Heterocycles 47(1), 509-516 (1998)

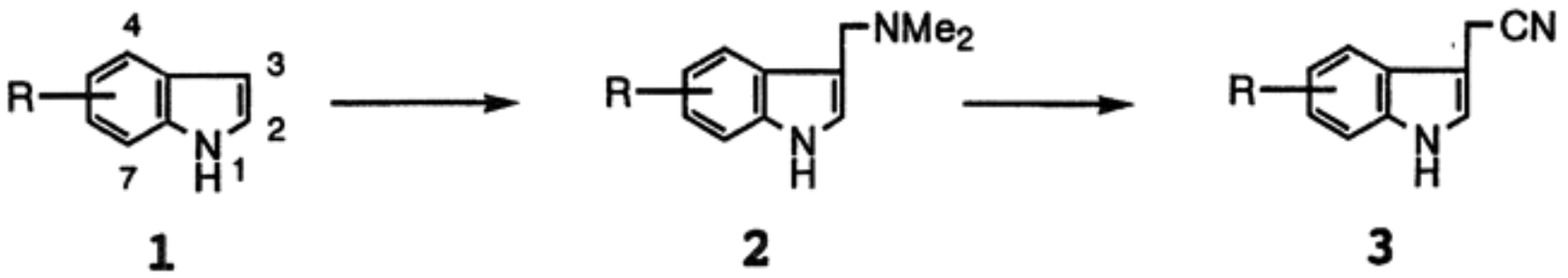
SIMPLE ONE STEP SYNTHESES OF INDOLE-3-ACETONITRILES FROM INDOLE-3-CARBOXALDEHYDES[1]

Fumio Yamada, Tomoko Hashizume, and Masanori Somei*
Faculty of Pharmaceutical Sciences, Kanazawa University,
13-1 Takara-machi, Kanazawa 920, Japan

Abstract ——— One step conversion method of indole-3-carboxaldehydes into indole-3-acetonitriles is developed. Applying the method, 4-nitro- (**7a**), 4-phenyl- (**7b**), 4-iodo- (**7c**), 4-methoxy- (**7d**), and 4-benzyloxyindole-3-acetonitrile (**7e**) are available in two steps from indole-3-carboxaldehyde (**4**).

Indole-3-acetonitriles (**3**) are known not only as plant growth regulators[2] but also as important building blocks for tryptamines and natural products.[3~5] Probably the most common synthesis approach to them is the nucleophilic substitution with cyanide[6] for the dimethylamino group of gramines (**2**) which are readily obtained by Mannich reaction of indoles (**1**), as shown in Scheme 1.

