A Facile Route to β-Carbolines+

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Summary: N-imidotryptamines may be converted to the corresponding β-carbolines is high yields by treatment with $NaBH_4$-HCl.

Our continuing interest on the development of new synthetic methods[1-7] has led us to report new synthetic approaches to β-carbolines from N-imidotryptamines[8-10] by treatment of the imides with Meerweins reagent[8] or with $POCl_3$ and zinc.[9] We now report another high yield synthetic route to β-carbolines.

When N-imidotryptamines were treated with $NaBH_4$-HCl in ethanol, they were found to be converted to the corresponding β-carbolines in excellent yields. During the reaction the immonium intermediates may be formed by the acid treatment of the hydroxylactams, and subsequent cyclization is effected by the intramolecular electrophilic attack at the indole 2-position (Scheme 1,2).

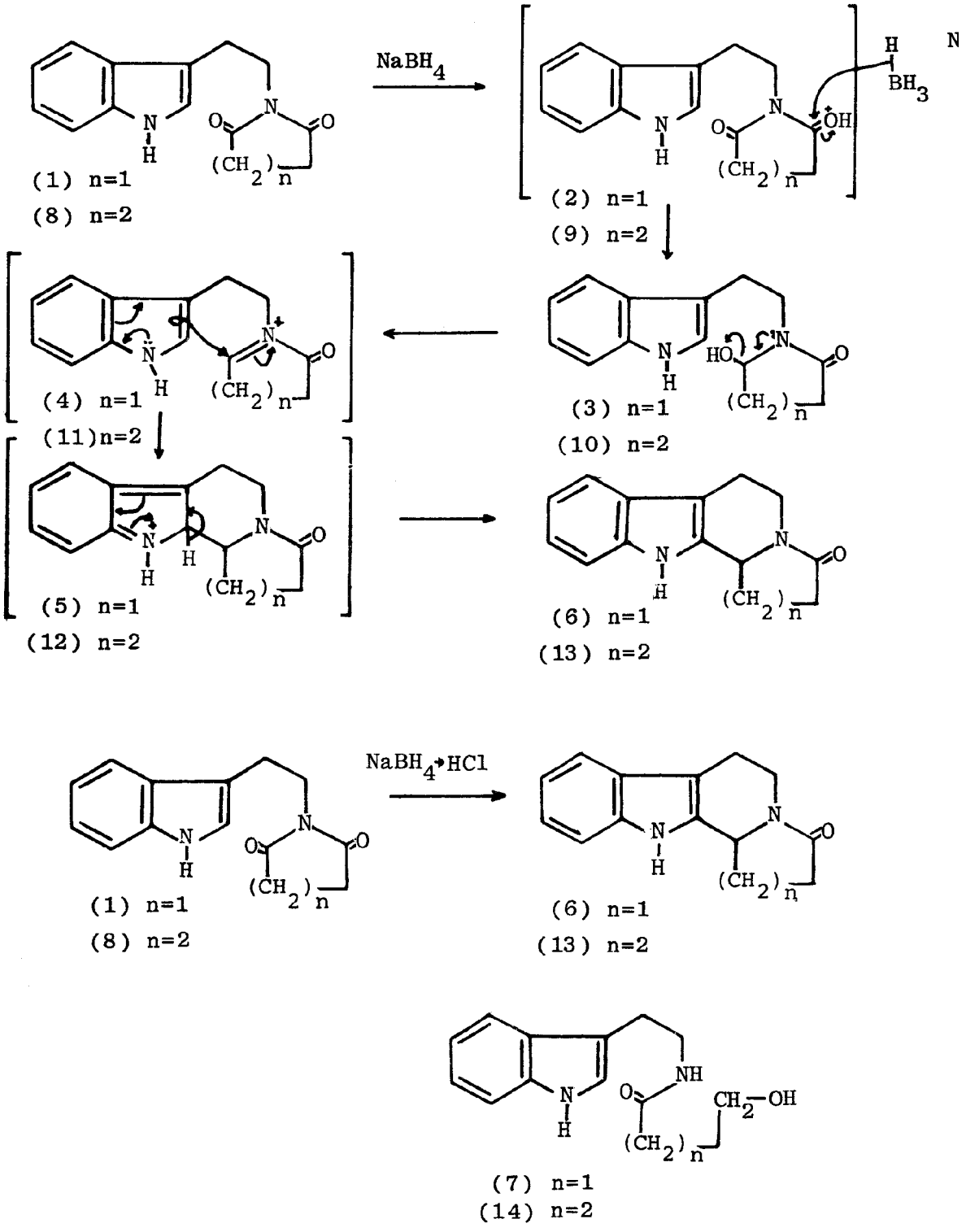
N-Succinimidotryptamine (11) on treatment with $NaBH_4$ and 2N HCl in ethanol at 0-6°C for five hours afforded the cyclized β-carboline lactam (6) (Scheme No. 1) in 98% yield. The ultraviolet spectrum of the product was typically indolic and the amide carbonyl absorption appeared at 1662 cm^{-1} in its infra-red spectrum. The mass spectrum of the compound showed the molecular ion at m/e = 226, as expected. The other fragments were also in accordance with the expected structure. The NMR spectrum of the compound was in complete agreement with the structure (6). The product was found to be identical to the β-carboline obtained by the zinc dust treatment of vilsmeier complex.[28,29] When the same reaction was repeated at room temperature (24°C), t.l.c. showed the formation of two compounds after twenty minutes. These two products were isolated through preparative t.l.c. The minor faster running material was identified as the β-carboline lactam (6) obtained in 15% yield. The structure was established by comparing it with the authentic product (6). The major slower moving material possessed a normal indolic absorption in the ultra-violet spectrum. The infra-red spectrum showed the amide carbonyl absorption pattern in accordance with the expected structure and the molecular ion appeared at m/e = 246. The NMR spectrum of the compound was in complete agreement with the assigned structure (7). The pure product was obtained in 75% yield, m.p. 68°C.

