)	(15)	(11)	% Product (30°C) (12)	(14)	(15)	(11)
Blank reaction	10	T			M	10			90
	30	10			90	25		5	70
	60	40			60	60		20	20
	120	60			40	40		50	10
$CuCl_2$	10	25			75	60			40
	30	55			45	80			20
$2H_2O$	60	80			20	M		T	T
	120	M			T	60		40	T
$CoCl_2$	10	T			M	60		20	20
	30	20			80	65		20	15
	60	60		T	40	60		40	
	120	95		T	5	30		70	
$FeCl_3$	10	40			60	90		5	
	30	60			40	60		30	10
	60	90			10	55		45	
	120	M			T	40		60	
$HgCl_2$	10	25			75	80		10	10
	30	50			50	60		40	
	60	60			40	20		80	
	120	60			40	T		M	
$SnCl_2$	10	50			50	60		10	30
	30	80			20	60		20	20
	60	100				40		30	10
	120	90		10	T	25		70	5
$SrCl_2$	10	40			60	20		20	60
	30	70			30	30		20	50
	60	80			20	40		40	20
	120	85		5	10	40		50	10
$CdCl_2$	10	T			M	T			M
	30	10			90	10			90
	60	10		T	70	30			70
	120	40		T	60	40		T	60

$SbCl_3$	10	5			95	20		80
	30	20			80	30	5	65
	60	45			55	45	25	30
	120	60			40	40	50	10
$NiCl_2$.	10	30			70	60	20	20
	30	60			40	65	20	15
$6H_2O$	60	80			20	65	35	T
	120	90		T	10	30	70	T
$MnCl_2$.	10	45			55	40		60
	30	80			20	70	T	30
$4H_2O$	60	95			5	80	T	20
	120	M			T	85	5	10
$CeCl_3$	10	40			60	20	20	60
	30	50			50	30	20	50
	60	70			50	40	35	25
	120	90	T	T	10	40	50	10
$BaCl_2$	10	T			M	10		90
	30	5			M	25	5	70
	60	10			90	60	20	20
	120	30			70	50	40	10

T = Trace formation of the products.
M = Major formation of the products (above 95% estimated yield).

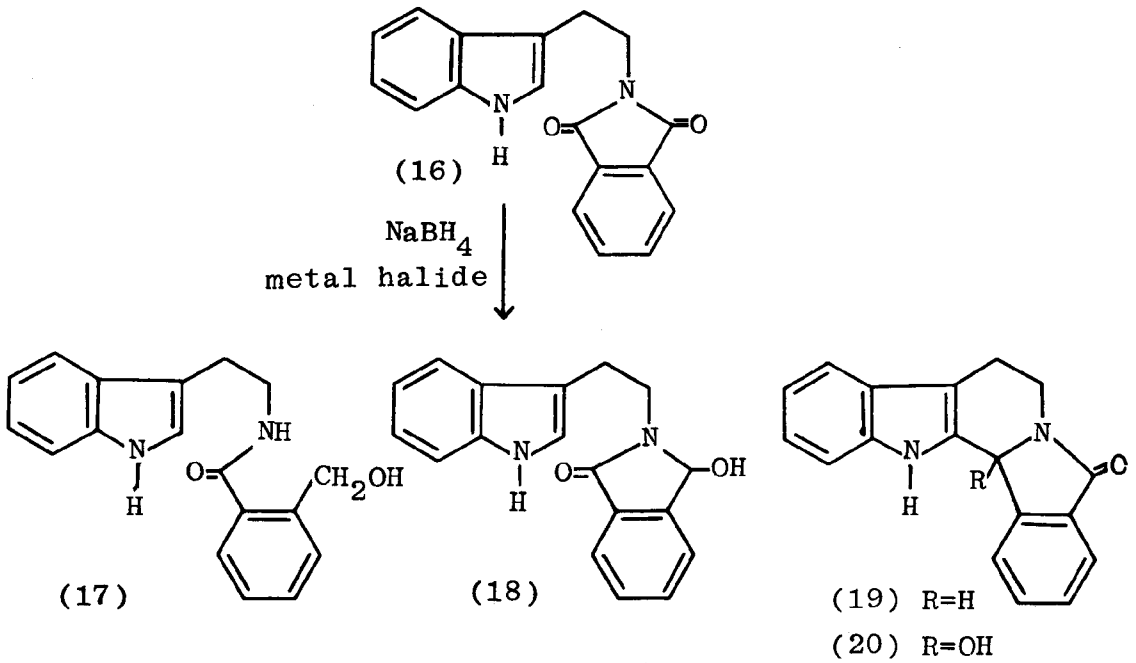
dium borohydride in the presence of various metal halides behaved similarly.[8] In these reductions, in addition to the corresponding amide alcohol (17), hydroxy lactam (18) and cyclized β-carboline lactam (19), another product (20) was also isolated, in which cyclization had occurred (Scheme 4).