Scheme 1



1 **2** **3**

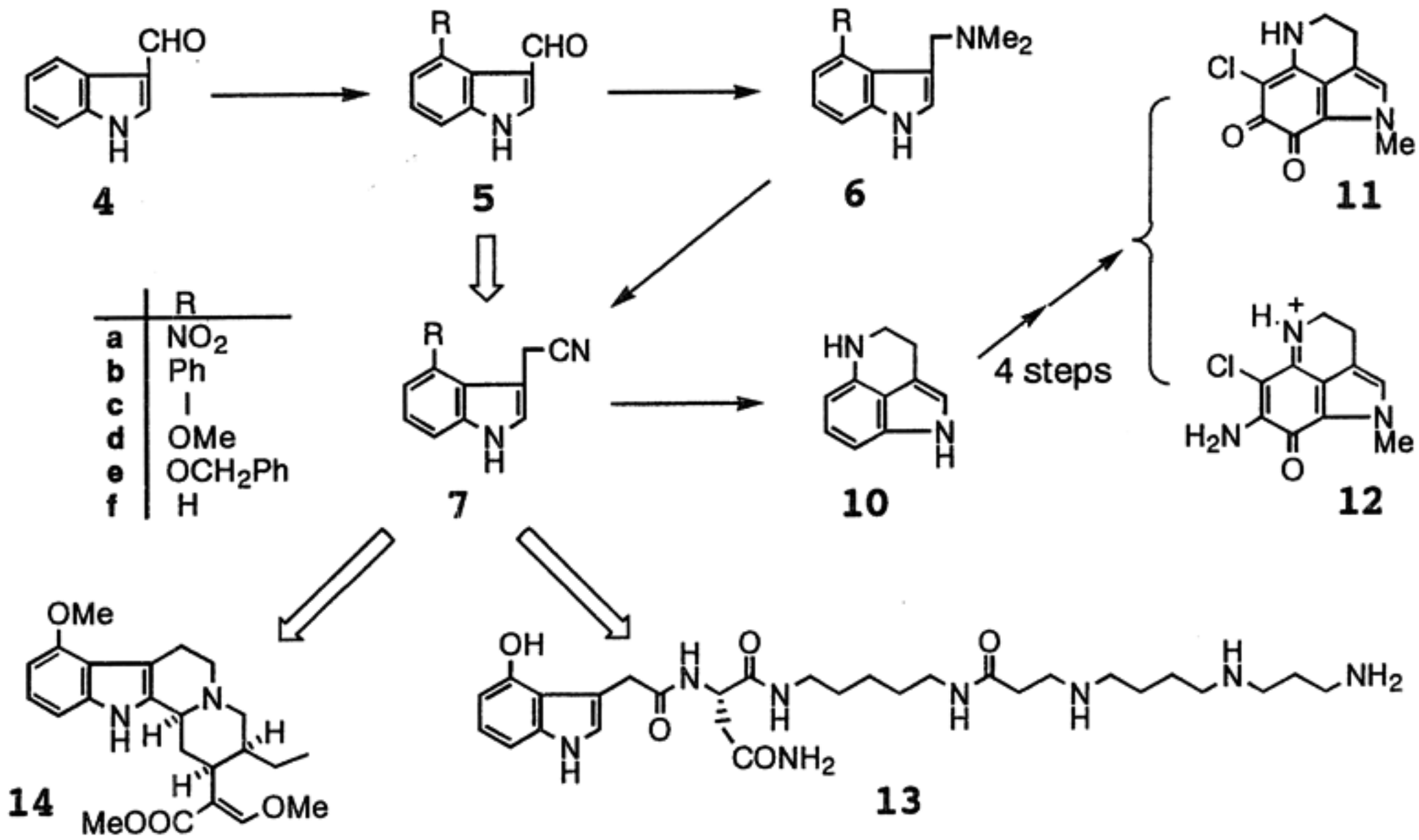
R = An appropriate substituent

On the other hand, even at present, 4-substituted indole-3-acetonitriles (**7**, Scheme 2) are difficult to obtain due to the lack of simple preparation method for 4-substituted gramines (**6**). Our contribution in the indole chemistry has realized one pot syntheses[7] of 4-substituted indole-3-carboxaldehydes (**5**) from indole-3-carboxaldehyde (**4**) and a direct conversion of **5** into **6**.[8] However, the need of one step method for transforming **5** into **7** is still remained, because the method would easily supply valuable building blocks (**7a-e**) and consequently provide a short cut for various natural products syntheses such as batzelline C (**11**),[3] isobatzelline C (**12**),[3] SF 2140,[4] nephilatoxins (**13**),[5] and so on. Now, we wish to report the discovery of the desired reaction.

In order to accumulate basic knowledge, we chose 4-nitroindole-3-carboxaldehyde[9] (**5a**) as a substrate and tested various trials employing cyanating reagents in the presence of reducing agents, such as Me_3SiCl-

NaI-KCN-Et_3SiH, Me_3SiCl-NaI-KCN-$NaBH_4$, Me_3SiCN-$NaBH_4$, and so on. During these studies,[8] we observed that simple treatment of **5a** sequentially with $NaBH_4$, and then with NaCN in MeOH, produced 4-nitroindole-3-acetonitrile[9] (**7a**) and 4-nitroindole[9,10] (**8**). Based on the finding, further examinations of the reaction conditions were carried out, and the combination of about 1.3 mol eq. of $NaBH_4$ and about 10 mol eq. of NaCN was found to be suitable for our purposes as shown in Table 1 (Entry 1), affording **7a** and **8** in 36 and 53% yields, respectively. Furthermore, when the solvent was changed to MeOH-MeNHCHO (1:1, v/v), the yield of **7a** increased slightly (Entry 2). Change in solvent to MeOH-DMF (1:1, v/v) increased the yield of **7a** to 62% (Entry 3). It is interesting to note that NH_2CHO dramatically suppressed the formation of **8** and the yield of **7a** was improved (Entry 4) in comparison with the results of Entries 1 and 2. Therefore, various mixed solvents using MeOH and NH_2CHO were examined and finally 1:1 mixture of MeOH-NH_2CHO was found to be a solvent of choice, producing **7a** in 88% yield together with *N*-(4-nitroindol-3-yl)methylformamide (**9a**) as a by-product in 9% yield (Entry 5). When the same reaction was carried out without NaCN, **9a** was exclusively produced in 75% yield together with 4% yield of **8**. Under similar reaction conditions, **9 b-f** were prepared in 68, 72, 57, 62, and 64% yields, respectively.

