STUDIES ON SYNTHESIS AND APPLICATION OF FUNCTIONALIZED AZAINDOLES

SATOSHI MINAKATA

OSAKA UNIVERSITY

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(官能化アザインドール類の合成と応用に関する研究)

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Preface

The work presented in this thesis has been carried out under the guidance of Professor Yoshiki Ohshiro at Osaka University during 1988-1992.

Satoshi Minakata

Department of Applied Chemistry
Fuculty of Engineering
Osaka University
Yamadaoka 2-1, Suita,
Osaka 565,
Japan

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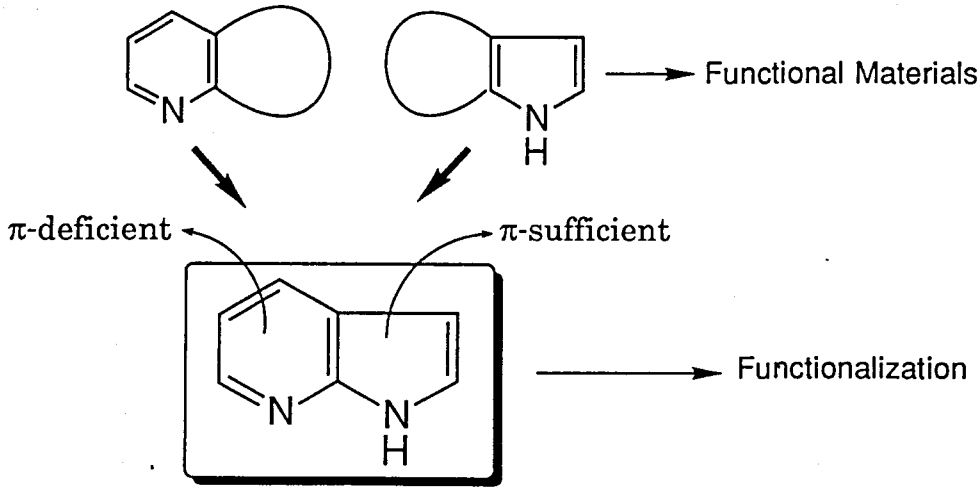
GENERAL INTRODUCTION

In recent years, biologically active substances and functional materials have been drawing much attention and the basic research on them is in need in both academic and industrial fields. Bicyclic compounds containing heteroatoms are not only the fundamental skeletons of such functional materials, but also synthetic intermediates for them.[1)] Thus this class of compounds is one of the major targets in organosynthetic chemistry and in fine chemicals industries.

Bicyclic pyrroles and bicyclic pyridines are the important key compounds of functional heterocyclic systems containing nitrogen atoms. So multifunctionalization of them is highly significant for development of functional materials. However, it is not easy to functionalize these bicyclic rings because of the changes in chemical properties caused by ring condensation. It is strongly desired to develop facile methods for introduction of functional groups directly and selectively to fused heterocyclic compounds in order to synthesis advanced functional materials.



From these points of view, this thesis deals with the synthesis and application of functionalized azaindoles focusing on characteristic azaindole skeleton consists of condensed π-deficient pyridine ring and π-sufficient pyrrole ring. Azaindoles are utilized for various purposes, since the skeleton is unique bicyclic ring system. For example, existence of a basic nitrogen atom of the pyridine ring and an acidic hydrogen atom of the pyrrole ring in azaindole draws much attention of physicochemists.[2,3] Thus, physicochemical properties of 7-methyl-7*H*-7-azaindole which is readily formed from 7-azaindole are also highly interesting, and its structure, charge distribution, dipole moment and basicity were studied.[4] Among them, the contribution of the polarized resonance structure to 7-methyl-7*H*-7-azaindole is one of the most important subjects, but the detailed conclusion has not been established.[5,6]

Functionalization of azaindole skeleton is essential for development of new or improved properties, whereas nucleophilic substitution of the pyridine ring is so difficult.[7] The procedure of direct functionalization of 7-azaindole at 6-position has rarely been known.[8] Hence, development of convenient methods for introduction of functional groups onto the azaindole ring is desired.

As another important property of 7-azaindole, the two nitrogen atoms of 7-azaindole are favorably located so that it readily forms various binuclear complexes with metals[9] and interacts with an alcohol or itself through hydrogen bonds.[2,3] So 7-azaindoles are expected to be very useful for complexing agents.

On the other hand, polymers containing heterocyclic compounds have been widely investigated as functional materials.[10,11] Thus we may expect some new or advanced functions for the polymers containing azaindole rings because of the aforementioned characteristic nature of the ring, but such polymers have never been prepared.

Azaindoles are also interesting compounds in terms with biological activity, since azaindoles are the azaanalogs of indole alkaloids. The biological activities of a few azaindole derivatives have been studied,[12] but their biological activities as agrochemicals have rarely been investigated.[13]

With these backgrounds, synthesis and application of functionalized azaindoles were investigated. In Chapter 1, the consideration on the contribution of resonance structures of 7-methyl-7*H*-7-azaindole and related compounds is described. In Chapter 2, regioselective direct functionalization of 7- and 4-azaindoles by use of Reissert-Henze type reaction is stated. Chapter 3 deals with synthesis and some basic applications of functionalized 7-azaindoles which are chelating agents and polymers. In Chapter 4, application of 7-azaindole derivatives as agricultural fungicides and examination of structure-activity correlation are described.

References

1) "*Comprehensive Heterocyclic Chemistry*", ed. O. Meth-Cohn; Pergamon, Oxford, 1984, Vol. 1.
2) J. A. Walmsley, *J. Phys. Chem.*, **85**, 3181 (1981).
3) K. C. Ingham and M. A. El-Bayoumi, *J. Am. Chem. Soc.*, **96**, 1674 (1974).
4) J. Catalan, L. G. de Paz, M. Yanez, F. Amat-Guerri, R. Hourient, E. Rolli, R. Lehringer, P. Oelhafen, R. W. Taft, F. Anvia, and J. H. Qian, *J. Am. Chem. Soc.*, **110**, 2699 (1988).
5) R. H. Cox and S. Sanker, *Org. Magn. Res.*, **14**, 150 (1980).
6) J. Catalan, O. Mo, P. Perez, M. Yanez, and F. Amat-Guerri, *Nouv. J. Chim.*, **8**, 87 (1984).
7) L. N. Yakhontov, *Russ. Chem. Rev.*, **37**, 551 (1968).
8) B. A. J. Clark and J. Parrick, *J. Chem. Soc., Perkin Trans. 1* **1974**, 2270.