A possible explanation for the catalysis may involve the complexation of the metal ion with the lone pair of electrons on the imide nitrogen atom and/or the carbonyl oxygen atom. This would increase the electrophilic character of the carbonyl function and thus facilitate the hydride attack, particularly with transition metal ions such as Cr, Fe, Mn, Co and Ni where the ability to form complex species is at a maximum because of a combination of such favourable acceptor factors as cation size, larger nuclear or ionic charges and suitable electronic configurations. A parallel increase in the electrophilic character of the carbonyl carbon was earlier observed when the imide oxygen was alkylated by Meerwein's reagent to generate the oxonium (or iminium) compound (2) thereby promoting cyclization on the indolic nucleus.[7]

The method described above offers a facile and high yield route to the synthesis of β-carboline systems, and should find wide application in indole alkaloid syntheses.

Experimental

NOTES: The I.R. spectra were recorded on a Jasco infra-red spectrophotometer or a Pye-Unicam SP-200-G instrument. The U.V. spectra were recorded on a Pye-Unicam SP-800 spectrometer. The NMR spectra were recorded on a Jeol PMX-60 NMR spectrometer. The mass spectra were recorded on a VG-Micromass MM-12 mass spectometer or a Varian 112 mass spectrometer. T.l.c. was performed on silica gel PF-254 plates. Yields have been determined by chromatographic comparisons on t.l.c. plates with



Scheme IV

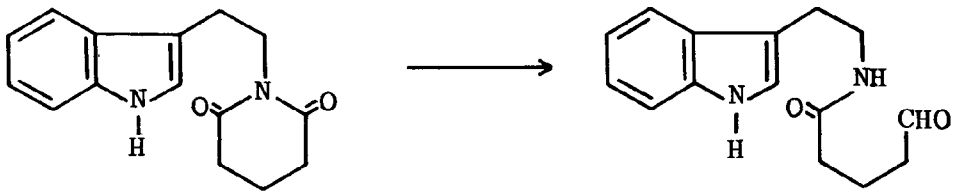
solutions of known concentrations; an error factor of ± 5% of the reported yield is estimated.

Reduction of N-Glutarimidotryptamine with $NaBH_4$ in the presence of Metal Halides

$CuCl_2$, $2H_2O$ (1.7 mg., 0.01 mmol), $CoCl_2$ (1.2 mg., 0.01 mmol), $CrCl_3$. $6H_2O$ (2 mg., 0.01 mmol), $FeCl_3$ (1.6 mg., 0.01 mmol), $HgCl_2$ (2 mg., 0.01 mmol), $SrCl_2$ (1.2 mg., 0.01 mmol, $CdCl_2$ (1.8 mg., 0.01 mmol), $SbCl_3$ (2 mg., 0.01 mmol), $NiCl_2$. $6H_2O$ (2 mg., 0.01 mmol), $MnCl_2$. $4H_2O$ (1.9 mg., 0.01 mmol), $CeCl_3$ (2 mg., 0.01 mmol) and $BaCl_2$ (2 mg., 0.01 mmol), were each dissolved in 13 different flasks in absolute ethanol (0.5 ml) To each flask was added N_b-glutarimidotryptamine (2 mg., 0.01 mmol) and the contents were gently warmed to make homogenous solution. The resulting solutions were than cooled to ice-salt temperature (0 to - 6°C), and $NaBH_4$ (1.5 mg., 0.05 mmol) added to each flask at the same temperature. A blank reaction was run at the same time with the imide (2 mg., 0.01 mmol) in absolute ethanol (0.5 ml) and $NaBH_4$ (1.5 mg., 0.05 mmol). The reactions were followed by t.l.c. (on 20 x 20 cms Merck plates precoated with silica gel PF_{254} in 95% chloroform-5% methanol). Aliquots were drawn at an intervals of 10, 30, 60 and 120 min. respectively. The chromatographic plates were viewed in iodine vapours. The same set of reactions was next identically repeated at room temperature (30-31°C). The results are given in Table 1.