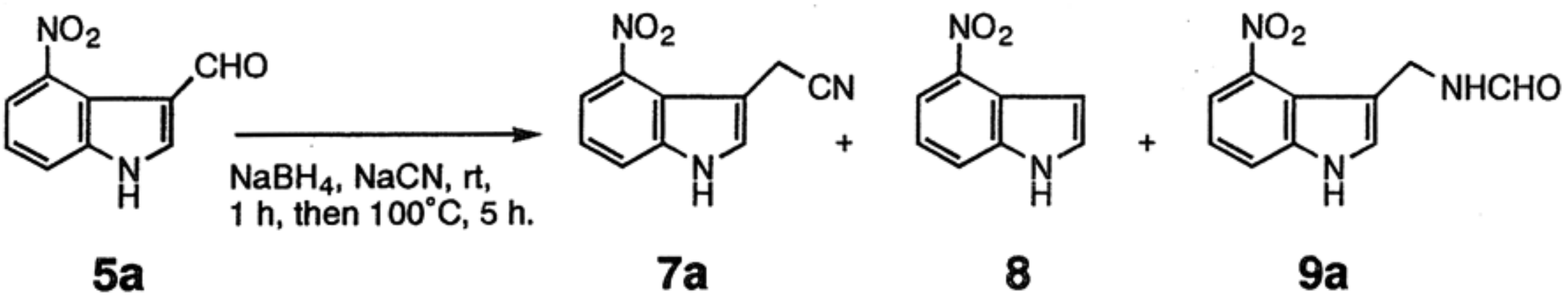
Scheme 2



Employing the above reaction conditions, various indole-3-acetonitriles (**7b-f**) having phenyl, halogen, oxygen functional groups, were obtained in excellent to good yields as shown in Table 2 in one step from the corresponding indole-3-carboxaldehydes (**5b-f**) together with a small amount of **9b-f**, respectively.

Thus, we succeeded in developing a simple one step conversion method of indole-3-carboxaldehydes into

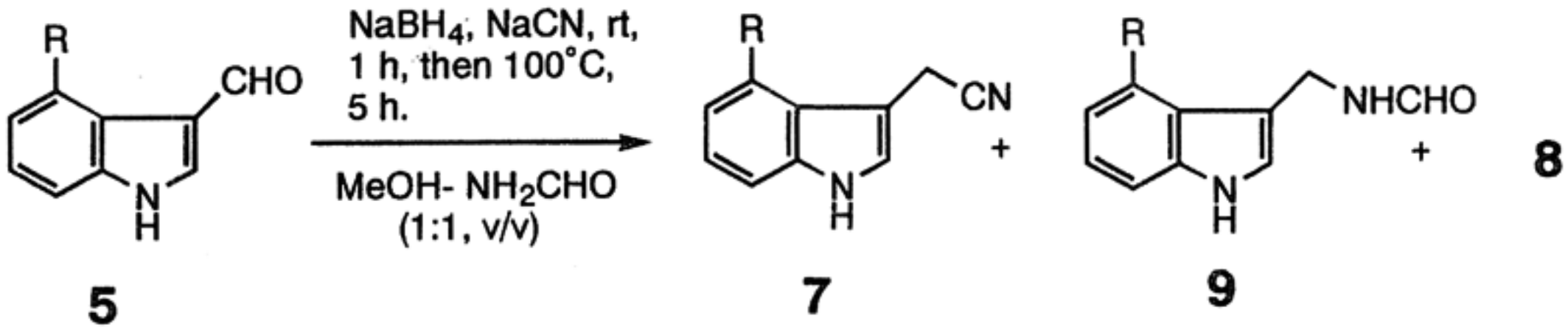
Table 1



5a **7a** **8** **9a**

Entry	Solvent	Yield (%) of 7a	8	9a
1	MeOH	36	53	0
2	MeOH-MeNHCHO (1:1, v/v)	52	27	0
3	MeOH-DMF (1:1, v/v)	62	31	0
4	NH_2CHO	61	6	3
5	MeOH-NH_2CHO (1:1, v/v)	88	2	9
6	MeOH-NH_2CHO (1:7, v/v)	69	9	5

