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| 著者 | Yamada Fumio, Tamura Mayumi, Somei Masanori |
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A FIVE-STEP SYNTHESIS OF PSILOCIN FROM INDOLE-3-CARBALDEHYDE¹

Fumio Yamada, Mayumi Tamura, and Masanori Somei*

Faculty of Pharmaceutical Sciences, Kanazawa University,

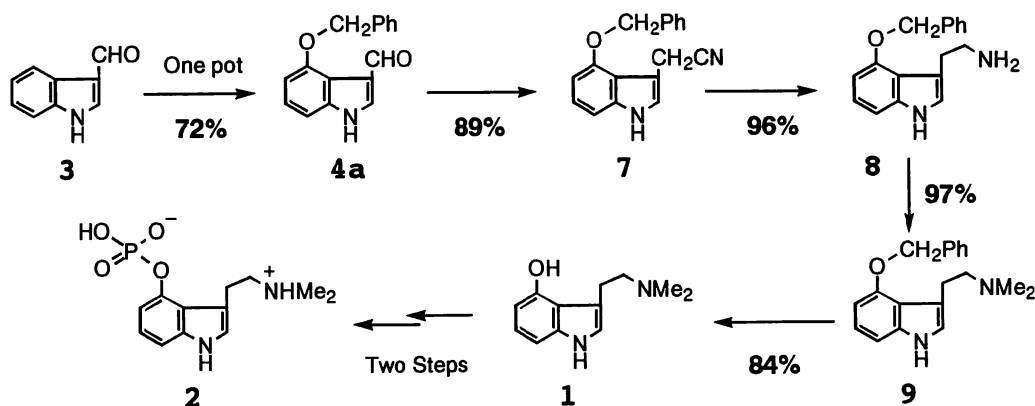
13-1 Takara-machi, Kanazawa 920-0934, Japan

Abstract ————— A novel preparative method of psilocin was established in only five steps from indole-3-carbaldehyde in 50% overall yield.

Psilocin² (**1**, Scheme 1) and psilocybin² (**2**) are known to enter the central nervous system through the gastrointestinal tract³ and cause powerful psychotomimetic effect.²⁻⁴ Although considerable efforts^{2,4} have been devoted to the syntheses of psilocin analogs, there still remains to establish structure-activity relationships. While, recently, psychotic diseases such as depression, schizophrenia, Alzheimer's disease, and so on, are becoming social problems and the development for their medicines has been waited. With a hope to find a lead compound among psilocin analogs possessing suitable pharmacological effects, we have needed an effective preparative method of **1** which makes it possible to pursue systematic structure-activity relationship studies. In this paper, we wish to report the desired five-step preparative method of **1** from indole-3-carbaldehyde (**3**) as shown in Scheme 1.

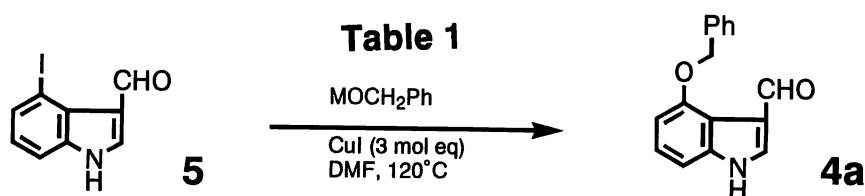
We have already reported one pot procedure⁵ for preparing **4a** from indole-3-carbaldehyde (**3**). The overall yield of

Scheme 1

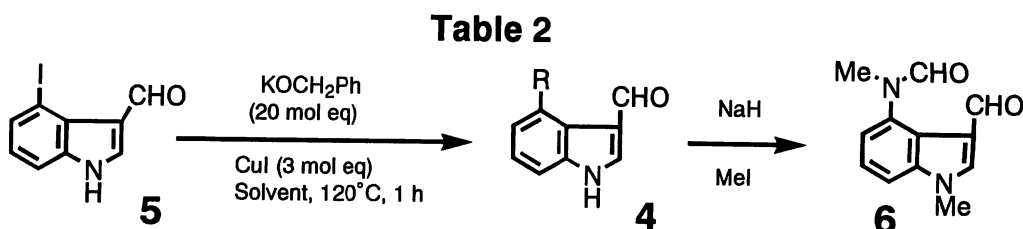


4a, however, did not exceed 58% and varied depending on the reaction conditions. The one pot procedure consists of three reactions: 1) regioselective thallation of the 4-position, 2) transformation of C-Tl bond to C-I bond, and 3) conversion of the C-I bond to C-OCH₂Ph bond.