9) R. W. Brookes and R. L. Martin, *Inorg. Chem.*, **14**, 528 (1975).

10) Y. Shirota, N. Noma, and H. Mikawa, *J. Chem. Soc., Chem. Commun.*, **1984**, 470.

11) K. Kawabata, T. Hashizume, and T. Matsumoto, *Agric. Biol. Chem.*, **50**, 1551 (1986).

12) G. Goto and Y. Saji, *Jpn. Kokai Tokkyo Koho,* 61 130290 (1986); *Chem. Abstr.*, **106**, 33014 (1987).

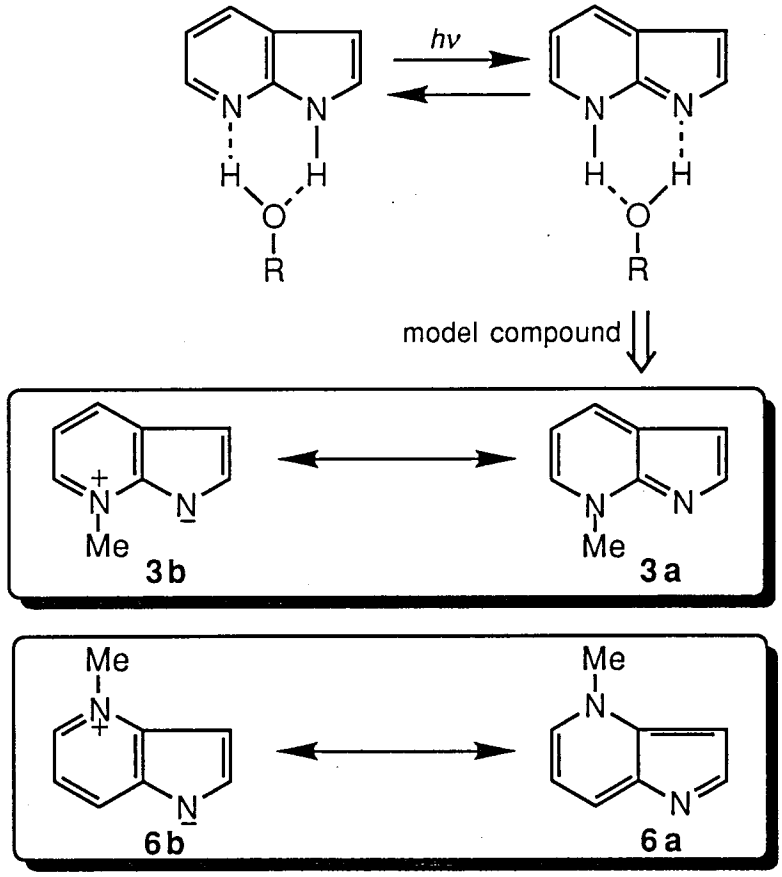
13) R. F. Willete, *Adv. Heterocycl. Chem.*, **9**, 27 (1968).

CHAPTER 1. CONSIDERATION ON CONTRIBUTION OF RESONANCE STRUCTURES OF 7-METHYL-7-*H*-7-AZAINDOLE AND RELATED COMPOUNDS

1-1. Introduction

1*H*-Pyrrolo[2,3-*b*]pyridine (7-azaindole: **1**) and its derivatives are currently attracting much interest in biochemical and physico-chemical studies owing to their characteristic condensed ring system, consisting of pyridine and pyrrole rings which have opposite π-electron densities.[1] Among them, existence of a basic nitrogen atom of the pyridine ring and an acidic hydrogen atom of the pyrrole ring in 7-azaindole is of interest to physico-chemists. While 7-azaindole readily forms various binuclear complexes with metals,[2] its two nitrogen atoms are favorably located so that this compound interacts with an alcohol (1 : 1 adduct formation) or itself (dimerization) through hydrogen bonds.[3,4] It is known that these types of 7-azaindole complexes undergo a unique photoinduced double proton transfer reaction to form tautomers.[5] This behavior was widely investigated by El-Bayoumi and co-workers, who employed 7-methyl-7*H*-pyrrolo[2,3-*b*]pyridine (**3**) as the model compound of the tautomers. Since other physico-chemical properties of 7-methyl-7*H*-pyrrolo[2,3-*b*]pyridine (**3**) are also of great interest, its structure, charge distribution, dipole moment and basicity were studied using molecular orbital calculations by comparing with those of its isomer, 1-methyl-7-azaindole (**13**).[6] Among them, the contribution of the polarized structure **3b** to 7-methyl-7*H*-pyrrolo[2,3-*b*]pyridine (**3**) is one of the most important subjects, but the problem has only been discussed from the

standpoints of absorption spectra[7] and ^{1}H- and ^{13}C-NMR spectra.[8] Furthermore, the detailed conclusion has not been established.

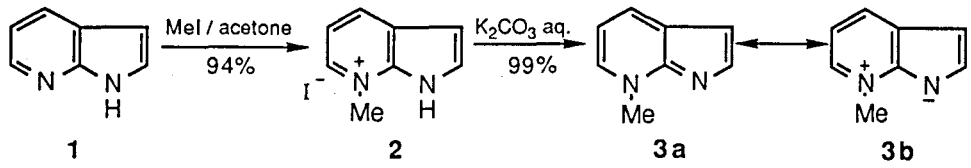


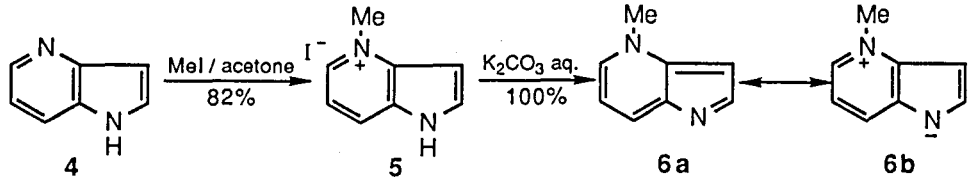
In this chapter, the consideration on contribution of the polarized structure **3b** to 7-methyl-7*H*-pyrrolo[2,3-*b*]pyridine (**3**) as well as of the corresponding polar structure **6b** to 4-methyl-4*H*-pyrrolo[3,2-*b*]pyridine (**6**) was carried out on the basis of multinuclear magnetic resonances (^{1}H, ^{13}C and ^{15}N) and *ab initio* molecular orbital calculations using 6-31G basis set.[9]

1-2. Results and Discussion

1-2-1. Synthesis of 7-methyl-7-*H*-pyrrolo[2,3-*b*]pyridine and related compounds