N-Glutarimidotryptamine (8) on identical treatment with with sodium borohydride and 2N hydrochloric acid for one hour in ethanol at 0-6°C afforded the cyclized β-carboline lactam (13) in 97% yield, m.p. 244-6°C (Scheme 1,2). The ultra-violet spectrum of the compound showed normal indolic absorptions while the infra-red spectrum showed amide carbonyl absorptions at 1612 cm^{-1}. The mass spectrum exhibited the molecular ion at m/e =240 and other fragments were also in accordance with the expected structure (13). The product was found to be identical with the compound obtained by the zinc dust treatment of the Vilsmeier complex in an earlier synthesis.[9,12]

When the same reaction was repeated at room temperature (24°C) it was found that the imide (8) afforded two products after twenty minutes. The crude mixture was subjected to preparative t.l.c. and the minor faster running material was identified to be the cyclized β-carboline lactam (13) (8% yield). The major slower running material obtained in 78% yield was identified as the amide alcohol (14). It afforded a typically indolic U.V. spectrum and the amide carbonyl absorption appeared at 1632 cm^{-1} in its infra-red spectrum. The mass spectrum showed the molecular ion at m/e = 260 as expected and the other fragments were also in accordance with the expected structure (14).

N-Phthalimidotryptamine (15) was similarly dissolv-

+Published as a short communication in *Tetrahedron Letters* (19), 1715 (1979); a similar approach has been independently developed by Speckamp and co-workers.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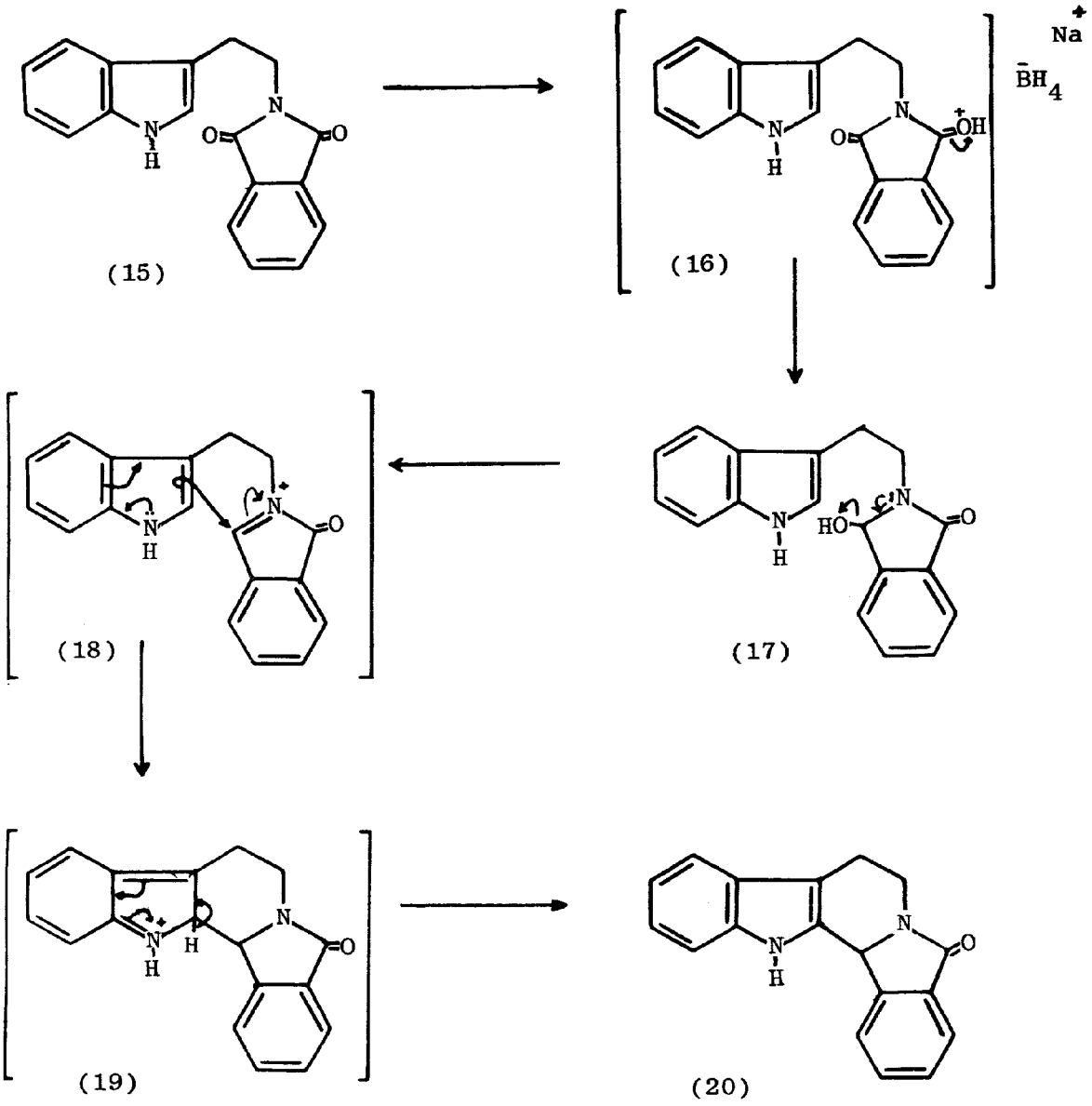
(8) n=2
(2) n=1
(9) n=2
(3) n=1
(10) n=2
(4) n=1
(11)n=2
(5) n=1
(12) n=2
(6) n=1
(13) n=2
NaBH4+HCl
(1) n=1
(8) n=2
(6) n=1
(13) n=2
(7) n=1
(14) n=2