Table 2



5 **7** **9**

	R	Yield (%) of 7	9	8
a	NO_2	88	9	2
b	Ph	89	5	0
c	I	88	7	0
d	OMe	86	11	0
e	OCH_2Ph	89	9	0
f	H	95	4	0

indole-3-acetonitriles. Owing to the present method, 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline[3,8] (**10**) is obtained from **4** in three steps and our previous eight steps synthesis of marine alkaloids, batzelline C[3] (**11**) and isobatzelline C (**12**),[3] become shorter by one step (Scheme 2). The present two steps synthesis of 4-benzyloxyindole-3-acetonitrile (**7e**) from **4** could substitute for an expensive four steps synthesis[5] of **7e** from 4-hydroxyindole and would be utilized for the synthetic studies of nephillatoxins such as **13**.[5] 4-Methoxyindole-3-acetonitrile (**7d**), the aglycon of SF 2140,[4] is now available in only two steps from **4** and could be applied for the syntheses of Mitragyna alkaloids such as **14**.[11]
The present method is widely applicable for effective syntheses of indole natural products.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were determined with a Shimadzu IR-420 spectrophotometer, and proton nuclear magnetic resonance (^{1}H-NMR) spectra with a JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a JEOL SX-102A spectrometer. Preparative thin-layer chromatography was performed on Merck Kiesel-gel GF_{254} (Type 60)(SiO_2). Column chromatography was performed on silica gel (SiO_2, 100-200 mesh, from Kanto Chemical Co. Inc.).

General procedure ------- $NaBH_4$ (1.3 mol eq.) was added to a solution of indole-3-carboxaldehyde in MeOH and NH_2CHO. After stirring at rt for 1 h, NaCN (10 mol eq.) was added to the reaction mixture and the whole was refluxed on oil bath at 100°C for 5 h with stirring. After cooling, brine was added and the whole was extracted with MeOH-$CHCl_3$ (5:95, v/v). The organic layer was washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to leave the residue, which was column chromatographed on SiO_2 with an appropriate solvent as an eluent.

4-Nitroindole-3-acetonitrile (7a), 4-nitroindole (8), and *N*-(4-nitroindol-3-yl)methyl-formamide (9a) from 4-nitroindole-3-carboxaldehyde (5a): Table 1, Entry 5 ---------- In the general procedure, 23.4 mg (0.619 mmol) of $NaBH_4$, 86.0 mg (0.453 mmol) of **5a**,[7g] 4 mL of MeOH and 4 mL of NH_2CHO, 230.5 mg (4.70 mmol) of NaCN were used. The residue was column chromatographed on SiO_2 with $CHCl_3$ and then MeOH-$CHCl_3$ (5:95, v/v) as an eluent to give **8** (1.8 mg, 2%) as the early part of the fractions. From the middle part, **7a** (80.0 mg, 88%) was obtained. From the later part, **9a** (8.5 mg, 9%) was obtained. **7a** and **8** are identical with the authentic samples prepared according to our procedures.[9,10] **9a**: mp 224.0-225.0°C (yellow needles, recrystallized from MeOH). IR (KBr): 3330, 3270, 1623, 1509, 1317 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 27°C, rotational isomers existed) δ: 4.53 (16/9H, d, *J*=5.4 Hz), 4.57 (2/9H, d, *J*=6.1 Hz), 7.28 (1H, t, *J*=8.1 Hz), 7.61 (1/9H, d, *J*=2.2 Hz), 7.63 (8/9H, d, *J*=2.2 Hz), 7.83 (8/9H, dd, *J*=8.1 and 1.0 Hz), 7.84 (1/9H, dd, *J*=8.1 and 1.0 Hz), 7.86 (1/9H, dd, *J*=8.1 and 1.0 Hz), 7.88 (8/9H, dd, *J*=8.1 and 1.0 Hz), 8.00 (8/9H, dt, *J*=2.0 and 1.0 Hz), 8.06 (1/9H, d, *J*=11.7 Hz), 8.16 (1H, br s, disappeared on addition of D_2O), 11.88 (1H,

br s, disappeared on addition of D_2O). MS *m/z* : 219 (M^+). *Anal.* Calcd for $C_{10}H_9N_3O_3$: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.70; H, 4.15; N, 19.08.

