SIMPLE SYNTHESES OF 1,3,4,5-TETRAHYDROPYRROLO[4,3,2-DE]-QUINOLINE AND 5-HYDROXY-4-NITROINDOLE (SYNTHETIC STUDY FOR INDOLES HAVING A NITROGEN CONTAINING FUNCTIONAL GROUP AT THE 4-POSITION)[1]

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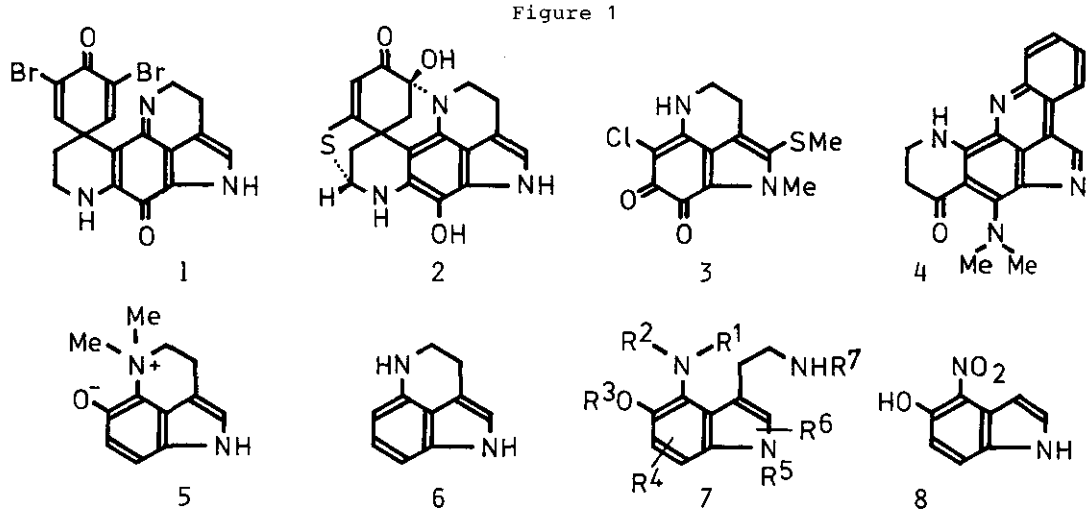
Abstract —— A simple four (or three) step synthesis method for 1,3,4,5-tetrahydropyrrolo[4,3,2-de]quinoline (6) from indole-3-carboxaldehyde (9) is developed. A single step preparation of 5-hydroxy-4-nitroindole (8) by the oxidation of 4-aminoindole (16) is also reported.

Discorhabdins (1),[2] prianosins (2),[3] batzellins (3),[4] plakinidins (4),[5] and dehydrobufotenin (5)[6,7] are biologically active natural products and involve a 1,3,4,5-tetrahydropyrrolo[4,3,2-de]quinoline nucleus as a common structure (Figure 1). In