7-Azaindole (**1**) or 4-azaindole (**4**) readily forms the quaternary derivative, 7-methyl-7-azaindolium iodide (**2**) or 4-methyl-4-azaindolium iodide (**5**), when stirred with excess iodomethane. On treatment with alkali, these salts yield yellow basic substances (**3** and **6**) which can be readily extracted with ether or dichloromethane, respectively .[10)]





1-2-2. ^{15}N-NMR chemical shift of compounds 1-6

To obtain a better insight into molecular structures, ^{15}N-NMR spectra in DMSO-d_6 were measured on these six compounds[11)] and their chemical shifts are shown in Figure 1 along with those of relevant heterocyclic compounds **7-12**. On quaternization of 7-azaindole (**1**) to 7-methyl-7-azaindolium iodide (**2**), the signal of the pyrrole nitrogen did not show any significant shift. But upfield shift of the pyridine nitrogen by about 100 ppm well agreed with the change of ^{15}N-

chemical shift from pyridine (**7**) to pyridinium salt (**8**).[12] In the deprotonation step of the pyrrole hydrogen from **2** to **3**, considerable downfield shift of the pyrrole nitrogen was observed. This change was considered to correspond to anion formation of a pyrrole having an electron-withdrawing group such as **10**.[13] This result appears to indicate that the contribution of the structure **3b** to **3** is larger than that of the structure **3a**. On the other hand, the chemical shifts of the two nitrogens of **3** were similar to those of *N*-methylimidazoles **11** and **12**,[14] and were not shifted either in a polar solvent (DMSO-d_6) or in a non-polar solvent ($CDCl_3$). This result was not in accord with the above assumption that the contribution of the structure **3b** is predominant. A similar tendency of chemical

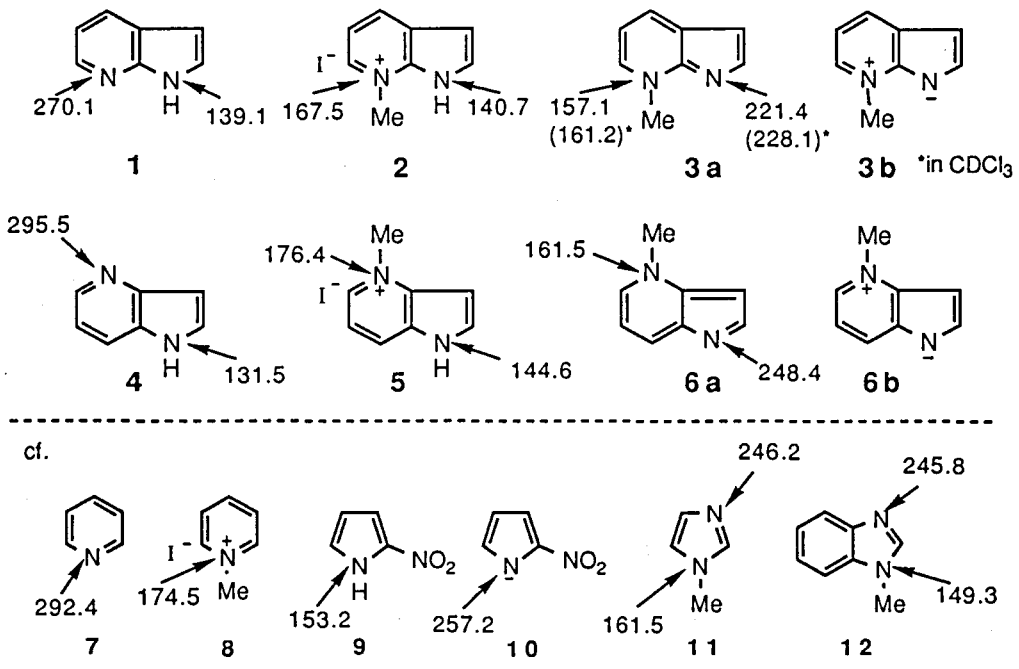


Figure 1. ^{15}N-NMR chemical shifts of compounds **1**–**6** (in DMSO-d_6 ppm from anhydrous liq. NH_3)

shift changes was also observed for 4-azaindole derivatives. On the basis of these experimental results, we could not confirm whether the major contributing structure is the nonpolarized **3a** or the polarized **3b**.

1-2-3. ^{1}H- and ^{13}C-NMR chemical shift of compounds 1-6

In addition to the above ^{15}N-NMR results, the contribution of the polarized structure **3b** to **3** was examined by means of ^{1}H- and ^{13}C-NMR spectra. The ^{1}H and ^{13}C chemical shifts of the compounds **1-6** are given in Table 1. For the ^{1}H-NMR chemical shifts, marked changes were observed when the azaindole **1** was compared with the 7-methyl derivative **3**, with downfield shift of H-2 on the pyrrole ring and upfield shifts of H-5 and H-6 on the pyridine ring. If the contribution of the pyridinium salt **3b** is larger than that of **3a**, the α-hydrogen on the pyridine ring (H-6) would not show an upfield shift. In ^{13}C-NMR measurements, the relation between chemical shifts of C-2 and C-6 was reversed when **1** was converted into **3**. This result suggested that the electronic natures of

Table 1. ^{1}H- and ^{13}C-NMR chemical shifts of compounds **1-6**

	^{1}H-NMR chemical shift[a]						^{13}C-NMR chemical shift[a]					
compound	H-2	H-3	H-4	H-5	H-6	H-7	C-2	C-3	C-4	C-5	C-6	C-7
1[b]	7.37	6.50	7.95	7.10	8.32	—	125.4	100.4	129.0	115.6	142.1	—
2[c]	7.99	7.00	8.74	7.65	8.76	—	129.7	103.5	136.8	116.0	137.4	—
3[b]	7.89	6.66	8.08	6.79	7.52	—	145.4	101.4	130.5	108.8	129.6	—
4[b]	7.50	6.70	—	8.49	7.12	7.70	128.7	102.3	—	142.6	116.5	119.0
5[c]	8.33	7.06	—	8.76	7.68	8.58	123.9	92.8	—	134.9	113.4	132.2
6[b]	8.27	6.39	—	7.50	6.87	8.11	152.6	91.7	—	130.0	109.6	127.5

a) ppm from TMS b) in $CDCl_3$ c) in DMSO-d_6

the pyrrole ring and the pyridine ring of 7-azaindole skeleton were exchanged. Hence the contribution of **3a** becomes larger than that of **3b**. The 4-azaindole derivatives **4-6** also indicated similar changes in chemical shifts, which seems to indicate a major contribution of the resonance structure **6a**.