We have attempted to improve the yield of **4a** as well as the reproducibility in order to utilize the one pot procedure as the first step in the preparative method of **1**. Among the three reactions involved, we thoroughly reexamined the third reaction of 4-iodoindole-3-carbaldehyde (**5**) with metal benzyloxide (20-26 mol eq) in the presence of CuI (3 mol eq) in DMF at 120°C.⁵ Table 1 provides a comparative example to present that not only the preparation method of metal benzyloxide but also the metal itself is an important factor for controlling the overall yield.



| Entry | MOCH ₂ Ph (mol eq) | Reaction Time (h) | Yield (%) of 4a |
|-------|---------------------------------|-------------------|------------------------|
| 1 | Na / PhCH ₂ OH (26) | 2 | 24 |
| 2 | NaH / PhCH ₂ OH (21) | 1 | 48 |
| 3 | K / PhCH ₂ OH (26) | 2 | 54 |
| 4 | KH / PhCH ₂ OH (20) | 1 | 70 |



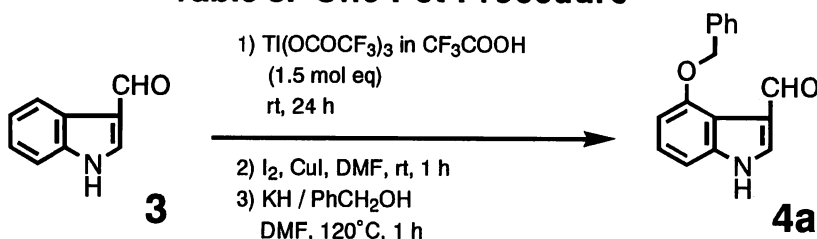
| Entry | Solvent | R | Yield (%) of 4 |
|-------|-------------------------------------|-------------------------|-----------------------|
| 1 | Me ₂ NCHO | a) -OCH ₂ Ph | 70 |
| 2 | (Me ₂ N) ₃ PO | -OCH ₂ Ph | 48 |
| 3 | PhCH ₂ OH | -OCH ₂ Ph | 30 |
| 4 | MeNHCHO | b) -NHMe | 46 |
| 5 | NH ₂ CHO | c) -NHCHO | 77 |

As can be seen from Entry 1, treatment of **5** with sodium benzyloxide (NaOCH_2Ph), prepared from sodium and benzyl alcohol (PhCH_2OH), afforded **4a** in 24% yield. When NaH was employed to produce NaOCH_2Ph , the yield doubled to 48% (Entry 2). In contrast, when potassium was used instead of sodium, further improvement in the yield was observed (54%, Entry 3). Finally, KH was found to be the reagent of choice and thereby the yield was raised up to 70% (Entry 4).

Table 2 summarizes the solvent dependence on the transformation of **5** to **4a** using KH and PhCH_2OH . Among the tested solvents, DMF was found to give the best yield of **4a** (70%, Entry 1). Replacement of DMF by either HMPA or PhCH_2OH dropped the yield to 48 or 30%, respectively (Entries 2 or 3). It is interesting to note that in cases where methylformamide (Entry 4) and formamide (Entry 5) were used as a solvent, the products were **4b** and **4c**, respectively, and in both cases **4a** was not formed at all. Consequently, a novel reaction for introducing amino functional group into the 4-position of indole nucleus was discovered. The structure of **4c** was confirmed by the spectral data and converting it to **6** in 76% yield by the reaction with MeI in the presence of NaH.