All the reductions were also repeated at the two temperatures with an increased concentration of $NaBH_4$ to 10 equivalents and the results are tabulated in Table 1.

Preparation of Hydroxy Lactam (9): Finely powdered $NaBH_4$ (73.8 mg., 1.98 mmol) was added to a magentically stirred solution of glutarimidotryptamine (100 mg., 0.39 mmol) and $CrCl_3$. $6H_2O$ (104 mg., 0,39 mmol) in anhydrous ethanol (20 ml) at 0 to 6°C. T.l.c. (95% chloroform: 5% ethanol) after 2.5 hours showed the coversion of the starting imide to one major and one minor product. Excess $NaBH_4$ was filtered off and the solvent evaporated under reduced pressure at room temperature (32°C). The products were extracted from the residue with ethyl acetate and the major product separated by preparative t.l.c. on silica gel PF_{254} coated plates. The silica gel powder was scratched off the plates and the compound extracted with ethyl acetate. Filtration and evaporation of the filtrate afforded a white crystalline product, yield: 75 mg (75%).



(5) Scheme V (10)

Mass Spectrum: m/e = 258 (M+, 48%), 254 (6%), 239 (5%), 238 (22%), 237 (10%), 221 (7%), 217 (14%), 215 *5%), 203 (6%), 184 (5%), 183 (14%), 182 (5%), 169 (6%) 168 (7%), 167 (10%), 166 (7%), 165 (15%), 158 (9%), 157 (16%), 156 (13%), 155 (8%), 154 (7%), 153 (6%), 148 (13%), 147 (74%), 145 (5%), 144 (5%), 143 (15%), 142 (80%), 141 (100%), 140 (28%), 139 (11%), 138 (6%), 133 (5%), 130 (17%), 129 (38%), 128 (20%), 127 (8%), 125 (5%), 123 (7%), 122 (5%), 121 (6%), 119 (5%), 118 (10%), 117 (24%), 116 (12%), 115 (36%), 114 (5%), 113 (11%), 112 (19%), 109 (9%), 107 (5%), 105 (10%), 104 (19%), 103 (36%), 102 (20%), 101 (20%), 100 (6%), 99 (5%), 98 (8%), 97 (15%), 96 (6%), 95 (12%), 94 (5%), 93 (9%), 91 (12%), 89 (8%), 87 (9%), 85 (46%), 84 (11%), 83 (82%), 82 (9%), 81 (15%), 79 (%), 78 (8%), 77 (12%), 76 (13%), 75 (5%), 73 (12%), 72 (7%), 71 (24%), 70 (18%), 69 (29%), 68 (7%), 67 (12%), 65 (8%), 63 (6%), 60 (11%), 59 (7%), 58 (9%),

I.R. Spectrum (KBr): ν_{max} 3478 cm^{-1} (OH), 3400 cm^{-1} (NH, indole), 1658 cm^{-1} (C = O, amide), *U.V. Spectrum (MeOH) :* λ_{max} 222, 275, 282, 291 nm; *N.M.R. Spectrum ($CDCl_3$):* δ 3.08 (2H, t J = 7Hz CH_2 -CH_2 -N), δ 3.75 (sH, t, J = 10 Hz - CH_2 -CH_2 -N), δ 6.9 - 7.8 (4H, m, aromatic), δ 8.2 (1H, s, NH-indole), δ 4.74 (1H, broad s, CHOH).

