A simple four step synthesis and optical resolution of 4-nitro-1,3,4,5-tetrahydrobenz[cd]indole, and the synthesis of 1-hydroxy derivatives of 4-nitro- and 4-amino-1,3,4,5-tetrahydrobenz[cd]indole

A SIMPLE FOUR STEP SYNTHESIS AND OPTICAL RESOLUTION OF 4-NITRO-1, 3, 4, 5-TETRAHYDROBENZ[*cd*]INDOLE, AND THE SYNTHESES OF 1-HYDROXY DERIVATIVES OF 4-NITRO- AND 4-AMINO-1, 3, 4, 5-TETRAHYDROBENZ[*cd*]INDOLES[1]

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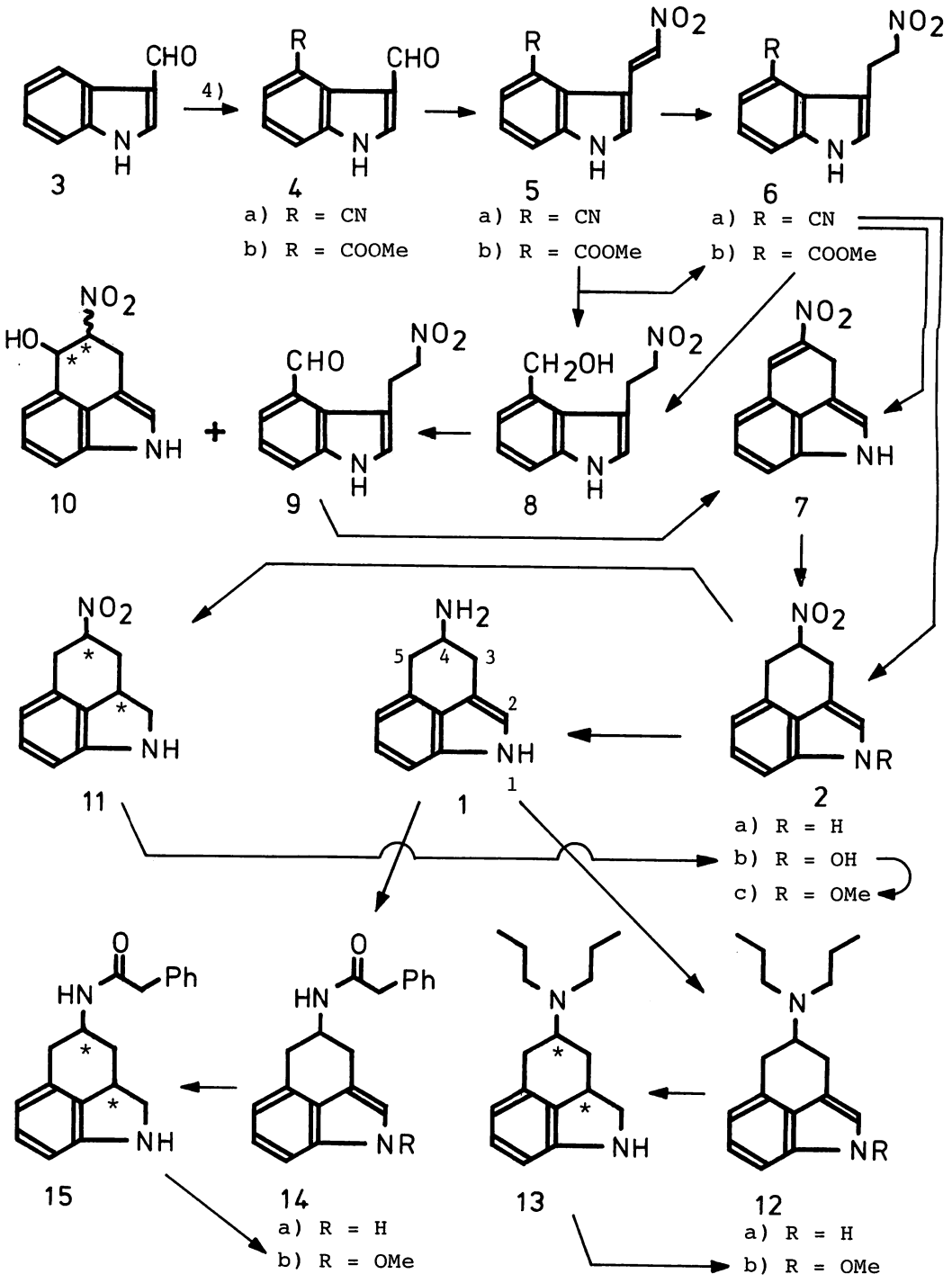
Abstract ——— 4-Nitro-1, 3, 4, 5-tetrahydrobenz[*cd*]indole was synthesized from indole-3-carboxaldehyde in four steps with an overall yield of 30%. Optical resolution of its enantiomers by chiral column chromatography was successful. Syntheses of 1-hydroxy derivatives of 4-nitro- and 4-amino-1, 3, 4, 5-tetrahydrobenz[*cd*]indoles are also reported.