4-Phenylindole-3-acetonitrile (7b) and *N*-(4-phenylindol-3-yl)methylformamide (9b) from 4-phenylindole-3-carboxaldehyde (5b) ---------- In the general procedure, 22.6 mg (0.597 mmol) of $NaBH_4$, 102.8 mg (0.465 mmol) of **5b**,[7b,d] 4 mL of MeOH and 4 mL of NH_2CHO, 230.8 mg (4.71 mmol) of NaCN were used. The residue was column chromatographed on SiO_2 with $CHCl_3$ and then MeOH-$CHCl_3$ (5:95, v/v) as an eluent to give **7b** (96.1 mg, 89%) as the early part of the fractions. From the later part, **9b** (5.6 mg, 5%) was obtained. **7b**: colorless oil. IR (film): 3380, 3320, 2250, 1611, 1484, 1411, 1335 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.25 (2H, d, *J*=1.2 Hz), 7.03 (1H, dd, *J*=7.2 and 1.0 Hz), 7.27 (1H, dd, *J*=8.1 and 7.2 Hz), 7.31 (1H, dt, *J*=2.4 and 1.2 Hz), 7.39-7.48 (6H, m), 8.32 (1H, br s). High resolution MS *m/z*: Calcd for $C_{16}H_{12}N_2$: 232.1001. Found: 232.1000. **9b**: mp 197.0-198.0°C (colorless leaves, recrystallized from MeOH). IR (KBr): 3270, 3150, 1631, 1532, 1355 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 27°C, rotational isomers existed) δ: 3.86 (14/8H, d, *J*=5.4 Hz), 3.94 (2/8H, d, *J*=6.1 Hz), 6.82 (7/8H, dd, *J*=7.1 and 1.0 Hz), 6.84 (1/8H, dd, *J*=7.1 and 1.0 Hz), 7.13 (7/8H, dd, *J*=8.1 and 7.1 Hz), 7.14 (1/8H, dd, *J*=8.1 and 7.1 Hz), 7.23 (7/8H, dt, *J*=2.4 and 1.2 Hz), 7.25 (1/8H, s), 7.34-7.48 (50/8H, m), 7.86 (7/8H, s), 7.87 (7/8H, br s, disappeared on addition of D_2O), 11.16 (7/8H, br s, disappeared on addition of D_2O), 11.19 (1/8H, br s, disappeared on addition of D_2O). MS *m/z*: 250 (M^+). *Anal.* Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.62; H, 5.60; N, 11.15.

4-Iodoindole-3-acetonitrile (7c) and *N*-(4-iodoindol-3-yl)methylformamide (9c) from 4-iodoindole-3-carboxaldehyde (5c) ---------- In the general procedure, 21.0 mg (0.555 mmol) of $NaBH_4$, 121.0 mg (0.447 mmol) of **5c**,[7a,c] 4 mL of MeOH and 4 mL of NH_2CHO, 226.0 mg (4.61 mmol) of NaCN were used. The residue was column chromatographed on SiO_2 with MeOH-$CHCl_3$ (1:99, v/v) and then MeOH-$CHCl_3$ (5:95, v/v) as an eluent to give **7c** (111.3 mg, 88%) as the early part of the fractions. From the later part, **9c** (9.9 mg, 7%) was obtained. **7c** is identical with the authentic samples prepared according to our procedures.[9] **9c**: mp 207.0-209.0°C (colorless needles, recrystallized from MeOH). IR (KBr): 3270, 3120, 1628, 1532, 1353 cm^{-1}. ^{1}H-NMR (DMSO-d_6, 27°C, rotational isomers existed) δ: 4.65 (20/11H, d, *J*=5.4 Hz), 4.74 (2/11H, d, *J*=5.9 Hz), 6.83 (1H, dd, *J*=8.1 and 7.6 Hz), 7.32 (1/11H, d, *J*=2.2 Hz), 7.37 (10/11H, d, *J*=2.7 Hz), 7.42 (1H, dd, *J*=8.1 and 1.0 Hz), 7.46 (1/11H, dd, *J*=7.6 and 1.0 Hz), 7.47 (10/11H, dd, *J*=7.6 and 1.0 Hz), 7.86 (1/11H, br s,. disappeared on addition of D_2O), 8.07 (10/11H, dt, *J*=2.0 and 1.0 Hz), 8.17 (1/11H, d, *J*=11.7 Hz), 8.21 (10/11H, br s, disappeared on addition of D_2O), 11.28 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 300 (M^+). *Anal.* Calcd for $C_{10}H_9IN_2O$: C, 40.02; H, 3.02; N, 9.33. Found: C, 40.06; H, 2.99; N, 9.09.