Scheme I



Scheme II

ed in warm ethanol and a few drops of 2N HCl were added to the solution with constant stirring at 0-6°C (Scheme No. 2). Excess of sodium borohydride was then added. After twenty minutes t.l.c. revealed the formation of a new slower moving compound which was identified as the hydroxylactam (17). On work up of the reaction mixture t.l.c. revealed the formation of two compounds. The faster moving substance obtained in 70% yield was identified as the cyclized β-carboline lactam (20). The compound possessed a normal indolic chromophore and the amide carbonyl absorption appeared at 1672 cm^{-1} in its infra-red spectrum. The mass spectrum afforded the molecular ion at m/e = 274 as expected, and other fragments were in accordance with the expected structure (20). The NMR spectrum was in complete agreement with the expected structure. The minor slower moving substance was isolated in 25% yield and identified as the hydroxylactam (17). The ultra-violet spectrum of the compound was typically indolic and the amide carbonyl absorption appeared at 1662 cm^{-1} in its infra-red spectrum. The mass spectrum of the compound showed the molecular ion at m/e = 292 as expected. Other prominent peaks appeared at m/e = 274, 217, 115, 143, and 130. The NMR spectrum showed the signals at δ 6.80-7.86 (m, 9H, aromatic), δ 5.80 (d, 1H, CHOH) and δ 6.60 (d, 1H, CHOH). When the same reaction was repeated with the imide (15) at room temperature (24°C), t.l.c. on an aliquot of the reaction mixture did not show the presence of the cyclized β-carboline lactam (20) but only the hydroxylactam (17) was formed. However, after aqueous work up the cyclized β-carboline (20) was mainly obtained in high yields while the hydroxy lactam (17) was present only in low yields. The proposed mechanism of the reaction is shown in Scheme 2. The protonation of the OH group of the hydroxylactam (17) during aqueous work up probably cleaves the C-OH bond and an immonium intermediate (18) is generated The cyclization then proceeds by the intramolecular electrophilic attack at the indole 2-position. The hydroxylactam on treatment with concentrated hydrochloric acid at room temperature (34°C) was found to be converted to the cyclized β-carboline lactam (20) in qunatitative yields which was identical with the product obtained previously by the zinc dust treatment of the of the vilsmeier complex in aprotic medium.[9,12] Wenkert and others have previously reported difficulties in synthesising β-carbolines from N-imidotryptamines.[13] The procedure describes here represents a singificant improvement to those previously reported for the synthesis of β-carbolines.[8,9,12]

Experimental

Preparation of 1,5,6,11b-Tetrahydro-11H-Indolizino-(8,7-b)-Indol-3(2H)-one (6).

N-Succinimidotryptamine (1) (100 mg. 0.000413 mole) was dissolved in warm ethanol (12 ml) and 2N HCl (1 ml, 0.002 mole) was added to it with constant stirring at 0-6°C followed by the addition of $NaBH_4$ (400 mg., 0.01057 mole). After five hours, examination of the reaction mixture by TLC (MeOH:$CHCl_3$, 0.5:9.5) showed complete conversion of (1) to a slower moving product (Rf, 0.55 identified as the β-carboline lactam (6). Excess of $NaBH_4$ was filtered off and ethanol was evaporated under vacuum. The resulting residue was partitioned between water (75 ml) and ethyl acetate (75 ml). The ethyl acetate layer on drying over anhydrous sodium sulphate and evaporation afforded a white crystalline product, which on recrystallization from hot methanol yielded the pure β-carboline lactam (6) (91.5 mg, 98% yield) m.p. 252°C (lit. 253-254°C), observed mass: 226.1132, calculated mass for $C_{14}H_{14}N_2O$: 226.1106; U.V. spectrum: λ_{max}: 223,280,290 nm, ξ_{max}: 40680,994,8362; λ_{min} 245,286 nm, ξ_{min}: 4520,7910; IR spectrum (KBr): ν_{max} = 1662 cm^{-1} (amide C=O), 3240 cm^{-1} (indole NH); mass spectrum m/e = 226 (100$, M^+), 225 (94%), 198 (9%), 197 (9%), 182 (15%), 170 (12%), 169 (32%), 168 (19%), 167 (19%), 157 (9%), 156 (8%), 154 (8%), 149 (11%), 146 (15%), 143 (8%), 129 (10%), 128 (9%), 115 (10%), 111 (9%), 101 (10%), 97 (10%), 95 (8%), 85 (12%), 83 (12%), 83 (14%), NMR spectrum: (DMSO d_6); 6.90-7.80 (m, 4H, aromatic), 11.96 (s, 1H, indole NH).