Figure 1



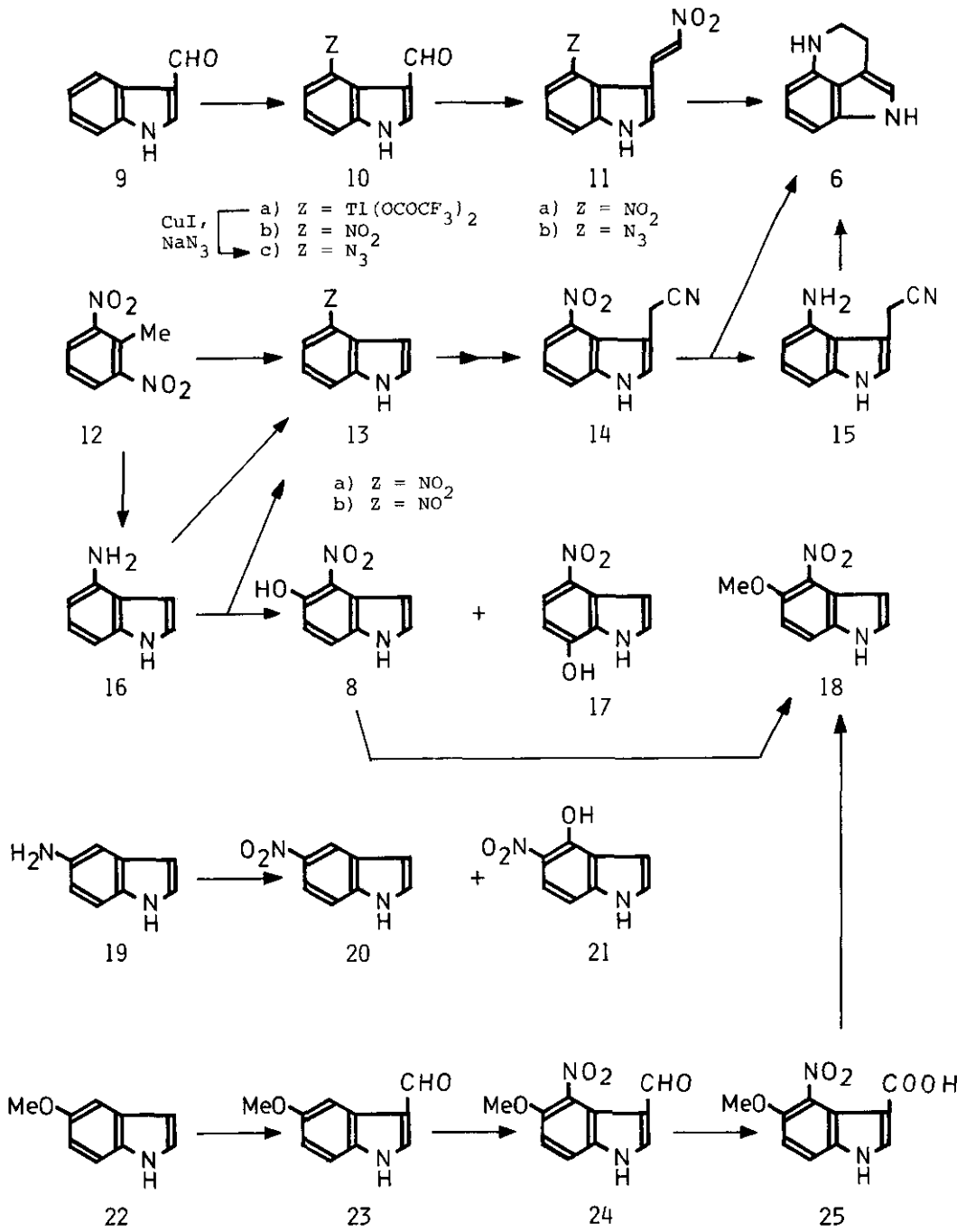
our synthetic projects aimed at the above alkaloids, we settled 1,3,4,5-tetrahydropyrrolo[4,3,2-de]quinoline (6) as a suitable starting material, which is not readily available as yet.[7] On the other hand, much efforts have been focused on the synthesis of serotonin derivatives[8a] because in central nervous system serotonin is believed to control important physiological actions such as anxiety, feeding behavior, sleep, and sexual function.[8b] In order to understand these actions, we needed various 4-amino-5-hydroxytryptamine derivatives (7), hoping that they would be selective ligands which bind to the specific receptor of enzyme. In this communication, we describe simple synthesis methods for both 1,3,4,5-tetrahydropyrrolo[4,3,2-de]quinoline (6) and 5-hydroxy-4-nitroindole (8), which is an important building block for 7.

I. Simple synthesis of 1,3,4,5-tetrahydropyrrolo[4,3,2-de]quinoline (6)

In the previous paper,[9] we have established one pot (or two step) synthesis method for 4-nitro- (10b) and 4-azidoindole-3-carboxaldehyde (10c) from indole-3-carboxaldehyde (9) via thallium compound 10a[10] (Scheme 1). However, the yield (31%) of 10c remained to be improved. Now, we could raise its yield to the extent of 87% only by changing copper catalyst from the originally used[9] cupric sulfate to cuprous iodide in the reaction of 10a with sodium azide in N,N-dimethylformamide-water (1:1, v/v).[9] With 10b and 10c in hand, aldol condensation reaction of them with nitromethane was carried out to afford the corresponding nitrovinyl compounds (11a) and (11b) in 93% and 95% yields, respectively. Subsequent catalytic hydrogenation of 11a or 11b over 10% Pd/C at 70-76°C and 60-70 atm generated the desired 6 in 35% and 19% yields, respectively.