The other important factor to keep reproducibility in the one pot procedure was the relative ratio of iodination reagents (I_2 and CuI) to KOCH_2Ph . The typical results examined are summarized in Table 3. The results obtained in Entries 1 to 4 show the suitable amount of KOCH_2Ph is 25 mol eq to the starting material (**3**).

Table 3. One Pot Procedure



| Entry | I_2 (mol eq) | CuI (mol eq) | KOCH_2Ph (mol eq) | Yield (%) of 4a |
|-------|--------------------------|-----------------|--------------------------------------|---------------------------|
| 1 | 3.0 | 4.1 | 20 | 43 |
| 2 | 3.1 | 4.2 | 25 | 65 |
| 3 | 3.0 | 4.0 | 36 | 60 |
| 4 | 3.0 | 4.1 | 41 | 56 |
| 5 | 3.1 | 5.1 | 25 | 63 |
| 6 | 3.0 | 3.1 | 26 | 72 |

Fixing the amount of KOCH_2Ph to about 25 mol eq, the ratio of I_2 to CuI was changed in Entries 2, 5, and 6 culminating in finding the best reaction conditions, where the desired **4a** was produced in 72% overall yield from **3** with an excellent reproducibility (Entry 6).

As the second step in the preparative method of **1**, **4a** was transformed to 4-benzyloxyindole-3-acetonitrile (**7**) in 89% yield utilizing our reaction,⁶ thus by treating **4a** with NaBH_4 in the presence of NaCN in MeOH and formamide. Reduction of **7** with LiAlH_4 in Et_2O is the third step giving the known 4-benzyloxytryptamine^{2a} (**8**) in 96% yield. Interestingly, when THF was used as a solvent in the place of Et_2O , the yield of **8** decreased dramatically to the range of 25 to 46%. As the fourth step, dimethylation of **8** was carried out with formaldehyde and sodium cyanoborohydride⁷ in AcOH to produce **9**^{2c} in 97% yield. The final step of debenylation of **9** was the catalytic hydrogenation using 10% Pd/C producing **1**^{2d} in 84% yield. Since **1** was converted to psilocybin (**2**) in two steps by Hoffman and co-workers,^{2c} the present method constitutes a seven-step synthesis of **2** as well.

In conclusion, we could establish a simple five-step preparative method of **1** in 50% overall yield and 50% originality rate.⁸ Utilizing **1** and its intermediates, the syntheses of psilocin analogs and particularly the compounds having substituents in the benzene part are in progress.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were determined with a Shimadzu IR-420 spectrophotometer, and $^1\text{H-NMR}$ spectra with a JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. MS were recorded on a JEOL SX-102A spectrometer. Column chromatography was performed on silica gel (SiO_2 , 100-200 mesh, from Kanto Chemical Co. Inc.).

4-Benzyloxyindole-3-carbaldehyde (4a) from 4-Iodoindole-3-carbaldehyde (5): Table 1, Entry 4 — A solution of PhCH_2OH (1.063 g, 9.85 mmol) in THF (4.0 mL) was added to 35% KH (1.129 g, 9.86 mmol, washed with hexane) cautiously at 0°C with stirring. After additional stirring for 30 min at rt, the solvent was evaporated *in vacuo* to dryness leaving KOCH_2Ph . A solution of **5** (133.1 mg, 0.49 mmol) in DMF (3.0 mL, 0.49 mmol) and CuI (303.5 mg, 1.59 mmol) were added to the solution at rt. The mixture was heated at $120\text{--}130^\circ\text{C}$ for 1 h with stirring. After cooling, saturated $\text{NH}_4\text{Cl-H}_2\text{O}$ was added and the whole was extracted with EtOAc . The extract was washed with brine, dried over Na_2SO_4 , and evaporated to dryness under reduced pressure. The crude product was purified by column chromatography on SiO_2 with EtOAc-hexane (1:1, v/v) as an eluent to give **4a**⁵ (85.9 mg, 70%).