Various biologically active compounds[2] have been derived from 4-amino-1, 3, 4, 5-tetrahydrobenz[*cd*]indole (**1**, Scheme 1) as a parent compound, and much efforts have been devoted on developing a simple synthetic method for **1**.[2] Its shortest synthetic route among thus far known[2,3] is the one through indole-4-carboxaldehyde[3] using 2-methyl-3-nitrobenzoic acid as a starting material. Nevertheless, it still requires cumbersome nine steps with low overall yield.[2]

In this communication, we describe a simple four step synthetic method of 4-nitro-1, 3, 4, 5-tetrahydrobenz[*cd*]indole[2g] (**2a**), a synthetic precursor of **1**, from indole-3-carboxaldehyde (**3**). We also succeeded in the optical res-

Scheme 1


CHO
4)
R
CHO
NO2
R
NO2
R
3
4
a) R = CN
b) R = COOMe
5
a) R = CN
b) R = COOMe
6
a) R = CN
b) R = COOMe
NO2
HO
NH
10
CHO
NO2
9
CH2OH
NO2
8
NO2
NH
7
NO2
NH
11
NH2
5 4 3
2
NH
1
1
NO2
NR
2
a) R = H
b) R = OH
c) R = OMe
O
HN
Ph
NH
15
O
HN
Ph
NR
14
a) R = H
b) R = OMe
N
NH
13
N
NR
12
a) R = H
b) R = OMe

olution of both enantiomers of **2a** by chiral column chromatography and in the syntheses of 1-hydroxy derivatives of 4-nitro- and 4-amino-1,3,4,5-tetrahydrobenz[*cd*]indoles.

I. A simple four step synthesis of 4-nitro-1,3,4,5-tetrahydrobenz[*cd*]-indole (**2a**)

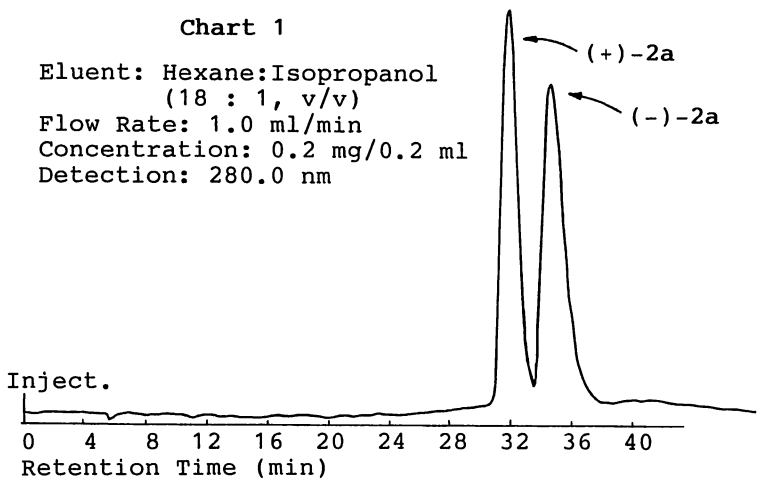
4-Cyano-3-(2-nitroethyl)indole (**6a**) was prepared through **4a** and **5a** in three steps from **3**, according to the reported procedure[4] in 53% oveall yield. Next, sequential treatment of **6a**, initially with diisobutylaluminum hydride (DIBAL) in anhydrous tetrahydrofuran (THF) at room temperature for 30 min, then with methanol (MeOH)-water at reflux for 30 min, was found to produce 1,3-dihydro-4-nitrobenz[*cd*]indole (**7**, mp 190-190.5°C) in 52% yield. Since the compound (**7**) was cleanly reduced to **2a** (mp 138.5-139°C, lit.,[2g] mp 134-135°C) in 80% yield with sodium borohydride ($NaBH_4$) in MeOH, the attempt at effecting one pot conversion of **6a** to **2a** was readily attained in 57% yield by adding the $NaBH_4$ reduction procedure to the above DIBAL and MeOH-water treatment. Consequently, a simple four step synthetic method for **2a** from **3** with an overall yield of 30% was established with the originality rate[5] of 60%. However, every attempt to convert **5a** into **2a** in one pot operation was unsuccessful at present. Finally, **2a** was reduced to **1** (mp 125-126°C, lit.,[2g] mp 119-121°C) with amalgamated zinc-aqueous hydrogen chloride at reflux in 99.5% yield.

