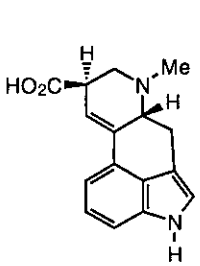
SYNTHESIS OF 4-(2-AMINOETHYL)INDOLES THROUGH CLAISEN *ORTHO*-AMIDE REARRANGEMENT OF 3-HYDROXY-2-METHOXYINDOLINES

Tomomi Kawasaki, Hiroaki Ohtsuka, Ado Mihira, and Masanori Sakamoto*
Meiji College of Pharmacy, 1-35-23 Nozawa, Setagaya-ku, Tokyo 154, Japan

Abstract — Reaction of 3-hydroxy-2-methoxyindolines (**5**) with amide acetal (**6**) and ketene aminal (**13**) gives 4-carbamoylmethylindole (**9**) and -indoline (**11**), which are converted into 4-(2-aminoethyl)indole (**7**) by treatment of the indoline (**11**) with hydrochloride followed by sodium hydroxide to form the indole (**9**), and then by reduction of **9** with lithium aluminum hydride.

The indole ring system possessing a C-C-N unit such as aminoethyl or carbamoyl at the ring 4-position is a key structural feature of many biologically active indoles, such as the well known ergot alkaloids [e.g., lysergic acid (**1**)],[1] serotobenine (**2**),[2] and synthetic dopamine agonists [e.g., **3**[3] and **4**[4]]. In nature, compounds like **1** are invariably biosynthesized from tryptophan, with isoprene unit being introduced in the indole 4-position by enzyme dimethylallylpyrophosphate tryptophan dimethylallyl transferase.[5] In the laboratory, direct functionalization of the indole 4-position using the intermolecular reaction is extremely



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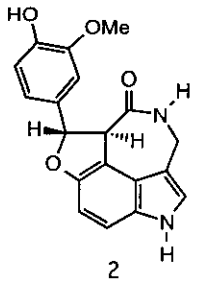

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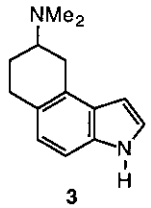

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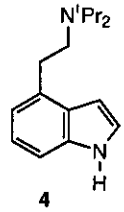

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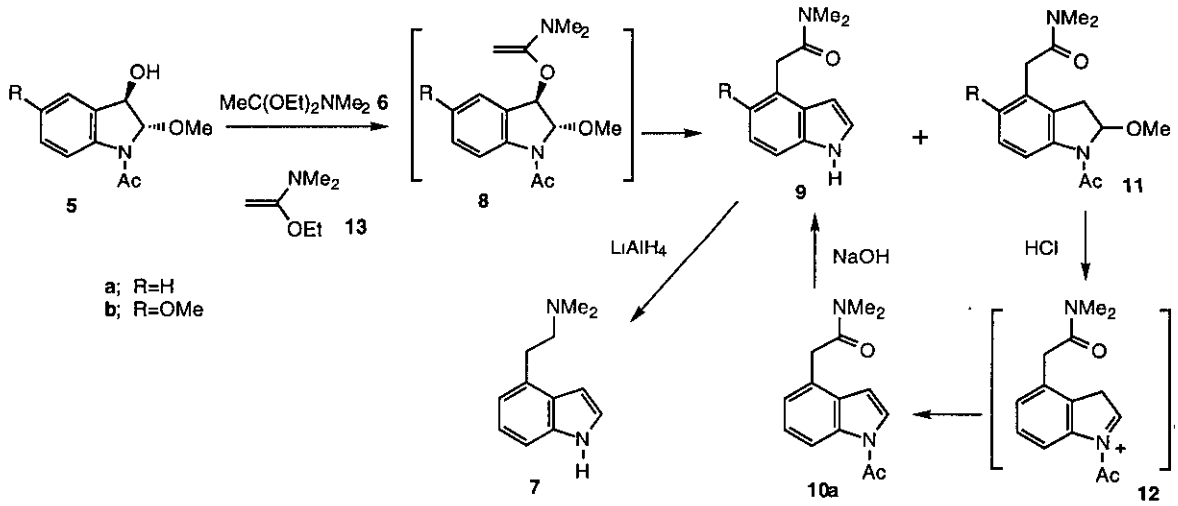
difficult due to high reactivity of pyrrole moiety, although there are a few examples: the reactions of indole-tricarbonylchromium complex[6] and the reactions *via* selective mutilations at the 4-position caused by chelation with carbonyl[7] and aminomethyl groups[8] at the 3-position. The intramolecular reaction of 3-substituted indoles and indolines is more effective for accomplishing functionalization at the indole 4-position,[9] the cyclization such as the intramolecular addition,[10] Pummerer reaction,[11] photoalkylation,[12] and Friedel-Crafts acylation.[13] However, these reactions are limited to the synthesis of the 3,4-disubstituted indoles such as **1** and **2**, and are difficult to apply to that of a real 4-substituted indole like **3** or

4.