4-Benzyloxyindole-3-carbaldehyde (4a) from indole-3-carbaldehyde (3): Table 3, Entry 6 — A 0.88 mol solution⁹ of $\text{Ti}(\text{OCOCF}_3)_3$ in CF_3COOH (TFA, 1.71 mL, 1.50 mmol) was added to a solution of **3** (145.7 mg, 1.00 mmol) in TFA (1.0 mL) and the mixture was stirred for 24 h at rt. The solvent was evaporated *in vacuo* to leave a residue, which was dissolved in DMF (5.0 mL). To the solution, I_2 (768.0 mg, 3.0 mmol) and CuI

(582.0 mg, 3.1 mmol) were added and stirring was continued for 1 h at rt. The reaction mixture was added to KOCH₂Ph or KOCH₂Ph was added to the reaction mixture using DMF (15.0 mL) and the whole was heated at 120°C for 1 h with stirring. KOCH₂Ph was prepared in advance as follows: addition of a solution of PhCH₂OH (2.760 g, 25.6 mmol) in THF (8.0 mL) to 35% KH (2.925 g, 25.5 mmol, washed with hexane), stirring for 30 min at rt, and evaporation of the solvent *in vacuo* to dryness. After cooling, saturated NH₄Cl-H₂O and MeOH-CHCl₃ (5:95, v/v) were added to the reaction mixture. After removing the precipitates by filtration, water layer was extracted with MeOH-CHCl₃ (5:95, v/v). The filtrate and the extract were combined and washed with brine, dried over Na₂SO₄, and evaporated to dryness *in vacuo*. The crude product was purified by column chromatography on SiO₂ with EtOAc-hexane (1:1, v/v) as an eluent to give **4a**⁵ (180.4 mg, 72%).

4-Methylaminoindole-3-carbaldehyde (4b) from 5: Table 2, Entry 4—— A solution of PhCH₂OH (1.039 g, 9.63 mmol) in THF (4.0 mL) was added to 35% KH (1.110 g, 9.94 mmol, washed with hexane) cautiously at 0°C with stirring. After additional stirring for 30 min at rt, the solvent was evaporated *in vacuo* to dryness leaving KOCH₂Ph. A solution of **5** (130.3 mg, 0.48 mmol) in *N*-methylformamide (3.0 mL) and CuI (278.6 mg, 1.46 mmol) were added to the flask containing KOCH₂Ph at rt. The mixture was heated at 120°C for 1 h with stirring. After cooling, saturated NH₄Cl-H₂O was added and the whole was extracted with EtOAc. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave an oil, which was column chromatographed on SiO₂ with EtOAc-hexane (1:1, v/v) as an eluent to give **4b** (38.7 mg, 46%). **4b**: mp 180.0-182.0°C (decomp, colorless needles, recrystallized from MeOH). IR (KBr): 3320, 3240, 1625, 1592 cm⁻¹. ¹H-NMR (DMSO-d₆) δ: 2.83 (3H, d, *J*=4.9 Hz, collapsed to s on addition of D₂O), 6.14 (1H, d, *J*=7.8 Hz), 6.65 (1H, dd, *J*=8.1, 0.7 Hz), 7.05 (1H, dd, *J*=8.1, 7.8 Hz), 7.43 (1H, q, *J*=4.9 Hz, disappeared on addition of D₂O), 8.16 (1H, d, *J*=2.9 Hz, collapsed to s on addition of D₂O), 9.57 (1H, s), 12.06 (1H, br s, disappeared on addition of D₂O). MS *m/z*: 174 (M⁺). *Anal.* Calcd for C₁₀H₁₀N₂O: C, 68.95; H, 5.79; N, 16.08. Found: C, 69.20; H, 5.86; N, 16.19.