1-2-4. Effect of concentration on ^{1}H-NMR chemical shifts of compounds 3 and 6

Further, changes in chemical shifts depending on concentration were studied for azaindoles **3** and **6**, since it has been reported that the signals of H-2 and H-6 of 7-azaindole (**1**) shift downfield with increasing concentration in CCl_4, which is due to formation of a dimer through hydrogen bonds.[7] As reference samples 1-methyl-7-azaindole (**13**) and 1-methyl-4-azaindole (**14**) were employed, to which a contribution of polarized resonance structures is unlikely. The effects of concentration on the chemical shifts of H-2, H-6 and H-5 of these four compounds (**3, 13, 6, 14**) are shown in Figures 2 and 3. The signals for compound

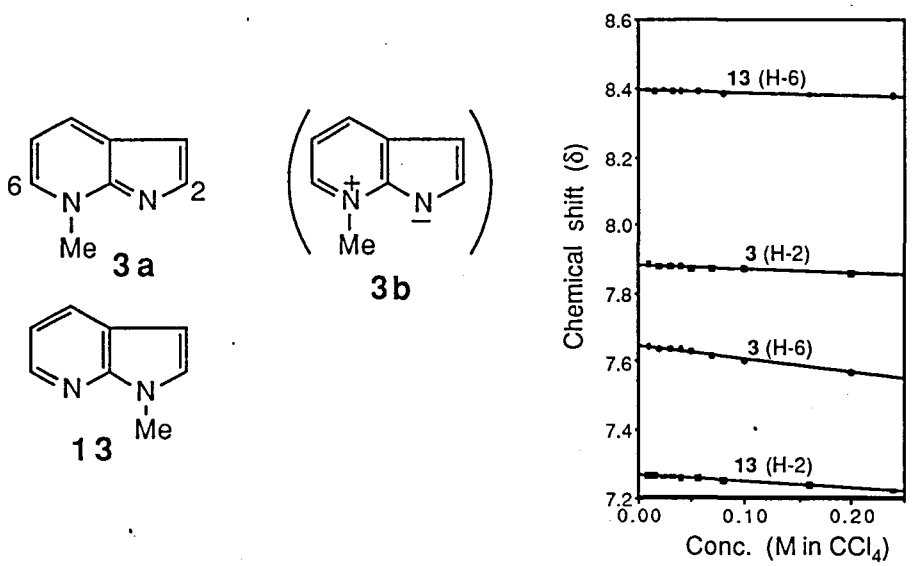


Figure 2. Effect of concentration on ^{1}H-NMR chemical shift of compounds **3** and **13**

3, which was methylated at 7-position, were shifted upfield to some extent with increasing concentration. If the slope of this variation due to intermolecular interaction is large, we may postulate that the betaine structure **3b** is the major contributing form. However, the slope of variation for **3** was not very different from that of the compound **13**, which does not dimerize. 4-Azaindole derivatives **6** and **14** also showed similar tendency. Therefore, it is reasonable to consider that the nonpolarized resonance structure **3a** or **6a** contributes predominantly to **3** or **6**, respectively.

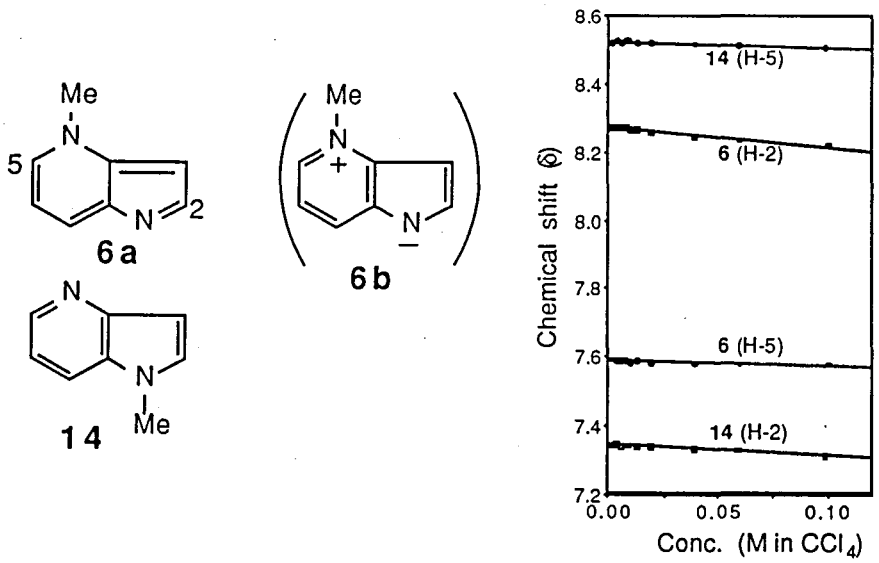


Figure 3. Effect of concentration on ^{1}H-NMR chemical shift of compounds **6** and **14**

1-2-5. Bond lengths of compounds 1, 3, 4 and 6 calculated by *ab initio* 6-31G method

Recently, J. Catalan et al. have studied the gas-phase basicity of heterobicyclic compounds including 7-azaindole derivatives using both experimental measurement and *ab initio* calculations at the STO-3G and 4-31G levels.[9e] In order to clarify the contribution of the polarized structure **3a** or **6a** to