Although Claisen rearrangement is a more powerful synthetic method,[14] there has been little known about the synthesis of the 4-substituted indole except for Claisen rearrangement of 5-allyloxyindoles to 4-allyl-5-hydroxyindoles.[15] We previously reported the migration of the 3-site substituent into the indole 4-position *via* Claisen *ortho*-amide rearrangement of the 3-hydroxy-2-methoxyindoline (**5**) with the amide acetal (**6**).[16] This paper describes full details of this work including transformation of the rearranged product (**9**) to 4-(2-aminoethyl)indole (**7**).



The indolines (**5**) were readily obtained by our previously described method,[17] and the amide acetal (**6**) was prepared by Meerwein's technique.[18] When the indoline (**5a**) was treated with 1.5 equivalent of amide acetal (**6**) in a sealed tube at 200 ℃ for 25 h, Claisen rearrangement of an intermediary 3-vinyloxyindoline (**8**) proceeded to give an inseparable mixture of 4-dimethylcarbamoylmethylindole (**9a**) and its acetate (**10a**), which was thoroughly treated with sodium hydroxide to convert **10a** to **9a** in 31% yield from **5a**. The structure of **9a** was established by the following spectral data: ^{1}H-NMR spectrum shows five signals due to aromatic protons; *i. e.*, a broad singlet of 3-H at 6.62, two doublets (both J = 7 Hz) of 5- and 7-H at 6.84 and 7.94, and two doublets (J = 2.5 and 7 Hz, respectively) of 3- and 6-H at 7.17 and 7.15 ppm; its IR spectrum shows absorptions based on NH and amide at 3500 and 1636 cm^{-1}. Reaction of **5a** with 3 equivalent of **6** for 14 h under the same conditions proceeded smoothly to give the indole (**9a**) and 4-carbamoylmethylindoline (**11a**) in 33% and 11% yield, respectively. The structure of **11a** was confirmed by its spectral data and chemical transformation of **11a** to **9a**. In the ^{1}H-NMR spectrum of **11a**, three signals due to aromatic protons appeared as two doublets (J = 8 Hz) at 6.84 and 7.94, and a triplet (J = 8 Hz) at 7.15 ppm. The indoline (**11a**) was readily converted into the indole (**9a**). Thus, treatment of **11a**

with hydrogen chloride caused demethoxylation through an iminium intermediate (**12**) to afford 1-acetylindole (**10a**) in 84% yield, which was deacetylated with sodium hydroxide in methanol to yield the indole (**9a**) (90%). Instead of amide acetal (**6**), Claisen rearrangement using ketene aminal (**13**) was also attempted; heating of **5a** and **13** in a sealed tube at 200 ℃ for 14 h afforded **9a** and **11a** in 18% and 27% yield, respectively. An attempt to use Claisen *ortho*-ester rearrangement of **5a** with ethyl *ortho*-acetate in the presence of propionic acid failed. Similarly, Claisen *ortho*-amide rearrangement of 5-methoxyindoline (**5b**) with **6** gave 4-carbamoyl-methylindoline (**11b**) and the indole (**9b**) in 27% and 18% yields, respectively. Finally, reduction of the indole (**9a**) with lithium aluminum hydride in tetrahydrofuran gave 4-(2-amino-ethyl)indole (**7**) in 63% yield.

In conclusion, we have devised a convenient procedure by introduction of carbamoylmethyl or aminoethyl group to the indole 4-position *via* Claisen *ortho*-amide rearrangement. Application of this reaction to the short synthesis of related alkaloids is in progress in this laboratory.

EXPERIMENTAL

All mps are uncorrected, and were measured on a Yanagimoto micro melting point apparatus. IR spectra were recorded with a Hitachi 270-30 or a Shimadzu FTIR-8100 spectrophotometer. NMR spectra were determined with a JEOL JNM-GX 400 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained with a JEOL JMS-DX302 instrument with a direct inlet system operating at 70 eV. Elemental analyses were obtained using a Perkin-Elmer Model 240B elemental analyzer. Column chromatography was carried out on silica gel (Kanto Chemical Co. Inc., 100-200 mesh and Merck, 400 mesh). *trans*-1-Acetyl-3-hydroxy-2-methoxyindolines (**5**),[17] *N,N*-dimethylacetamide diethylacetal (**6**),[18] and 1-(*N,N*-dimethylamino)-1-ethoxy-ethene (**13**)[18] were prepared according to the reported procedures, respectively.