Preparation of N-2-(3-indolyl)-ethyl-seco-succinamide alcohol (7).

On repeating the above reaction with identical quantities of reactions at 24°C, examination of the reaction mixture by T.L.C. after twenty minutes showed complete conversion of the starting imide (1) into two

slower moving compounds. Similar work up afforded a crude residue, which was subjected to preparative T.L.C. The minor faster moving product was identified as (6) (14 mg, 15%) and the major slower moving product was found to be the amide alcohol (7) (76 mg, 75% yield), m.p. 68°C, observed mass (of 7): 230.1432, calculated for $C_{14}H_{18}N_2O$: 230.1419; U.V. spectrum (MeOH): λ_{max} 220,280,290 nm; ξ_{max} 35916,7380, 6396; λ_{min} 245,286 nm; ξ_{min} 2952,5904; I.R. spectrum (KBr) disc: ν_{max} 1630 cm^{-1} (amide C=O); mass spectrum: m/e 246 (26% M^+), 228 (40%), 169 (14%), 160 (28%), 149 (21%), 144 (46%), 143 (100%), 142 (12%), 135 (11%), 132 (16%), 131 (68%), 130 (94%), 129 (20%), 128 (13%), 115 (16%), 111 (12%), 105 (14%), 103 (28%), 102 (12%), 99 (36%), 98 (47%), 97 (16%), 95 (13%), 94 (11%), 86 (13%), 85 (11%), 82 (20%), 81 (16%), 77 (36%), 71 (25%), 70 (19%), 69 (68%), 67 (12%), 58 (13%); NMR spectrum (DMSO-d_6): δ 6.90-7.90 (4H, aromatic) δ 4.43 (-CH_2-OH), δ 10.9 (indole N-H).

Preparation of 1,2,6,7, 12b-Hexahydroindolo-(2,3a)-quinolizino-4 (3H)-one (13).

N-glutarimidotryptamine (8) (100 mg., 0.00039 mole) was dissolved in warm ethanol (10 ml) and 2N HCl (0.5 ml) and $NaBH_4$ (210 mg, 0.00554 mole) were added to the solution with constant stirring at 0-6°C. After one hour t.l.c. (MeOH-$CHCl_3$, 0.5:9.5) showed complete conversion of the starting imide (8) into the cyclized β-carboline lactam (13) (Rf 0.71). Excess of $NaBH_4$ was filtered off and the solvent was evaporated under vacuum. The resulting residue was partitioned between water (75 ml) and ethyl acetate, (75 ml). The organic layer was dried with anhydrous Na_2SO_4, filtered and evaporated to afford a white crystalline material. Recrystallization from hot MeOH afforded the pure cyclized β-carboline lactam (13), (90.0 mg. 97% yield) m.p. 244-246°C (lit. 245-247°C); observed mass 240.1273, calculated for $C_{15}H_{16}N_2O$: 240.1262; U.V. spectrum (MeOH); λ_{max} 223,280,290 nm; ξ_{max} = 35520,8640, 7200, λ_{min} 247, 286 nm, ξ_{min} 4560, 6720 IR spectrum (KBr): ν_{max} 1612 cm^{-1}, (lactam C=O); mass spectrum: m/e = 240 (100% M^+), 239 (55%), 225 (10%), 212 (10%), 211 (15%), 196 (14%), 185 (11%), 184 (22%), 183 (10%) 182 (12%), 181 (12%) 171 (10%), 170 (38%), 169 (53%), 168 (29%), 167 (12%), 158 (8%), 155 (11%), 154 (12%), 149 (9%) 114 (9%), 143 (11%), 142 (11%), 130 (8%), 129 (13%), 128 (12%), 115 (36%), 114 (12%), 100 (15%), 97 (9%), 88 (8%), 87 (28%), 86 (9%), 85 (12%), 83 (10%), 77 (9%), 73 (10%), 71 (11%), 70 (12%), 69 (13%), 61 (10%). NMR specturm (DMSO-d_6): δ 6.86-7.33 (4H, aromatic), δ 10.83 (indole N-H).