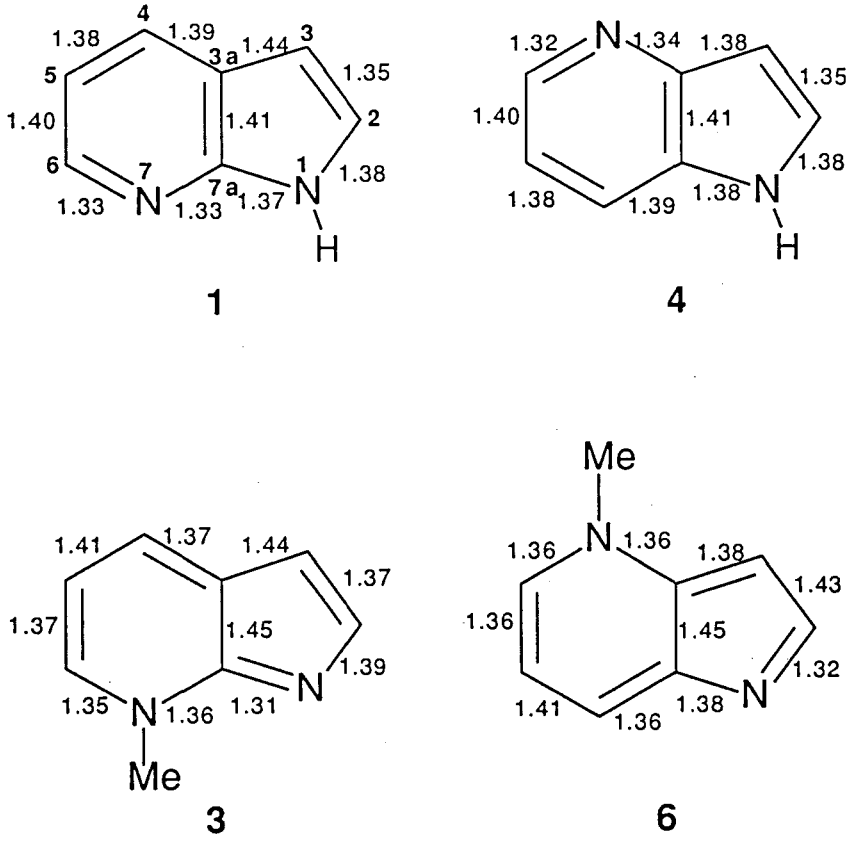


Figure 4. Bond lengths of compounds **1**, **3**, **4** and **6** calculated by the *ab initio* 6-31G method

7-methyl-7*H*-pyrrolo[2,3-*b*]pyridine (**3**) or 4-methyl-4*H*-pyrrolo[3,2-*b*]pyridine (**6**) more precisely, we carried out molecular orbital calculations for the compounds **1, 3, 4** and **6** using the *ab initio* 6-31G method. So far as we know, no report on molecular orbital calculation of 4-azaindole derivatives has appeared. The calculated bond lengths of these compounds are shown in Figure 4. It was found that the N1-C7a, C3a-C4 and C5-C6 bonds in **3** are shorter than the corresponding ones in **1**. In the case of 4-azaindole derivatives, the N1-C2, C5-C6 and C7-C7a bonds in **6** are shorter compared to **4**. As one of the characteristics of these azaindoles, the bridged bonds (C3a-C7a) in **3** and **6** were longer compared to those in **1** and **4**. These results imply that the structures **3** and **6** rather resemble to **3a** and **6a**, respectively.

1-2-6. Dipole moments and total atomic charges of compounds 1, 3, 4 and 6 calculated by the *ab initio* 6-31G method

Figure 5 showed the total atomic charges and the dipole moments of compounds **1, 3, 4** and **6**. Comparison of the calculated atomic charges of compounds **3** and **6** with those of the azaindoles **1** and **4** indicated that some atomic charge migrates from the pyrrole ring to the pyridine ring. These atomic charges on carbons explain well the features of the aforementioned chemical shifts in ^{13}C-NMR spectra of **3** and **6**. The remarkable changes in the direction of the dipole moments also supported the charge migration. Thus, in compounds **1** and **4** the dipole moments were directed toward the pyrrole ring from the pyridine ring, but the directions were reversed in **3** and **6**.

The results of the calculation suggested that the anions on N-1 of the betaine structures **3b** and **6b** migrated to the pyridine ring to form the non-polarized structures **3a** and **6a**.

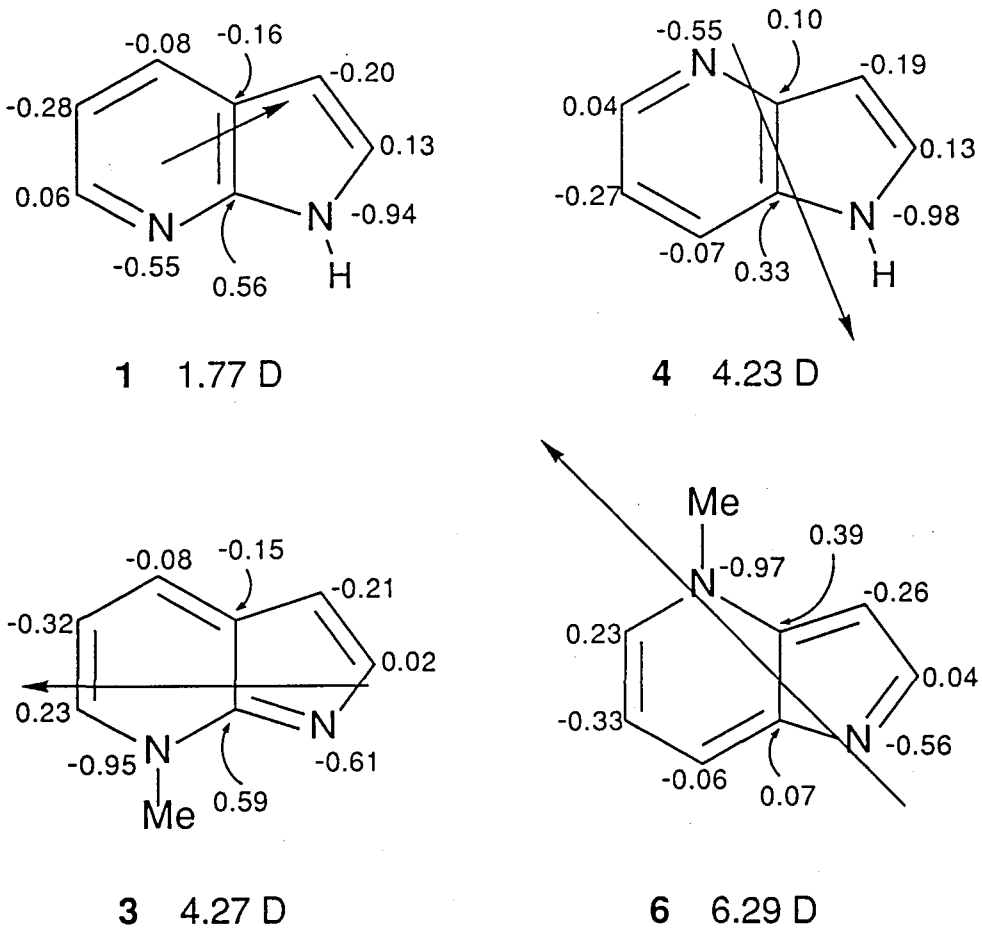


Figure 5. Dipole moments and total atomic charges of compounds **1**, **3**, **4** and **6** calculated by the *ab initio* 6-31G method

As a consequence, the electronic natures of the pyrrole ring and the pyridine ring of azaindole skeleton were exchanged. It is concluded from both experimental and calculated results that the contribution of the nonpolarized

structure **3a** or **6a** to azaindole **3** or **6** is greater than that of the polarized structure **3b** or **6b**.