Claisen rearrangement of trans-1-acetyl-3-hydroxy-2-methoxyindoline (5a)

a) Using 1.5 equivalent of *N,N*-dimethylacetamide diethylacetal (**6**): A solution of **5a** (500 mg, 2.4 mmol) and **6** (615 mg, 3.8 mmol) in dry *o*-dichlorobenzene (3.3 mL) was heated at 200 ℃ in a sealed tube for 25 h under argon. The reaction mixture was concentrated under reduced pressure to give a residue, which was chromatographed with ethyl acetate-methylene chloride (1 : 4) to give a mixture of 4-(*N,N*-dimethyl-carbamoylmethyl)indole (**9a**) and its acetate (**10a**). Attempts to separate the two products were unsuccessful. The obtained mixture (170 mg) was then treated with NaOH (15 mg, 0.38 mmol) in methanol (0.4 mL) at rt overnight and extracted with chloroform (30 mL). The extract was dried over Na_2SO_4 and the solvent was evaporated to give **9a** (150 mg, 31%); mp 144-146 ℃ (ethyl acetate). Anal. Calcd for $C_{12}H_{14}N_2O$; C, 71.26; H, 6.98; N, 13.85. Found: C, 71.42; H, 7.01; N, 13.86. IR ν ($CHCl_3$); 3500, 1636 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$); 2.96 (3H, s, NMe), 2.98 (3H, s, NMe), 4.00 (2H, s,

CH_2-CON), 6.62 (1H, br s, Ar-H^3), 6.96 (1H, d, *J*=7 Hz, Ar-H^5), 7.12 (1H, t, *J*=7 Hz, Ar-H^6), 7.17 (1H, t, *J*=2.5 Hz, Ar-H^2), 7.28 (1H, d, *J*=7 Hz, Ar-H^7), 8.51 (1H, br s, NH). MS *m/z*; 202 (M^+, 44%), 130 (100), 72 (44).

b) Using 3 equivalent of **6**: A solution of **5a** (1.26 g, 6.1 mmol) and **6** (2.97 g, 18.4 mmol) in dry *o*-dichlorobenzene (10 mL) was heated at 200 ℃ in a sealed tube for 14 h under argon. The reaction mixture was concentrated under reduced pressure to give a residue, which was chromatographed with ethyl acetate-methylene chloride (1 : 4) to give **9a** (0.41 g, 33%) and 1-acetyl-4-(*N*,*N*-dimethylcarbamoylmethyl)-2-methoxyindoline (**11a**) (0.19 g, 11%).

11a; mp 87-89 ℃ (ethyl acetate-hexane). Anal. Calcd for $C_{15}H_{20}N_2O_3$; C, 65.19; H, 7.30; N, 10.14. Found: C, 65.29; H, 7.47; N, 10.03. IR ν ($CHCl_3$); 1646 cm^{-1}. ^{1}H-NMR δ (CD_3CN); 2.27 (3H, s, Ac), 2.88 (3H, s, NMe), 3.02 (1H, d, *J*=17 Hz, H^3), 3.03 (3H, s, NMe), 3.16 (1H, dd, *J*=17 and 7 Hz, H^3), 3.64 (1H, d, *J*=18 Hz, CH-CON), 3.65 (1H, d, *J*=18 Hz, CH-CON), 5.65 (1H, d, *J*=17 Hz, H^2), 6.84 (1H, d, *J*=8 Hz, Ar-H^5), 7.15 (1H, t, *J*=8 Hz, Ar-H^6), 7.94 (1H, d, *J*=8 Hz, Ar-H^7). MS *m/z*; 276 (M^+, 0.2%), 244 (M-MeOH, 44), 172 (17), 130 (74), 72 (100).

c) Using ketene aminal (**13**): A solution of **5a** (2.1 g, 10 mmol) and **13** (3.6 g, 31 mmol) in dry dimethylformamide (30 mL) was heated at 200 ℃ in a sealed tube for 14 h under argon. The reaction mixture was concentrated under reduced pressure to give a residue, which was chromatographed with ethyl acetate-methylene chloride (1 : 4) to give **9a** (0.43 g, 21%).

*Claisen rearrangement of trans-1-acetyl-3-hydroxy-2,3-dimethoxyindoline (**5b**) with **6***

A solution of **5b** (400 mg, 1.69 mmol) and **6** (816 mg, 5.07 mmol) in dry *o*-dichlorobenzene (3 mL) was heated at 200 ℃ in a sealed tube for 14 h under argon. The reaction mixture was concentrated under reduced pressure to give a residue, which was chromatographed with ethyl acetate-chloroform (7 : 3) to give 4-(*N*,*N*-dimethylcarbamoylmethyl)-5-methoxyindole (**9b**) (69 mg, 18%) and 1-acetyl-4-(*N*,*N*-dimethylcarbamoylmethyl)-2,5-dimethoxyindoline (**11b**) (141 mg, 27%).