Preparation of N-2-(3-Indolyl ethyl-secoglutaramide Alcohol (14).

When the above reaction was allowed to proceed at 24°C with identical quantities of reactants for 20 minutes, t.l.c. (MeOH:$CHCl_3$, 0.5:9.5) of the reaction mixture showed complete conversion of (8) into two slower moving compounds. Excess of $NaBH_4$ was filtered off and EtOH evaporated under vacuum. The residue thus obtained was partitioned between water (75 ml) and ethyl acetate (75 ml). The organic layer was dreid with anhydrous Na_2SO_4, filtered, and evaporated under vacuum and the resulting residue was subjected to preparative t.l.c. (MeOH:$CHCl_3$, 0.5:9.5). The minor faster moving product (Rf. 0.71) was identified as the cyclized β-carboline lactam (13) (16 mg, 17% yield) and the major slower moving product (Rf 0.23) was identified as the amide alcohol (14) (80 mg, 78% yield) m.p. 68°C; observed mass: 260.1522, calculated for $C_{15}H_{20}N_2O_2$: 260.1525; U.V. spectrum: λ_{max} 222,280,290 nm; ξ_{max} 41600,8320,7280; λ_{min} 245,280 nm. ξ_{min} 3640, 6660; I.R. spectrum: (KBr disc): ν_{max} 1632 cm^{-1} (amide C=O); mass spectrum: m/e = 260 (26%, M^+), 257 (9%), 256 (9%), 240 (9%), 239 (9%), 226 (13%), 225 (15%), 211 (12%), 197 (99%), 185 (20%), 183 (10%), 169 (20%), 168 (10%), 167 (20%), 161 (8%), 160 (10%), 159 (29%), 155 (11%), 153 (8%), 151 (9%), 150 (9%), 149 (49%), 148 (8%), 147 (9%), 145 (17%), 144 (48%), 143 (100%), 142 (19%), 141 (13%), 140 (8%), 139 (13%), 137 (14%), 135 (13%), 133 (11%), 132 (9%), 131 (34%), 130 (77%), 129 (20%), 128 (16%), 127 (15%), 126 (8%), 125 (19%), 123 (18%), 121 (15%), 120 (9%), 119 (13%), 118 (10%), 117 (22%), 116 (15%), 115 (47%), 114 (24%), 113 (24%), 112 (26%), 111 (27%), 110 (29%), 109 (19%), 108 (12%), 107 (12%), 105 (19%), 104 (10%), 103 (26%), 102 (15%), 101 (20%), 100 (21%), 99 (23%), 98 (20%), 97 (36%), 96 (17%), 95 (26%), 93 (15%), 91 (14%), 96 (36%), 85 (37%), 84 (21%), 83 (36%), 82 (19%), 81 (17%

78 (14%), 77 (32%), 73 (21%), 72 (12%), 71 (39%), 70 (30%). NMR spectrum (DMSO-d_6): δ 7.0-7.9 (m,4H, aromatic), δ 4.43 (t, 2H,-CH_2 OH), δ 10.83 (s, 1H, ind-NH).

Preparation of 5,7,8,13b-Tetrahydro-5-oxo-13H-indolo-(2,3-c)-isoindolo-2,1-a-pyridine (20).