1-3. Experimental and Calculation

General

The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-EX270 spectrometer with tetramethylsilane as an internal standard. The ^{15}N NMR spectra in DMSO-d_6 or $CDCl_3$ solutions at a concentration of 1.0 M were recorded on a JEOL JNM-GSX400 spectrometer with formamide as an external standard and chemical shifts are given in ppm from anhydrous liquid ammonia. IR spectra were measured on a Hitachi 270-30 infrared spectrometer. Mass spectra were obtained by electron impact (EI) on a Shimadzu GCMS-QP2000 or a JEOL JMS-DX303 mass spectrometer. Melting points were obtained with a Yanagimoto micro melting point apparatus or a Yamato melting point apparatus model MP-21 and are uncorrected. The molecular orbital calculations by the *ab initio* method at the 6-31G level was carried out using the GAUSSIAN 90 program system.

1*H*-Pyrrolo[2,3-*b*]pyridine (**1**), purchased from Aldrich Chemical, was used after recrystallization from hexane/benzene and 1*H*-pyrrolo[3,2-*b*]pyridine (**4**) was prepared as described previously.[16)]

7-Methyl-7-azaindolium iodide (2)

To a solution of 7-azaindole (**1**: 590 mg, 5 mmol) in anhydrous acetone (10 ml) was added iodomethane (7.1 g, 50 mmol) under a nitrogen atmosphere at room temperature. After stirring for 24 h at the same temperature, the precipitated solid was filtered and washed with diethyl ether. The crude product was subjected to recrystallization from methanol/ether to give **2** (1.28 g, 99 %) as

colorless plates: mp 153-154 °C (lit.[10] mp 154-155 °C); IR (KBr) 3392 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ = 4.45 (3H, s, Me), 7.00 (1H, d, J = 3.4 Hz, H-3), 7.65 (1H, dd, J = 6.5, 7.7 Hz, H-5), 7.99 (1H, d, J = 3.4 Hz, H-2), 8.74 (1H, d, J = 7.7 Hz, H-4), 8.76 (1H, d, J = 6.5 Hz, H-6); ^{13}C NMR (DMSO-d_6) δ = 42.5 (Me), 103.5 (C-3), 116.0 (C-5), 125.6 (C-3a), 129.7 (C-2), 136.8 (C-4), 137.4 (C-6), 139.5 (C-7a); MS (EI) m/z (relative intensity) 133 (M^+, 12), 132 (M^+ - H, 100), 118 (M^+ - Me, 3).

7-Methyl-7*H*-pyrrolo[2,3-*b*]pyridine (3)

To a solution of 7-methyl-7-azaindolium iodide (2: 780 mg, 3.0 mmol) in water (15 ml) was added gradually solid K_2CO_3 (15 g) at room temperature. After stirring for 24 h at the same temperature, the solution was extracted with diethyl ether (30 ml x 5), dried (K_2CO_3) and concentrated in vacuo. The residue was stored in a refrigerator to afford yellow solid, which was recrystallized from hexane to give **3** (425 mg, 100 %) as yellow plates: mp 42 °C (lit.[10] mp 44 °C); IR (NaCl) 1622, 1564 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 4.26 (3H, s, Me), 6.66 (1H, d, J = 2.5 Hz, H-3), 6.79 (1H, dd, J = 6.1, 7.6 Hz, H-5), 7.52 (1H, d, J = 6.1 Hz, H-6), 7.89 (1H, d, J = 2.5 Hz, H-2), 8.08 (1H, d, J = 7.6 Hz, H-4); ^{13}C NMR ($CDCl_3$) δ = 40.1 (Me), 101.4 (C-3), 108.8 (C-5), 129.6 (C-6), 130.3 (C-7a), 130.5 (C-4), 145.4 (C-2), 149.1 (C-3a); MS (EI) m/z (relative intensity) 132 (M^+, 100), 131 (M^+ - H, 80), 104 (M^+ - H - HCN, 21).

4-Methyl-4-azaindolium iodide (5)

Following the procedure for the preparation of **2**, **4** (118 mg, 1 mmol) was treated with iodomethane (1.42 g, 10 mmol) in acetone (2 ml) to afford **5** (213 mg, 82 %) as colorless plates: mp 180-181 °C (dec); IR (KBr) 3116 (NH), 1596 cm^{-1}; ^1H NMR (DMSO-d_6) δ = 4.42 (3H, s, Me), 7.06 (1H, d, J = 2.6 Hz, H-3), 7.68 (1H, dd, J = 6.0, 8.6 Hz, H-6), 8.33 (1H, d, J = 2.6 Hz, H-2), 8.58 (1H, d, J = 8.6 Hz, H-7), 8.76 (1H, d, J = 6.0 Hz, H-5); ^{13}C NMR (DMSO-d_6) δ = 40.3 (Me), 92.8 (C-3), 113.4 (C-6), 123.7 (C-2), 128.6 (C-7a), 133.2 (C-7), 134.9 (C-5), 134.3 (C-3a); MS (EI) m/z (relative

intensity) 133 (M^+, 10), 132 (M^+ - H, 100), 118 (M^+ - Me, 41); Found: *m/z* 132.0678. Calcd for $C_8H_8N_2$: 132.0687 (M^+ - H).

4-Methyl-4*H*-pyrrolo[3,2-*b*]pyridine (6)

Following the procedure for preparation of **3**, **5** (260 mg, 1 mmol) was treated with K_2CO_3 (5 g) in water (5 ml) to afford **6** (131 mg, 100 %) as yellow plates from the ethereal extract on storage in a refrigerator: mp 40 °C; IR (NaCl) 1620, 1574 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 4.06 (3H, s, Me), 6.39 (1H, d, *J* = 1.7 Hz, H-3), 6.87 (1H, dd, *J* = 6.1, 7.6 Hz, H-6), 7.50 (1H, d, *J* = 6.1 Hz, H-5), 8.11 (1H, d, *J* = 7.6 Hz, H-7), 8.27 (1H, d, *J* = 1.7 Hz, H-2); ^{13}C NMR ($CDCl_3$) δ = 42.8 (Me), 91.7 (C-3), 109.6 (C-6), 127.5 (C-7), 130.0 (C-5), 141.2 (C-7a), 144.8 (C-3a), 152.6 (C-2); MS (EI) *m/z* (relative intensity) 132 (M^+, 100), 105 (M^+ -HCN, 11); Found: *m/z* 132.0677. Calcd for $C_8H_8N_2$: 132.0687.

