Syntheses of (±)-4-amino-1,3,4,5-tetrahydrobenz[cd]indole-4-carboxylic acid, (±)-4-N,N-dipropylamino-4-hydroxymethyl- and (±)-4-propyloxy-1,3,4,5-tetrahydrobenz[cd]indole

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SYNTHESES OF ($\pm$)-4-AMINO-1,3,4,5-TETRAHYDROBENZ[*cd*]INDOLE-4-CARBOXYLIC ACID, ($\pm$)-4-*N,N*-DIPROPYLAMINO-4-HYDROXYMETHYL- AND ($\pm$)-4-PROPYLOXY-1,3,4,5-TETRAHYDROBENZ[*cd*]INDOLE¹

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Abstract----Simple syntheses of the title compounds are reported starting from indole-3-carboxaldehyde.

In our synthetic project to develop biologically active indole compounds,² we have been much interested in 4-amino-1,3,4,5-tetrahydrobenz[*cd*]indole-4-carboxylic acid (**1**, Scheme 1), 4-*N,N*-dipropylamino-4-hydroxymethyl- (**2 a**), and 4-propyloxy-1,3,4,5-tetrahydrobenz[*cd*]indole (**3**). The amino acid (**1**) has a conformationally constrained structure³ of tryptophan as well as a part of skeleton of ergot alkaloids.⁴ Therefore, we could expect **1** not only as a dopamine agonist but also as a useful probe to obtain information about the bioactive conformation of a neuropeptide, such as cholecystokinin (CCK),³ by incorporating **1** into the peptide. While the compound (**2 a**) is an analog of a potent dopamine agonist, 4-*N,N*-dipropylamino-1,3,4,5-tetrahydrobenz[*cd*]indole⁵ (**4**), and **3** is its oxa-analog. In this communication, we wish to report facile syntheses of the title compounds in ($\pm$)-form from indole-3-carboxaldehyde (**5**).

($\pm$)-4-Nitro-1,3,4,5-tetrahydrobenz[*cd*]indole (**6 a**) was obtained in four steps in 29% overall yield from **5** according to our synthetic method,⁵ and then **6 a** was converted to **7** by the procedure of Kruse and co-worker⁶ in 88% yield. Since **7** is known to isomerize to 1,2-dihydro-4-hydroxybenz[*cd*]indole having stabler naphthalene skeleton than indole isomer,⁶ Bucherer reaction of **7** was investigated under careful control of reaction conditions and the results are summarized in Table I. As can be seen in the Table, α -aminonitrile^{7a} (**8**), hydantoin^{7b} (**9**), and cyanohydrin^{7c} (**10**) were produced using (NH₄)₂CO₃ and KCN (Entries 1-4), and under the

reaction conditions of Entry 2, **9** was obtained as major product. While, Strecker type reaction of **7** with NH_4Cl and KCN produced **8** as major product under the reaction conditions of Entry 6. Although **10** was a crystalline solid, it was unstable and gradually changed back to **7**. Isolation of stable 4-acetoxy-4-cyano compound^{7d} (**11**) in 43% yield by the treatment of **7** with KCN in AcOH , followed by the reaction of the resulting **10** with Ac_2O and pyridine, clearly established the structure of **10**. Next, **8** was converted to amide^{7e} (**12**) in 84% yield by the reaction with 2N- NaOH in the presence of 30% H_2O_2 . Subsequent hydrolysis of **12** with 2N- NaOH in MeOH produced the desired amino acid^{7f} (**1**) in a quantitative yield.

Table I. Bucherer and Strecker Type Reactions of **7**

$ \begin{array}{c} \text{7} \xrightarrow[\text{MeOH, } 60^\circ\text{C}]{\text{Ammonium Salt, KCN (3.5 mol)}} \text{8} + \text{9} + \text{10} + \text{Recovery} \end{array} $						
Entry	Ammonium Salt (mol)	Reaction Time (h)	8	Yield (%) 9	of 10	Recovery
1	$(\text{NH}_4)_2\text{CO}_3$ (10.5)	5	2	49	0	0
2	"	2	11	59	0	0
3	"	1	51	23	6	16
4	"	0.5	40	10	19	31
5	NH_4Cl (10.5)	2	15	0	7	6
6	"	1	56	0	10	26

For the synthesis of the target compound (**2a**), **6a** was initially treated with KO^tBu and 37% formalin to afford **13**^{7g} in 73% yield, which was reduced with Zn(Hg)-HCl to give **14**^{7h} in 94% yield. The reaction of **14** with propyl iodide (2 mol) in the presence of K_2CO_3 produced the mono-propyl⁷ⁱ (**15**) and the target compound^{7j} (**2a**) in 87 and 6% yields, respectively. Various attempts to improve the yield of **2a** were unsuccessful. While, treatment of **15** with propionyl chloride afforded **16**^{7k} and **17**^{7l} in 89 and 8% yields, respectively. Subsequent reduction of **16** with LiAlH_4 afforded **2a** in 91% yield. Furthermore, the 2-bromo compounds, (**2b**)^{7m} and (**6b**),⁷ⁿ were obtained in 92 and 87% yields, respectively, by reacting **2a** and **6a** with NBS.

The third target compound (**3**) was produced as follows. Reduction of **7** with NaBH_4 afforded 4-hydroxy-1,3,4,5-tetrahydrobenz[*cd*]indole⁷⁰ (**18**) in 99% yield. Successive treatment of **18** with NaH , and then with tosyl chloride produced *N*-tosyl^{7p} (**19**) and *N,O*-ditosyl compound^{7q} (**20**) in 37 and 27% yields, respectively, together with 34% recovery of unreacted starting material. Treatment of **19** with KH in DMF, and then with propyl iodide afforded 47% yield of the 4-propyloxy compound^{7r} (**21**), which was successfully converted to **3**^{7s} in 86% yield by hydrolysis with 2N- NaOH .

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7. All new compounds gave satisfactory spectral and elemental analysis data for crystals or high resolution mass data for oils. a) mp 129.0-132.0°C; b) mp 295.0-297.0°C; c) unstable crystals; d) mp 161.0-162.0°C; e) mp 81.0-82.0°C; f) mp 275.0-278.0°C (decomp.); g) mp 154.0-155.0°C; h) mp 173.5-174.0°C; i) mp 132.0-133.0°C; j) mp 93.5-95.0°C; k) mp 165.0-166.0°C; l) oil; m) mp 160.0-163.0°C (decomp.); n) mp 125.0-135.0°C (decomp.); o) mp 87.0-88.0°C; p) oil; q) oil; r) oil; s) oil.

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