4-Formylaminoindole-3-carbaldehyde (4c) from 5: Table 2, Entry 5 —— A solution of PhCH₂OH (1.091 g, 10.1 mmol) in THF (4.0 mL) was added to 35% KH (1.145 g, 9.99 mmol, washed with hexane) cautiously at 0°C with stirring. After additional stirring for 30 min at rt, the solvent was evaporated *in vacuo* to dryness leaving KOCH₂Ph. A solution of **5** (132.9 mg, 0.49 mmol) in formamide (5.0 mL) and CuI (296.7 mg, 1.56 mmol) were added to the flask containing KOCH₂Ph at rt. The mixture was heated at 120°C for 1 h with stirring. After cooling, saturated NH₄Cl-H₂O was added and the whole was extracted with EtOAc. The extract was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave crystals. Recrystallization from EtOAc-MeOH afforded **4c** (40.3 mg) as prisms. The mother liquor was column chromatographed on SiO₂ with EtOAc-hexane (1:1, v/v) as an eluent to give additional **4c** (31.1 mg). Total yield was 71.4 mg (77%). **4c**: mp 243.0-245.0°C (decomp, colorless prisms, recrystallized from MeOH). IR (KBr): 1673, 1638, 1613, 1591, 1425, 1311 cm⁻¹. ¹H-NMR (DMSO-d₆, 27°C, rotational isomers existed in the ratio of 7:3) δ: 7.21-7.28 (2H, m), 7.29-7.34 (3/10H, m), 8.23-8.27 (7/10H, m), 8.45 (3/10H, d, *J*=3.2 Hz, collapsed to s on addition of D₂O), 8.46 (7/10H, d, *J*=3.4 Hz, collapsed to s on addition of D₂O), 8.55 (7/10H, d, *J*=2.0 Hz, collapsed to s on addition of D₂O), 9.07 (3/10H, d, *J*=10.7 Hz, collapsed to s on addition of D₂O), 9.66 (3/10H, s), 9.67 (7/10H, s), 11.13 (3/10H, br d, *J*=10.7 Hz, disappeared on addition of D₂O), 11.64 (7/10H, br s, disappeared on addition of D₂O), 12.50 (3/10H, br s, disappeared on addition of D₂O), 12.52 (7/10H, br s, disappeared on addition of D₂O). MS *m/z*: 188 (M⁺). *Anal.*

Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.99; H, 4.21; N, 14.80.

1,N-Dimethyl-4-formylaminoindole-3-carbaldehyde (6) from 4c ——— 60% NaH (19.2 mg, 0.48 mmol) was added cautiously to a solution of **4c** (27.2 mg, 0.145 mmol) in DMF (3.0 mL) at 0°C. After additional stirring for 10 min at rt, MeI (0.04 mL, 0.64 mmol) was added and the mixture was stirred for 5 h at rt. After addition of saturated $NH_4Cl \cdot H_2O$, the whole was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 , and evaporated under reduced pressure to leave an oil, which was column chromatographed on SiO_2 with MeOH- $CHCl_3$ (3:97, v/v) as an eluent to give **6** (23.8 mg, 76%). **6**: mp 140.0-141.0°C (colorless prisms, recrystallized from EtOAc-hexane). IR (KBr): 1666, 1572, 1515, 1497, 1342 cm^{-1} . 1H -NMR (DMSO- d_6 , 27°C, rotational isomers existed in the ratio of 3:1) δ : 3.17 (9/4H, s), 3.29 (3/4H, s), 3.92 (3/4H, s), 3.93 (9/4H, s), 7.13 (1/4H, dd, $J=7.8$, 0.8 Hz), 7.20 (3/4H, dd, $J=7.8$, 0.8 Hz), 7.38 (1/4H, dd, $J=8.1$, 7.8 Hz), 7.40 (3/4H, dd, $J=8.1$, 7.8 Hz), 7.59 (1/4H, dd, $J=8.1$, 0.8 Hz), 7.64 (3/4H, dd, $J=8.1$, 0.8 Hz), 8.15 (3/4H, s), 8.24 (1/4H, s), 8.31 (1/4H, s), 8.37 (3/4H, s), 9.76 (1/4H, s), 9.78 (3/4H, s). MS m/z : 216 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.94; H, 5.52; N, 12.97.