Reduction of N-Succinimidotryptamine with $NaBH_4$ in the presence of Metal Halides

$CuCl_2 \cdot 2H_2O$ (1.7 mg., 0.01 mmol), $CoCl_2$ (1.3 mg., 0.01 mmol), $CrCl_3 \cdot 6H_2O$ (2.6 mg., 0.01 mmol), $HgCl_2$ (2.7 mg., 0.01 mmol), $SnCl_2$ (1.9 mg., 0.01 mmol), $SrCl_2$ (1.6 mg., 0.01 mmol), $CdCl_2$ (1.8 mg., 0.01 mmol), $SbCl_3$ (2.3 mg., 0.01 mmol), $NiCl_2$, $6H_2O$ (2.4 mg., 0.01 mmol), $MnCl_2 \cdot 4H_2O$ (2.0 mg., 0.01 mmol), $CeCl_3$ (2.5 mg., 0.01 mmil), $BaCl_2$ (0.2 mg., 0.01 mmol) were taken in different test tubes and each dissolved in anhydrous alcohol (0.5 ml). To each test tube was added N-succinimidotrypamine (2.4 mg., 0.01 mmol). The resulting solutions were taken to an ice-salt temperature. To each test tube was added $NaBH_4$ (0.3 mg., 0.01 mmol) at the same temperature. A blank reaction was simulataneously run without the metal halide. The reactions were followed by t.l.c. and aliquots drawn after 10, 30, 60 and 120 min. The plates were developed with iodine vapours. The reactions were identically repeated at room temperature (28-30°C). The observations are recorded in Table II.

In the next sets of experiments the concentration of $NaBH_4$ was increased to 5 equivalents and the reductions performed as above were carried out at 0 to – 6°C and at room temperature (30°C). The observations are tabulated in Table II.

Preparation of Hydroxy Lactam (12): To a solution of succinimidotryptamine (100 mg., 0.413 mmol) and $MnCl_2 \cdot 4H_2O$ (82 mg., 0.413 mmol) in absolute ethanol (25 ml) was added finely crushed $NaBH_4$ (78 mg., 2 mmol) at 0 to 6°C. The reaction was magnetically stirred at 0°C. T.l.c. at the end of this period showed the conversion of the starting imide to mainly a slower running product and traces of succinimido alcohol (15). Excess of $NaBH_4$ was filtered and the solvent evaporated under reduced pressure. The new product was isolated by preparative t.l.c. and identified as (12), yield: 80 mg (80%).

Mass Spectrum: m/e 244 (M^+, 25%), 226 (7%) 143 (100%), 130 (90%), 115 (7%), 103 (22%), 85 (9%), 77 (30%), 68 (18%); *I.R. Spectrum (KBr):* ν_{max} 1680 cm^{-1} (amide C = O) 3300-3440 (broad, indole NH and OH); *U.V. Spectrum (MeOH):* λ_{max} 224, 274, 284, 292 nm; λ_{min} 247, 279, 289 nm; *N.M.R. Spectrum ($CDCl_3$)* δ 3.7 (1H, t, J = 7Hz, CHOH), δ 8.4 (1H, s, indole NH).

Table 3. Reduction of N-Phthalimidotryptamine
5 equivalent $NaBH_4$

METAL-HALIDE	TIME min.	% Product (0°C) (18)	(20)	(17)	(16)	% Product (30°C) (18)	(20)	(17)	(16)
Blank	10	80			20			60	40
reaction	30	80			20			M	T
	60	90			10			M	
	120	M		T	T			100	
$CuCl_2$	10	40	60					100	
	30	40	60					100	
$2H_2O$	60	40	60					100	
	120	40	60					100	
$CoCl_2$	10	40	40		20			80	20
	30	50	40		10			M	T
	60	70	20	10				100	
	120	80	10	10				100	
$CrCl_3$	10	100			T			100	
	30	100						100	
	60	M	T					100	
	120	M	T	T				100	
$FeCl_3$	10	40	60					80	20
	30	40	60	T				100	
	60	40	60	T					
	120	40	60	T					
$HgCl_2$	10	M			T			100	
	30	M							
	60	100							
	120	90		10					
$SnCl_2$	10	M			T			100	
	30	M			T				
	60	M		T					
	120	90		10					
$SrCl_2$	10	80			20			80	20
	30	90			10			100	
	60	M		T	T				
	120	90		10					
$CdCl_2$	10	70			30			40	60
	30	80			20			60	40