4-Methoxyindole-3-acetonitrile (7d) and *N*-(4-methoxyindol-3-yl)methylformamide (9d) from 4-methoxyindole-3-carboxaldehyde (5d) ---------- In the general procedure, 23.0 mg

(0.608 mmol) of $NaBH_4$, 80.4 mg (0.459 mmol) of **5 d**,[7a] 4 mL of MeOH and 4 mL of NH_2CHO, 223.8 mg (4.57 mmol) of NaCN were used. The residue was column chromatographed on SiO_2 with $CHCl_3$ as an eluent to give **7 d** (73.5 mg, 86%) as the early part of the fractions. From the later part, **9 d** (10.2 mg, 11%) was obtained. **7 d**: mp 145.0-146.0°C (colorless prisms, recrystallized from $CHCl_3$-hexane). IR (KBr): 3360, 2270, 1617, 1590, 1509, 1355, 1260, 1091, 752, 733 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 3.92 (3H, s), 4.05 (2H, d, *J*=1.1 Hz), 6.50 (1H, d, *J*=8.0 Hz), 6.96 (1H, d, *J*=8.0 Hz), 7.09 (1H, dt, *J*=2.2 and 1.1 Hz), 7.12 (1H, t, *J*=8.0 Hz), 8.08 (1H, br s, disappeared on addition of D_2O). MS *m/z*: 186 (M^+). *Anal.* Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.98; H, 5.41; N, 15.11. **9 d**: mp 190.0-192.0°C (colorless prisms, recrystallized from MeOH). IR (KBr): 3230, 3180, 1635, 1354 cm^{-1}. ^1H-NMR (DMSO-d_6, 27°C, rotational isomers existed) δ: 3.84 (3H, s), 4.49 (2/6H, d, *J*=6.1 Hz), 4.51 (10/6H, d, *J*=5.6 Hz), 6.46 (1H, dd, *J*=7.6 and 0.7 Hz), 6.93 (5/6H, dd, *J*=8.1 and 1.0 Hz), 6.94 (1/6H, dd, *J*=8.1 and 1.0 Hz), 6.98 (5/6H, dd, *J*=8.1 and 7.6 Hz), 6.99 (1/6H, dd, *J*=8.1 and 7.6 Hz), 7.06 (1H, d, *J*=2.4 Hz), 7.72 (1/6H, br s, disappeared on addition of D_2O), 8.04 (5/6H, d, *J*=1.7 Hz), 8.05 (5/6H, br s, disappeared on addition of D_2O), 8.12 (1/6H, d, *J*=11.7 Hz), 10.88 (5/6H, br s, disappeared on addition of D_2O), 10.90 (1/6H, br s, disappeared on addition of D_2O). MS *m/z*: 204 (M^+). *Anal.* Calcd for $C_{11}H_{12}N_2O_2 \cdot 1/8H_2O$: C, 63.99; H, 5.98; N, 13.57. Found: C, 63.91; H, 5.87; N, 13.33.