4-Benzoyloxytryptamine (8) from 7 ——— $LiAlH_4$ (69.3 mg, 1.83 mmol) was added to a solution of **7** (31.4 mg, 0.12 mmol) in anhydrous Et_2O (3.0 mL) at 0°C with stirring. The whole was refluxed for 1 h with stirring. To the reaction mixture, MeOH and 10% aq. Rochelle salt were added and the whole was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 , and evaporated under reduced pressure to leave crystalline solid. The crude product was purified by column chromatography on SiO_2 with $CHCl_3$ -MeOH-28% aq. NH_3 (46:5:0.5, v/v) as an eluent to give **8** (30.6 mg, 96%). **8**: mp 123.5-124.5°C (colorless prisms, recrystallized from $CHCl_3$ -petroleum ether, lit.,^{2a} mp 117-120°C). IR (KBr): 3110, 2900, 1590, 1515, 1455, 1263, 1095, 1015, 960, 735 cm^{-1} . 1H -NMR (CD_3OD) δ : 2.86 (2H, t, $J=6.7$ Hz), 2.96 (2H, t, $J=6.7$ Hz), 5.16 (2H, s), 6.53 (1H, dd, $J=7.3$, 1.2 Hz), 6.91 (1H, s), 6.95 (1H, dd, $J=8.3$, 1.2 Hz), 6.98 (1H, dd, $J=8.3$, 7.3 Hz), 7.30-7.34 (1H, m), 7.37-7.42 (2H, m), 7.48-7.52 (2H, m). MS m/z : 266 (M^+). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.43; H, 6.75; N, 10.42.

N,N-Dimethyl-4-benzoyloxytryptamine (9) from 8 ——— A solution of 95% $NaBH_3CN$ (58.2 mg, 0.88 mmol) in MeOH (1.5 mL) was added to a solution of **8** (92.4 mg, 0.34 mmol) in AcOH (0.3 mL). To the mixture, a solution of 35% aq. HCHO (123.3 mg, 1.44 mmol) in MeOH (1.5 mL) was added and the whole was stirred at rt for 3 h. After evaporation of the solvent under reduced pressure, 1N NaOH was added to the residue and the whole was extracted with EtOAc. The extract was washed with brine, dried over Na_2SO_4 , and evaporated under reduced pressure to leave an oil, which was purified by column chromatography on SiO_2 with $CHCl_3$ -MeOH-28% aq. NH_3 (46:5:0.5, v/v) as an eluent to give **9** (98.7 mg, 97%). **9**: mp 129.5-131.0°C (colorless prisms, recrystallized from $CHCl_3$ -hexane, lit.,^{2c} mp 125-126°C). IR (KBr): 2820, 1520, 1465, 1370, 1260, 1170, 1075, 975, 855, 730 cm^{-1} . 1H -NMR ($CDCl_3$) δ : 2.16 (6H, s), 2.68 (2H, t, $J=8.1$ Hz), 3.08 (2H, t, $J=8.1$ Hz), 5.17 (2H, s), 6.56 (1H, d, $J=7.7$ Hz), 6.92 (1H, d, $J=2.2$ Hz), 6.98 (1H, dd, $J=8.1$, 0.7 Hz), 7.07 (1H, dd, $J=8.1$, 7.7 Hz), 7.31-7.36 (1H, m), 7.37-7.42 (2H, m), 7.48-7.52 (2H, m), 8.03 (1H, s). MS m/z : 294 (M^+). Anal. Calcd for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.47; H, 7.57; N, 9.53.