1-4. Rererences

1. (a) M. O. Monnet, T. Fauret, V. Levacher, G. Dupas, J. Bourguignon and G. Queguiner, *J. Heterocyclic Chem.*, **26**, 1029 (1989); (b) V. Levacher, R. Benoit, J. Bourguignon and G. Quiguiner, *Tetrahedron*, **47**, 429 (1991).
2. L. N. Yakhontov and A. A. Prokopov, *Russian Chemical Review*, **49**, 428 (1980).
3. G. W. Gribble, "Advances in Heterocyclic Natural Product Synthesis", ed by W. H. Pearson, JAI press, London (1990), Vol. 1 pp 43-94.
4. S. Minakata, M. Komatsu and Y. Ohshiro, *Synthesis*, 661 (1992).
5. S. Minakata, S. Itoh, M. Komatsu and Y. Ohshiro, *Bull. Chem. Soc. Jpn.*, in press.
6. (a) R. W. Brookes and R. L. Martin, *Aust. J. Chem.*, **27**, 1569 (1974); (b) R. W. Brookes and R. L. Martin, *Inorg. Chem.*, **14**, 528 (1975); (c) F. A. Cotton, D. Lay

and M. Millar, *Inorg. Chem.*, **17**, 186 (1978); (d) S. Peng and C. Lai, *J. Chin. Chem. Soc.*, **35**, 325 (1988); (e) F. Allaire and A. Beauchamp, *Inorganica Chim. Acta*, **156**, 241 (1989).

7. J. A. Walmsley, *J. Phys. Chem.*, **85**, 3181 (1981).
8. (a) C. A. Taylor, M. A. El-Bayoumi and M. Kasha, *Proc. Nat. Acad. Sci. U. S.*, **63**, 253 (1969); (b) K. C. Ingham, M. Abu-Elgheit and M. A. El-Bayoumi, *J. Am. Chem. Soc.*, **93**, 5023 (1971); (c) K. C. Ingham and M. A. El-Bayoumi, *J. Am. Chem. Soc.*, **96**, 1674 (1974); (d) P. Avouris, L. L. Yang and M. A. El-Bayoumi, *Photochem. Photobiol.*, **24**, 211 (1976); (e) J. Konijnenberg, A. H. Huizer and C. A. G. O. Varma, *J. Chem, Soc., Faraday Trans. 2*, **84**, 1163 (1988).
9. (a) J. Catalan, P. Perez and M. Yanez, *Tetrahedron*, **38**, 3693 (1982); (b) J. Catalan, O. Mo, P. Perez and M. Yanez, *Tetrahedron*, **39**, 2851 (1983); (c) J. Waluk, B. Pakula and G. Balakier, *Chem. Phys. Lett.*, **94**, 58 (1983); (d) J. Catalan, O. Mo, P. Perez, M. Yanez and F. Amat-Guerri, *Nouv. J. Chim.*, **8**, 87 (1984); (e) J. Catalan, L. G. de Paz, M. Yanez, F. Amat-Guerri, R. Hourient, E. Rolli, R. Zehringer, P. Oelhafen, R. W. Taft, F. Anvia and J. H. Qian, *J. Am. Chem. Soc.*, **110**, 2699 (1988); (f) L. Chen, R. Flammang, A. Maquestiau, R. W. Taft, J. Catalan, P. Cabildo, R. M. Claramunt and J. Elguero, *J. Org. Chem.*, **56**, 179 (1991).
10. J. P. Saxena, *Indian J. Chem.*, **5**, 73 (1967).
11. (a) H. Timpe, U. Müller, R. Worschech, *J. Prakt. Chem.*, **322**, 517 (1980); (b) R. H. Cox and S. Sankar, *Org. Magn. Res.*, **14**, 150 (1980).
12. *Gaussian 90*, M. J. Frisch, M. Head-Gordon, G. W. Truck's, J. B. Foresman, H. B. Schlegel, K. Raghavachari, M. A. Robb, J. S. Binkley, C. Gonzalez, D. J. Defrees, D. J. Fox, R. A. Whiteside, R. Seeger, C. F. Melius, J. Baker, R. L.

Martin, L. R. Kahn, J. J. P. Stewart, S. Topiol, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1990.

13. N. S. Rao, M. M. Das, G. B. Rao and D. Ziessow, *Spectroscopy Lett.*, **18**, 827 (1985).
14. R. O. Duthaler and J. P. Roberts, *J. Am. Chem. Soc.*, **100**, 4969 (1978).
15. E. Lippmaa, M. Magi, S. S. Novikov, L. I. Khmelnitski, A. S. Prihodko, O. V. Lebedev and L. V. Epishina, *Org. Mag. Res.*, **4**, 197 (1972).
16. T. Sakamoto, Y. Kondo, S. Iwashita and H. Yamanaka, *Chem. Pharm. Bull.*, **35**, 1823 (1987).

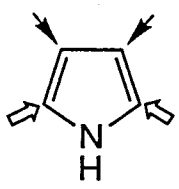
CHAPTER 2. REGIOSELECTIVE FUNCTIONALIZATION OF 7- AND 4-AZAINDOLES

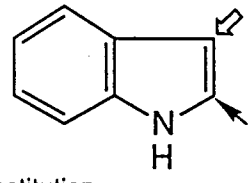
2-1. Introduction

As mentioned in Chapter 1, functionalized azaindoles have much larger dipole moments than non-functionalized azaindoles and, hence, they are expected to be functional materials or their precursors. On the other hand, 7-azaindole derivatives. attract much interest in biochemical studies,[1] since they are aza-analogs of indoles whose skeleton is often found in natural alkaloids and in synthetic pharmaceuticals.[2] So it is of great importance to functionalize the azaindole ring for development of materials having new or improved properties.

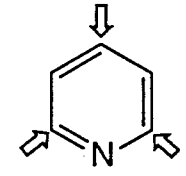
Thus in this Chapter, the functionalization of 1*H*-pyrrolo[2,3-*b*]pyridine (7-azaindole) and 1*H*-pyrrolo[3,2-*b*]pyridine (4-azaindole) was investigated.

Among the ring substitution reactions of heterocyclic compounds, electrophilic substitutions are achieved at 2- or 3-position in the case of pyrrole or indole which is π-sufficient, but π-deficient pyridine ring is attacked at 2-, 4- and 6-position by nucleophiles which considarable hardness.