Alternatively, the compound (**7**) could be prepared by the following route. 4-Methoxycarbonylindole-3-carboxaldehyde (**4b**), obtained in 53% yield from **3** by one pot procedure,[4] was converted into 4-methoxycarbonyl-3-(2-nitrovinyl)indole (**5b**, mp 121-122°C) in 91% yield by the aldol reaction with nitromethane. Subsequent reduction of **5b** with $NaBH_4$ in *N,N*-dimethylformamide-MeOH afforded 4-methoxycarbonyl-3-(2-nitroethyl)indole (**6b**, mp 106-107 °C) in 83% yield. DIBAL (3 mol eq.) reduction of **6b** in THF afforded 4-hydroxymethyl-3-(2-nitroethyl)indole (**8**, mp 118-119°C) in 99% yield, nevertheless attempts to convert **5b** directly to **8** by DIBAL (3 mol eq.) reduc-

tion were unsuccessful, giving **6b** in 31% yield in addition to 35% yield of starting material. On the other hand, lithium borohydride ($LiBH_4$) reduction of **5b** in THF at reflux did not realize complete conversion of **5b** into **8**, instead **6b** and **8** were produced in 36 and 33% yields, respectively. Similar behavior was observed on the reduction of **6b** with $LiBH_4$ (20 mol eq.), resulting in the formation of **8** in 31% yield together with 55% yield of recovery. Though oxidation of **8** with either active manganese dioxide or dimethyl sulfoxide-acetic anhydride afforded poor results, pyridinium chlorochromate (3 mol eq.) in pyridine produced 3-(2-nitroethyl)indole-4-carboxaldehyde (**9**, mp 159-160°C) and 5-hydroxy-4-nitro-1,3,4,5-tetrahydrobenz[*cd*]indole (**10**, as a mixture of diastereoisomers) in 32 and 13% yields, respectively. Subsequent treatment of **9** with triethylamine in MeOH at reflux for 1 h afforded **7** in 87% yield.

Ⅱ. Optical resolution of 4-nitro-1,3,4,5-tetrahydrobenz[*cd*]indole (**2a**)

With the desired compound (**2a**) in hand, we next tried its optical resolution on chiral column chromatography, and finally found that (+)-**2a** (mp 126.5-127.0°C, $[\alpha]_D^{23}$ +7.12° (99.5% EtOH, c=0.24)) and (-)-**2a** (mp 125.0-126.0°C, $[\alpha]_D^{23}$ -7.38° (99.5% EtOH, c=0.25)) were separable on chiralpak AS column (Daicel Kagaku) using isopropanol-hexane (1:18, v/v) as an



eluent, and the results are shown in Chart 1. Determination of their absolute configuration and syntheses of optically active derivatives of **2a** and **1** are currently under investigation.

Ⅲ. Syntheses of 1-hydroxy derivatives of 4-nitro- and 4-amino-1, 3, 4, 5-tetrahydrobenz[*cd*]indoles

We suppose that **1**, **2a**, and related indole compounds would be metabolized into the corresponding 1-hydroxyindoles *in vivo*.[1b, 6] Therefore, preparations of the expected compounds are of much interest.

Treatment of **2a** with sodium cyanoborohydride ($NaBH_3CN$) in trifluoroacetic acid (TFA) and acetic acid (AcOH) (2:3 mixture) produced 95% yield of indoline (**11**), which was an inseparable 2:1 mixture of diastereoisomers. Similarly, 4-dipropylamino-1, 3, 4, 5-tetrahydrobenz[*cd*]indole (**12a**), readily obtainable from **1** by treatment with propyl iodide,[2j] was converted to the corresponding indoline (**13**, 6:1 mixture of diastereoisomers) in 86% yield. Subsequent oxidation of **11** with sodium tungstate·dihydrate ($Na_2WO_4 \cdot 2H_2O$) and urea hydrogen peroxide addition compound[6c] ($urea \cdot H_2O_2$) afforded 52% yield of the desired 1-hydroxy-4-nitro-1, 3, 4, 5-tetrahydrobenz[*cd*]indole (**2b**) as prisms (mp 134.0-134.5°C), which could be stored at room temperature for 1 week without any decomposition. The reaction of **2b** with ethereal diazomethane afforded the corresponding 1-methoxy derivative (**2c**) in 64 % yield as a stable oil. By carrying out the above two procedures successively, one pot preparation of **2c** was realized in 33% yield. Similar one pot oxidation of the diastereoisomers (**13**) with $Na_2WO_4 \cdot 2H_2O$ and $urea \cdot H_2O_2$, followed by the methylation of the resultant 1-hydroxyindole with diazomethane afforded 4-dipropylamino-1-methoxy-1, 3, 4, 5-tetrahydrobenz[*cd*]indole (**12b**) in 46% yield as an unstable oil.

On the other hand, treatment of **1** with phenylacetyl chloride afforded 73% yield of amide compound (**14a**, oil). Reduction of **14a** with $NaBH_3CN$ in TFA and AcOH (1:4, v/v) produced the corresponding diastereoisomers, **15a** (mp 159-160°C) and **15b** (oil), in 41 and 47% yields, respectively. Subsequent

oxidation of the mixture of **15a** and **15b** with $Na_2WO_4 \cdot 2H_2O$ and urea$\cdot H_2O_2$, followed by the methylation of the resultant unstable 4-dipropylamino-1-hydroxy-1,3,4,5-tetrahydrobenz[*cd*]indole with dimethyl sulfate and potassium carbonate afforded 40% yield of the desired stable 1-methoxyindole derivative (**14b**, mp 138-139°C).

Reactivity and biological evaluations of the above mentioned 1-hydroxyindole derivatives are in progress.

ACKNOWLEDGMENT

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