4-Benzyloxyindole-3-acetonitrile (7e) and *N*-(4-methoxyindol-3-yl)methylformamide (9e) from 4-benzyloxyindole-3-carboxaldehyde (5e) ---------- In the general procedure, 26.2 mg (0.693 mmol) of $NaBH_4$, 111.0 mg (0.442 mmol) of **5 e**,[7a] 4 mL of MeOH and 4 mL of NH_2CHO, 222.7 mg (4.54 mmol) of NaCN were used. The residue was column chromatographed on SiO_2 with $CHCl_3$ and then MeOH-$CHCl_3$ (5:95, v/v) as an eluent to give **7 e** (102.8 mg, 89%) as the early part of the fractions. From the later part, **9 e** (11.2 mg, 9%) was obtained. **7 e**: mp 84.0-86.0°C (colorless needles, recrystallized from benzene). IR (KBr): 3380, 2260, 1616, 1590, 1507, 1261 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 4.02 (2H, d, *J*=1.2 Hz), 5.18 (2H, s), 6.59 (1H, d, *J*=7.8 Hz), 6.99 (1H, d, *J*=8.1 Hz), 7.11 (1H, dd, *J*=8.1 and 7.8 Hz), 7.12 (1H, dt, *J*=2.4 and 1.2 Hz), 7.35 (1H, br t, *J*=7.3 Hz), 7.42 (2H, br t, *J*=7.3 Hz), 7.49 (2H, br d, *J*=7.3 Hz), 8.12 (1H, br s). MS *m/z*: 262 (M^+). *Anal.* Calcd for $C_{17}H_{14}N_2O$: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.83; H, 5.39; N, 10.37. **9 e**: colorless oil. IR (film): 3370, 3260, 1661, 1502, 1260 cm^{-1}. ^1H-NMR (DMSO-d_6, 27°C, rotational isomers existed) δ: 4.51 (2/7H, d, *J*=6.1 Hz), 4.54 (12/7H, d, *J*=5.4 Hz), 5.20 (2H, s), 6.54-6.59, (1H, m), 6.94-6.99 (2H, m), 7.06 (1/7H, d, *J*=2.4 Hz), 7.08 (6/7H, d, *J*=2.4 Hz), 7.29-7.43 (3H, m), 7.52 (2H, br d, *J*=7.6 Hz), 7.70 (1/7H, br s, disappeared on addition of D_2O), 7.96 (1/7H, d, *J*=11.7 Hz), 8.02 (6/7H, dt, *J*=2.0 and 1.0 Hz), 8.08 (6/7H, br s, disappeared on addition of D_2O), 10.93 (1H, br s, disappeared on addition of D_2O). High resolution MS *m/z*: Calcd for $C_{17}H_{16}N_2O_2$: 280.1212. Found: 280.1208.

Indole-3-acetonitrile (7f) and *N*-(indol-3-yl)methylformamide (9f) from indole-3-car-

boxaldehyde (5f) ---------- In the general procedure, 23.4 mg (0.619 mmol) of $NaBH_4$, 68.4 mg (0.472 mmol) of **5 f**, 4 mL of MeOH and 4 mL of NH_2CHO, 237.0 mg (4.84 mmol) of NaCN were used. The residue was column chromatographed on SiO_2 with $CHCl_3$ and then MeOH-$CHCl_3$ (5:95, v/v) as an eluent to give **7 f** (70.1 mg, 95%) as the early part of the fractions. From the later part, **9 f** (3.6 mg, 4%) was obtained. **7 f** was identical with the commercially available sample. **9 f**: colorless oil. IR (film): 3370, 3260, 1656 cm^{-1}. ^1H-NMR (DMSO-d_6, 27°C, rotational isomers existed) δ: 4.42 (2/10H, d, *J*=5.9 Hz), 4.43 (18/10H, d, *J*=5.9 Hz), 6.99 (9/10H, ddd, *J*=8.1, 7.1, and 1.0 Hz), 7.00 (1/10H, ddd, *J*=8.1, 7.1, and 1.0 Hz), 7.08 (9/10H, ddd, *J*=8.1, 7.1, and 1.0 Hz), 7.09 (1/10H, ddd, *J*=8.1, 7.1, and 1.0 Hz), 7.24 (1/10H, d, *J*=2.4 Hz), 7.26 (9/10H, d, *J*=2.4 Hz), 7.35 (9/10H, dt, *J*=8.1 and 1.0 Hz), 7.36 (1/10H, dt, *J*=8.1 and 1.0 Hz), 7.54 (9/10H, br d, *J*=8.1 Hz), 7.56 (1/10H, br d, *J*=8.1 Hz), 8.04 (1/10H, br s, disappeared on addition of D_2O), 8.06 (9/10H, dt, *J*=2.0 and 1.0 Hz), 8.21 (1/10H, d, *J*=11.7 Hz), 8.25 (9/10H, br s, disappeared on addition of D_2O), 10.91 (1H, br s, disappeared on addition of D_2O). High resolution MS *m/z*: Calcd for $C_{10}H_{10}N_2O$: 174.0793. Found: 174.0793.

***N*-(4-Nitroindol-3-yl)methylformamide (9a) from 4-nitroindole-3-carboxaldehyde (5a)** ---------- In the general procedure, 25.0 mg (0.661 mmol) of $NaBH_4$, 86.0 mg (0.453 mmol) of **5a**, 4 mL of MeOH, and 4 mL of NH_2CHO were used. After stirring at room temperature for 1 h, the whole was refluxed on oil bath at 100°C for an additional 12 h with stirring. The residue was recrystallized from MeOH to afford **9a** as yellow needles (50.3 mg). Mother liquor was purified by column chromatography on SiO_2 with $CHCl_3$ and then MeOH-$CHCl_3$ (5:95, v/v) as an eluent to give **8** (3.2 mg, 4%) as the early part of the fractions. From the later part, **9a** (24.2 mg) was obtained. Total yield of **9a** was 74.5 mg (75%).