N-Phthalimidotryptamine (15) (100 mg, 0.00034 mole) was dissolved in warm MeOH (10 ml) and 2N HCl (0.5 ml) was added to it at 0-6°C with constant stirring. $NaBH_4$ (210 mg, 0.00554 mole) was added to the solution, and the reaction mixture was stirred for another 30 minutes at this temperature, when t.l.c. in MeOH-chloroform, (0.5:9.5) on an aliquot of the reaction mixture showed a single product (20). Excess of $NaBH_4$ was filtered off and water (25 ml) was added to the reaction mixture with constant shaking and cooling. The reaction mixture was then partitioned between ethyl acetate and water (100 ml). The organic layer on drying with anhydrous Na_2SO_4, filtration and evaporation afforded a white material which on t.l.c. showed two spots, which were separated by preparative t.l.c. The major faster moving product (Rf 0.60) was isolated as a white crystalline substance which was identified as the cyclized β-carboline lactam (20) (66 mg, 70% yield) m.p. 210-215°C (lit[3]. 210-214°C); observed mass: 274.112, calculated for $C_{13}H_{14}N_2O$: 274.1106; U.V. spectrum (MeOH): λ_{max} 223,280,290 nm; ξ_{max} 17810, 4658 and 3562, λ_{min} 247, 287, nm, ξ_{min} 4110 and 3288; I.R. spectrum (KBr): ν_{max} 1677 cm^{-1} (C=O stretching), 3320 cm^{-1} (indole N-H); mass spectrum m/e = 274 (100%, M^+), 273 (72%), 271 (13%), 270 (12%), 257 (8%), 246 (20%), 245 (46%), 218 (8%), 217 (22%), 216 (13%), 204 (8%), 149 (9%), 143 (25%), 137 (8%), 130 (25%), 115 (8%), 103 (8%), 97 (8%), 83 (10%), 77 (9%), 71 (12%), 69 (10%), 57 (33%); N.M.R. spectrum (DMSO d_6): δ 6.93-7.83 (8H, m, aromatic), δ 11.30 (indole N-H).

The slower moving product (Rf, 0.32) was also obtained as a white crystalline substance and was identified as the hydroxy lactam (17) (25.1 mg,-25% yield), m.p. 166-168°C; observed mass: 292. 1208, calculated for $C_{18}H_{16}N_2O_2$: 292. 1212; U.V. spectrum (MeOH): λ_{max} 221,280,290 nm; ξ_{max} 33288,7008,6132; λ_{min} 247, 2286 nm, ξ_{min} 5890,5548; I.R. spectrum (KBr): ν_{max} 1662 cm^{-1} (C=O), 3280 cm^{-1} (OH); mass spectrum: m/e 292 (74%, M^+), 275%, 274(38%), 273(10%), 270 (8%), 246 (10%), 245 (13%), 217 (9%), 162 (19%), 160 (8%), 150 (8%), 149 (19%), 146 (20%), 145 (61%), 144 (80%), 143 (78%), 135 (10%), 134 (27%) 133 (100%), 132 (15%), 131 (43%) 130 (90%), 129 (13%), 128 (16%), 119 (8%), 118 (21%), 117 (51%),116 (19%), 115 (38%), 106 (9%), 105 (54%), 104 (22%), 103 (50%), 102 (17%), 101 (10%), 98 (8%), 97 (8%), 94 (12%), 91 (11%), 90 (34%), 89 (25), 83 (10%), 79 (8%), 78 (17%), 77 (77%), 76 (23%), 75 (14%); N.M.R. spectrum (DMSO-d_6): δ 6.8-7.8 (m, 9H, aromatic H), δ 5.80 (d, 1H, *CH*OH), δ 6.60 (d, 1H, CHO*H*), δ 10.76 (s, 1H, indole N*H*).

In another experiment N-pthalimidotryptamine (15) (50 mg, 000172 mole) was dissolved in warm ethanol (5 ml), and 2N HCl (0.25 ml) was added to this solution with constant stirring followed by the addition of $NaBH_4$ (100 mg, 0.0031 mole). The reaction mixture was stirred at 24°C for another 30 minutes, when t.l.c. (MeOH:$CHCl_3$, 0.5:9.5) showed the complete conversion of the starting imide into the hydroxy lactam (17), which on aqueous work-up was converted to the cyclized β-carboline lactam (20) (42.5 mg 90% yield). A little hydroxy lactam (17) (2.5 mg, 5% yield) also reamined.

In a separate experiment the hydroxy lactam (17) (100 mg; 0.000243 mole) was dissolved in warm ethanol, conc. HCl (2 ml) was added to it and the resulting mixture, after being stirred for 15 minutes at 34°C, was checkedon t.l.c (MeOH: chloroform, 0.5:9.5) when it showed conversion of (17) (Rf. 0.32) into the cyclized β-carboline lactam (20) (Rf. 0.6) in quantitative yield).

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