Psilocin (1) from 9 — 10% Pd/C (24.5 mg) was added to a solution of **9** (60.3 mg, 0.21 mmol) in MeOH (10.0 mL) and the mixture was stirred under H₂ atmosphere at rt for 1 h. After evaporation of the solvent under reduced pressure, the residue was purified by column chromatography on SiO₂ with CHCl₃-MeOH-28% aq. NH₃ (46:5:0.5, v/v) as an eluent to give **1** (35.0 mg, 84%). **1**: mp 174.5-176.0°C (colorless prisms, recrystallized from EtOAc, lit.,^{2d} mp 173-176°C). IR (KBr): 3250, 1590, 1470, 1340, 1045, 835, 730, 690, 590, 480 cm⁻¹. ¹H-NMR (DMSO-d₆) δ: 2.22 (6H, s), 2.55 (2H, t, *J*=6.7 Hz), 2.88 (2H, t, *J*=6.7 Hz), 6.25 (1H, dd, *J*=7.3, 1.0 Hz), 6.73 (1H, dd, *J*=8.1, 1.0 Hz), 6.79 (1H, dd, *J*=8.1, 7.3 Hz), 6.90 (1H, d, *J*=2.2 Hz), 10.56 (1H, s), 10.71 (1H, br s). MS *m/z*: 204 (M⁺). *Anal.* Calcd for C₁₂H₁₆N₂O: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.39; H, 7.95; N, 13.57.

REFERENCES AND NOTES

1. a) Dedicated to the 80th birthday of Dr. Bernhard Witkop. b) This is Part 88 of a series entitled "The Chemistry of Indoles". Part 87: M. Somei, H. Morikawa, K. Yamada, and F. Yamada, *Heterocycles*, 1998, **48**, 1117.
2. a) A. Stoll, F. Troxler, J. Peyer, and A. Hofmann, *Helv. Chim. Acta*, 1955, **38**, 1452; b) A. Hofmann, *Experientia*, 1958, **14**, 107; c) A. Hofmann, R. Heim, A. Brack, H. Kobel, A. Frey, H. Ott, T. Petrzilka, and F. Troxler, *Helv. Chim. Acta*, 1959, **42**, 1557; d) F. Troxler, F. Seemann, and A. Hofmann, *Helv. Chim. Acta*, 1959, **42**, 2073; e) D. F. Downing, *Quart. Rev. (London)*, 1962, **16**, 133; f) A. Hofmann, *Bull. Narcotics*, 1971, **23**, 3.
3. R. W. Brimblecombe and R. M. Pinder, "Hallucinogenic Agents", Wright-Scientifica, 1975, pp. 106-108.
4. D. B. Repke, D. B. Grotjahn, and A. T. Shulgin, *J. Med. Chem.*, 1985, **28**, 892; D. B. Repke and W. J. Ferguson, *J. Heterocycl. Chem.*, 1982, **19**, 845; D. B. Repke, W. J. Ferguson, and D. K. Bates, *ibid.*, 1981, **18**, 175 and references cited therein.
5. M. Somei, F. Yamada, M. Kunimoto, and C. Kaneko, *Heterocycles*, 1984, **22**, 797.
6. F. Yamada, T. Hashizume, and M. Somei, *Heterocycles*, 1998, **47**, 509.
7. L. J. Street, R. Baker, J. L. Castro, M. S. Chambers, A. R. Guiblin, S. C. Hobbs, V. G. Matassa, A. J. Reeve, M. S. Beer, D. N. Middlemiss, A. J. Noble, J. A. Stanton, K. Scholey, and R. J. Hargreaves, *J. Med. Chem.*, 1993, **36**, 1529.
8. Definition of originality rate, written in Japanese: M. Somei, *J. Synth. Org. Chem.*, 1982, **40**, 387; M. Somei, Y. Makita, and F. Yamada, The 3rd International Kyoto Conference on New Aspects of Organic Chemistry, Abstracts Papers, Nov., 1985, p. 128; Definition, written in English: M. Somei, *Yakugaku Zasshi*, 1988, **108**, 361.
9. A. McKillop, J. D. Hunt, M. J. Zelesko, J. S. Fowler, E. C. Taylor, G. McGillivray, and F. Kienzle, *J. Am. Chem. Soc.*, 1971, **93**, 4841.

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