9b; mp 178-180 ℃ (benzene). HRMS; Found: M^+, 232.1216, $C_{13}H_{16}N_2O_2$ requires M, 232.1212. IR ν ($CHCl_3$); 3502, 1636 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$); 2.94 (3H, s, NMe), 3.01 (3H, s, NMe), 3.86 (3H, s, OMe), 4.00 (2H, s, CH_2-CON), 6.67 (1H, br s, Ar-H^3), 6.91 (1H, d, *J*=9 Hz, Ar-H), 7.19 (1H, br s, Ar-H^2), 8.25 (1H, d, *J*=9 Hz, Ar-H), 8.07 (1H, br s, NH). MS *m/z*; 232 (M^+, 66%), 160 (100), 130 (37), 72 (11).

11b; mp 154-156 ℃ (ethyl acetate-hexane). HRMS; Found: M^+, 306.1558, $C_{16}H_{22}N_2O_4$ requires M,

306.1580. IR ν ($CHCl_3$); 1650 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$); 2.24 (3H, s, Ac), 2.87 (3H, s, NMe), 3.00 (1H, d, *J*=17 Hz, H^{3a}), 3.10 (3H, s, NMe), 3.15 (1H, dd, *J*=17, 7 Hz, H^{3b}), 3.19 (3H, s, OMe), 3.62 (2H, s, CH_2-CON), 3.75 (3H, s, OMe), 5.63 (1H, d, *J*=7 Hz, H^2), 6.75 (1H, d, *J*=9 Hz, Ar-H^6), 7.89 (1H, d, *J*=9 Hz, Ar-H^7). MS *m/z*; 274 (M^+, 89%), 202 (100), 160 (66), 130 (30), 72 (25).

*Treatment of the indoline (**11a**) with HCl*

A solution of **11a** (82 mg, 0.3 mmol) and a catalytic amount of hydrogen chloride in chloroform (2 mL) was allowed to stand at rt for 2 h. The resultant mixture was concentrated under reduced pressure to give a residue, which was purified by column chromatography with ethyl acetate-methylene chloride (1 : 5) as an eluent to give 1-acetyl-4-(*N,N*-dimethylcarbamoylmethyl)indole (**10**) (61 mg, 84%); mp 119-120 ℃ (ethyl acetate-diethyl ether). Anal. Calcd for $C_{14}H_{16}N_2O_2$; C, 68.83; H, 6.60; N, 11.47. Found; C, 68.70; H, 6.61; N, 11.44. IR ν ($CHCl_3$); 1710, 1640 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$); 2.64 (3H, s, Ac), 2.98 (6H, s, NMe_2), 3.96 (2H, s, CH_2-CON), 6.83 (1H, br s, Ar-H^3), 7.12 (1H, d, *J*=8 Hz, Ar-H^5), 7.30 (1H, t, *J*=8 Hz, Ar-H^6), 7.43 (1H, br s, Ar-H^2), 8.36 (1H, d, *J*=8 Hz, Ar-H^7). MS *m/z*; 244 (M^+, 89%), 202 (15), 172 (26), 130 (100), 72 (80).

*Hydrolysis of 1-acetylindole (**10**) with NaOH*

A solution of **10** (28 mg, 0.11 mmol) and sodium hydroxide (33%,0.03 mL) in methanol (2 mL) was stirred at rt for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue, which was extracted with chloroform (30 mL). The extract was washed with water, dried over $MgSO_4$, and concentrated to give **9a** (20 mg, 90%).

*Reduction of the indole (**9**) with $LiAlH_4$*

A mixture of **9a** (72 mg, 0.36 mmol) and $LiAlH_4$ (40 mg, 1.0 mmol) in dry tetrahydrofuran (7 mL) was heated under reflux with vigorous stirring for 40 h, and extracted with methylene chloride (110 mL). The extract was washed with water, dried over $MgSO_4$, and concentrated to give the residue, which was chromatographed with methanol-methylene chloride (1 : 20) to give 4-(*N,N*-dimethylaminoethyl)indole (**7**) (42 mg, 63%) together with recovered **9a** (5 mg).

7: mp 92-94 ℃ (ligroine). Anal Calcd for Calcd for $C_{12}H_{16}N_2$; C, 76.55; H, 8.57; N, 14.88. Found: C, 76.18; H, 8.65; N, 14.63. IR ν ($CHCl_3$); 3500 cm^{-1}. ^{1}H-NMR δ ($CDCl_3$); 2.32 (6H, s, NMe_2), 2.45-2.85 (2H, s, CH_2), 2.9-3.35 (2H, m, CH_2), 6.50 (1H, br s, Ar-H_3), 6.7-7.3 (3H, m, Ar-H), 8.52 (1H,

br, NH). MS *m/z*; 188 (M^+, 17%), 130 (5), 58 (100).

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