	60	85			15		80	20
	120	90			10		100	
$SbCl_3$	10	M			T		100	
	30	M		T				
	60	95		5				
	120	95		5				
$NiCl_2$	10	40	60	T			90	10
	30	40	60			5	95	
$6H_2O$	60	40	50	10				
	120	40	50	10				
$MnCl_2$.	10	100		T		100		
	30	100		T				
$4H_2O$	60	100		T				
	120	95		5				
$CeCl_3$	10	100					100	
	30	100		T				
	60	95		5				
	120	95		5				
$BaCl_2$	10	80			20		60	40
	30	80			20		M	T
	60	90		T	10		100	
	120	M		T	T			

T = Trace formation of the products.
M = Major formation of the products (above 95% estimated yield).

Reduction of N-Phthal imidotryptamine with $NaBH_4$ in the Presence of Metal Halides

$CuCl_2$. $2H_2O$ (1.7 mg., 0.01 mmol), $CoCl_2$ (1.3 mg., 0.01 mmol), $CrCl_3$. $6H_2O$ (2.6 mg., 0.01 mmol), $HgCl_2$ (2.7 mg., 0.01 mmol), $SnCl_2$ (1.9 mg., 0.01 mmol), $SrCl_2$ (1.6 mg., 0.01 mmol), $CdCl_2$ (1.8 mg., 0.01 mmol), $SbCl_3$ (2.3 mg., 0.01 mmol), $NiCl_2$. $6H_2O$ (2.4 mg., 0.01 mmol), $MnCl_2$. $4H_2O$ (2.0 mg., 0.01 mmol), $CeCl_3$ (2.5 mg., 0.01 mmol), $BaCl_2$ (2 mg., 0.01 mmol), were taken in different flasks and each dissolved in anhydrous alcohol (0.5 ml). To each flask was added N-phthalimidotryptamine (2.9 mg., 0.01 mmol). The resulting solutions were cooled to -5°C. To each test tube was added $NaBH_4$ (0.37 mg., 0.01 mmol) at the same temperature. A blank reaction (without metal halide) was monitored by t.l.c. for comparison purposes. Aliquots drawn after 10, 30, 60 and 120 min. The plates were developed with iodine. The same set of reactions was repeated at room temperature (28-30). The observations are recorded in Table III. In another set of experiments the concentration of $NaBH_4$ was increase to 5 equivalents (1.9 mg., 0.05 mmol) and the reduction performed as above at 0 to -6°C and at room temperature (30°C). The observations are tabulated in Table III.

The products were identified as the amide alcohol (17), hydroxylactam (18) and alcohol (20) (Scheme No. 4) by spectroscopic comparisions with authentic samples.

Preparation of Alcohol (20): To a solution of N-phthalimidotryptamine (116 mg., 0.40 mmol) and $NiCl_2$. $6H_2O$ (96.0 mg., 0.40 mmol) in absolute ethanol (25 ml) was added finely crushed $NaBH_4$

(78 mg., 2 mmol) at 0°C. The reaction was magnetically stirred at 0°C. T.l.c. after 7 hours showed the formation of a slower running product and traces of unreacted N-phthalimidotryptamine. Excess $NaBH_4$ was filtered and the solvent evaporated under reduced pressure. the new product was isolated by preparative t.l.c. and identfied as the alcohol (20).

U.V. Spectrum (Methanol): λ_{max} 225, 282 and 290 nm; λ_{min}=245 and 288 nm; *I.R. Spectrum:* ν_{max} 1670 cm^{-1} (C = O), 3350-3200 cm^{-1} (OH, NH); *Mass Spectrum:* m/e 290 (M^+), 274, 160, 149, 148, 143, 130, 115, 109, 105, 104, 85, 76, 75, 74 73, 83, 77 and 69; *N.M.R. Spectrum (DMSO d):* δ 6.8 - 7.8 (m, aromatic protons), δ 10.89 (s, indole NH).

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