Similar experiments starting from **5 b-f** afforded **9 b-f** in 68, 72, 57, 62, and 64% yields, respectively.

REFERENCES AND NOTES

1. a) Dedicated to the 75th birthday of Dr. Koji Nakanishi. b) This is Part 83 of a series entitled "The Chemistry of Indoles". Part 82: M. Somei and K. Nakagawa, *Heterocycles*, 1997, **45**, submitted.
2. E. R. H. Jones and W. C. Taylor, *Nature*, 1957, **179**, 1138; T. Okamoto, Y. Isogai, T. Koizumi, H. Fujishiro, and Y. Sato, *Chem. Pharm. Bull.*, 1967, **15**, 163; M. Nomoto and S. Tamura, *Agr. Biol. Chem.*, 1970, **34**, 1590; D. Edgerton, A. Tropsha, and A. M. Jones, *Phytochemistry*, 1994, **35**, 1111 and references cited therein.
3. F. Yamada, S. Hamabuchi, A. Shimizu, and M. Somei, *Heterocycles*, 1995, **41**, 1905 and references cited therein.
4. T. Ito, K. Ohba, M. Koyama, M. Sezaki, H. Tohyama, T. Shomura, H. Fukuyasu, Y. Kazuno, T. Niwa, M. Kojima, and T. Niida, *J. Antibiotics*, 1984, **37**, 931; J. G. Buchanan, J. Stoddart, and R. H. Wightman, *J. Chem. Soc., Chem. Commun.*, 1989, 823. Synthetic work of the sugar part of

SF2140: D. Fattori and P. Vogel, *Tetrahedron*, 1992, **48**, 10587.

5. T. Shinada, M. Miyachi, Y. Itagaki, H. Naoki, K. Yoshihara, and T. Nakajima, *Tetrahedron Lett.*, 1996, **37**, 7099 and references cited therein.
6. R. J. Sundberg, "The Chemistry of Indoles", Academic Press, New York, 1970; R. T. Brown, J. A. Joule, and P. G. Sammes, "Comprehensive Organic Chemistry", Vol. 4, ed. by P. G. Sammes, Pergamon Press, Oxford, 1979, pp. 411-492; R. J. Sundberg, "Indoles", Academic Press, New York, 1996.
7. a) M. Somei, F. Yamada, M. Kunimoto, and C. Kaneko, *Heterocycles*, 1984, **22**, 797; b) M. Somei, H. Amari, and Y. Makita, *Chem. Pharm. Bull.*, 1986, **34**, 3971; c) F. Yamada and M. Somei, *Heterocycles*, 1987, **26**, 1173; d) M. Somei, F. Yamada, and K. Naka, *Chem. Pharm. Bull.*, 1987, **35**, 1322; e) M. Somei, M. Wakida, and T. Ohta, *ibid.*, 1988, **36**, 1162; f) M. Somei, T. Ohta, J. Shinoda, and Y. Somada, *Heterocycles*, 1989, **29**, 653; g) M. Somei, F. Yamada, H. Hamada, and T. Kawasaki, *ibid.*, 1989, **29**, 643; h) Review: M. Somei, *Yakugaku Zasshi*, 1988, **108**, 361 and references cited therein.
8. F. Yamada, K. Kobayashi, A. Shimizu, N. Aoki, and M. Somei, *Heterocycles*, 1993, **36**, 2783 and references cited therein.
9. M. Somei, K. Kizu, M. Kunimoto, and F. Yamada, *Chem. Pharm. Bull.*, 1985, **33**, 3696.
10. M. Somei and M. Tsuchiya, *Chem. Pharm. Bull.*, 1981, **29**, 3145. Other literatures for the preparation of 4-nitroindole are summarized in the reference of 8.
11. C. M. Lee, W. F. Trager, and A. H. Beckett, *Tetrahedron*, 1967, **23**, 375; H. M-Manga, J. Q-Leclerco, G. Llabres, M-L. B-Pinheiro, A. F. I. Da Rocha, and L. Angenot, *Phytochemistry*, 1996, **43**, 1125.