The compound (6) could also be produced by the following alternative route. According to our synthetic method,[11] 4-nitroindole-3-acetonitrile (14) was prepared in 28% overall yield from 2,6-dinitrotoluene (12) through 4-nitro- (13a) and then 3-dimethylaminomethyl-4-nitroindole. In the next step, though Hester[7] claimed the formation of 6 by the catalytic hydrogenation of 14 over 10% Pd/C at 45 psi (3 atm), in our hand we could not obtain 6, instead formation of 4-aminoindole-3-acetonitrile (15) was observed. After examining various reaction conditions, we finally found that catalytic hydrogenation of 14 over 10% Pd/C at 69-73°C and 70-80 atm could generate 6 in 57% yield together with 40% yield of 15. Catalytic hydrogenation of 15 at 90-95 atm was also found to produce 6 in 21% yield together with 71% yield of unreacted 15.

Scheme 1


CHO
Z
NO2
HN
NH
9
10
11
6
CuI, NaN3
a) Z = Tl(OCOCF3)2
b) Z = NO2
c) Z = N3
a) Z = NO2
b) Z = N3
NO2
Me
NO2
CN
NH2
12
13
14
15
a) Z = NO2
b) Z = NO
HO
MeO
OH
16
8
17
18
H2N
O2N
19
20
21
22
23
24
25
COOH

II. Simple synthesis of 5-hydroxy-4-nitroindole (8)

Since we reported the preparation of 4-aminoindole (16) in a single step from 2,6-dinitrotoluene (12) in a quantitative yield,[11] we have investigated its reactivity towards electrophiles (including oxidizing reagents) and recognized that the reactivity at the 3-position was comparatively lowered than that of benzene part. Based on the result, we attempted the oxidation of 16 expecting the generation of the desired 5- (8) and 7-hydroxy-4-nitroindole (17), though oxidation of 2,3-unsubstituted indoles is well known to afford miserable results.[12]

In practice, m-chloroperbenzoic acid (MCPBA) was found to be a reagent of choice for meeting our end, resulting in the formation of 8 and 17, and the representative results are summarized in Table I. We can alternatively obtain 17, which is also an excellent building block for our targets, in a short step in good overall yield from readily available 1-acetyl-2,3-dihydro-7-hydroxyindole[13] and the results will be reported in due course.

Table I. Oxidation of 4-Aminoindole (16) with m-Chloroperbenzoic Acid (MCPBA)

16 ⟶ 13a + 13b + 8 + 17

Run	MCPBA (mol eq.)	Solvent	Reaction Time (min.)	Additives	Yield (%) of 13a	13b	8	17
1	3.0	CH_3COCH_3 and CH_2Cl_2 (1:1, v/v)	35	Phosphate Buffer (pH 7.0)	15	21	14	0
2	5.2	"	35	Sat. $NaHCO_3$ (pH 9)	32	0	16	5
3	"	"	10	"	28	0	20	3
4	"	CH_2Cl_2 only	35	"	12	0	10	0

Similarly, oxidation of 19 with MCPBA gave 5-nitro- (20) and 4-hydroxy-5-nitroindole (21) in 50% and 4% yields, respectively. In contrast, oxidation of 16 with dimethyldioxirane[14] did not produce 8 even in a trace amount, instead 4-nitroindole (13a) was produced in poor yield (3%-17%) together with 4-nitrosoindole (13b, 6%-14%). Although the yields of 8 and 21 are still not satisfactory, we are now investigating to establish optimum reaction conditions and oxidizing reagents.

The structure of 8 was proved unequivocally by the following alternative synthesis. First, 8 was derived to 5-methoxy-4-nitroindole (18) by the reaction with diazo-

methane in 43% yield.[15] On the other hand, Vilsmeier-Haack reaction of commercially available 5-methoxyindole (22) afforded 92% yield of 5-methoxyindole-3-carboxaldehyde (23), which was then converted to 5-methoxy-4-nitroindole-3-carboxaldehyde (24) in 40% yield by the reaction with cupric nitrate in acetic anhydride. Oxidation of 24 with sodium chlorite afforded the corresponding carboxylic acid (25), which was then without purification decarboxylated in refluxing pyridine to afford 18 in 59% overall yield.

In conclusion, we can now produce 1,3,4,5-tetrahydropyrrolo[4,3,2-de]quinoline (6) and 5-hydroxy-4-nitroindole (8) quite easily. Syntheses of 1-5 and serotonin derivatives (7) are currently in progress.

ACKNOWLEDGMENT

This work is partly supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, and Culture of Japan, which is gratefully acknowledged.

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15. Because of the steric hindrance, methylation proceeded very slowly and the unreacted 8 was recovered in 54% yield.

Received, 11th January, 1991