Electrophilic Substitution



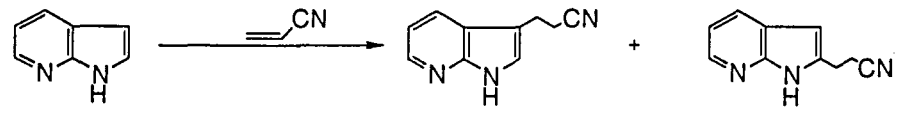
Nucleophilic Substitution

On the other hand, the chemical properties of azaindoles are reduced as compared with either pyridine ring or pyrrole ring since azaindoles consist of ring systems having opposite π-electron densities. Reactivity of electrophilic

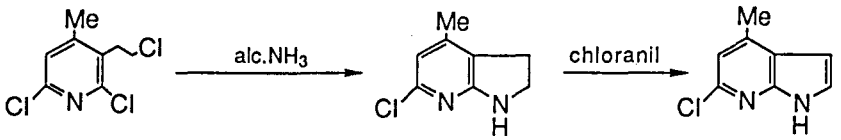
substitution on the pyrrole ring of azaindoles is slightly reduced as compared with reactivity of substitution on pyrrole and indole rings, whereas nucleophilic substitution of its pyridine ring is very difficult.[3)]

Hence, in general, 6-substituted 7-azaindoles have been synthesized by the ring closure of pyridine derivatives possessing functional groups[4)] and the procedure of direct functionalization at 6-position of 7-azaindole has rarely been known.[5)] The only known example is chlorination[5)] of 7-azaindole at 4-position by the reaction of its *N*-oxide with $POCl_3$.

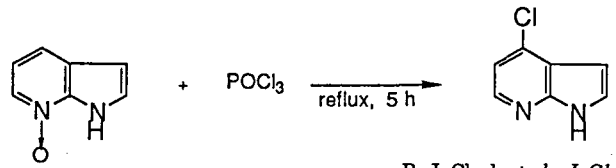
The lack of convenient functionalization method of azaindoles prompted me to investigate regioselective functionalization of 7-azaindole and 4-azaindole by Reissert-Henze type reaction. Thus halogeno (Cl, Br, I), cyano and thiocyanato groups were directly introduced to the pyridine ring of 7-azaindole, as well as chloro and cyano groups were introduced to the pyridine ring of 4-azaindole.



M. R. Bell, *Belg. Pat.* (1965)



L. N. Yakhontov, *Zhur. Ob. Khimi.* (1964)



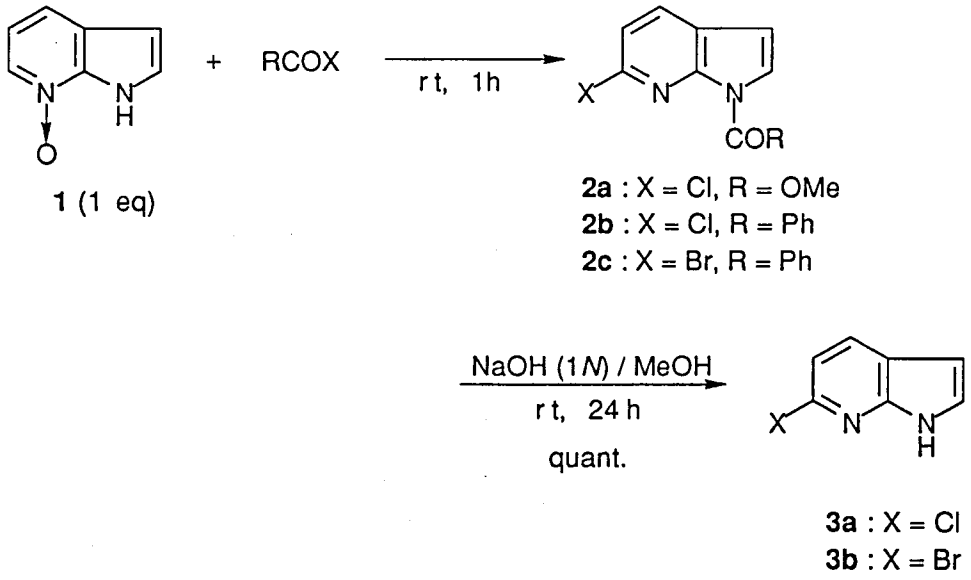
B. J. Clark *et al.*, *J. Chem. Soc. Perkin Trans. 1* (1974)

2-2. Results and Discussion

2-2-1. Regioselective functionalization of 7-azaindole via its *N*-oxide

a) Chlorination and bromination of 7-azaindole

7-azaindole *N*-oxide **1**[6] was treated with acid halides in anhydrous tetrahydrofuran to give 6-halo-7-azaindole derivatives **2a~c** in 57~66 % yields. Acyl groups on *N*-1 atom of **2** are readily removed by basic treatment to give **3** in quantitative yields. The results are listed in Table 1.



One of the important feature of the reaction is the halogenation reaction are completely regioselective and no 4-halogenated product was detected.

Though the present reaction did proceed in the absence of a base (run 1), addition of an organic or inorganic base caused an increase in the yield of the chlorinated product **2a**. Among them, 1,1,1,3,3,3-hexamethyldisilazane (HMDS) was the most effective (runs 7-9). Since unreacted pyridine *N*-oxide is often

Table 1 : Halogenation of 7-azaindole *N*-oxide

Run	X	R	RCOX (eq.)	Base (eq.)	Solv.	Product	Yield (%)[a]
1	Cl	OMe	2.0	——	THF	**2 a**	20
2	Cl	OMe	2.0	Et_3N (1.0)	THF	**2 a**	44
3	Cl	OMe	2.0	Et_3N (1.0)	PhH	**2 a**	46
4	Cl	OMe	2.0	Et_3N (2.0)	THF	**2 a**	46
5	Cl	OMe	2.0	DBU (1.0)	THF	**2 a**	45
6	Cl	OMe	3.0	K_2CO_3 (5.0)	THF	**2 a**	47
7	Cl	OMe	2.0	HMDS (0.5)	THF	**2 a**	63
8	Cl	OMe	2.0	HMDS (0.5)	PhH	**2 a**	63
9	Cl	OMe	2.5	HMDS (1.0)	THF	**2 a**	66
10	Cl	Ph	2.0	Et_3N (1.0)	THF	**2 b**	34
11	Cl	Ph	2.0	HMDS (0.5)	PhH	**2 b**	60
12	Br	Ph	2.0	Et_3N (1.0)	THF	**2 c**	38
13[b]	Br	Ph	2.5	HMDS (1.0)	PhH	**2 c**	57

a) Isolated yield (yields determined by ^{1}H-NMR are ca. 10 % higher than these values).

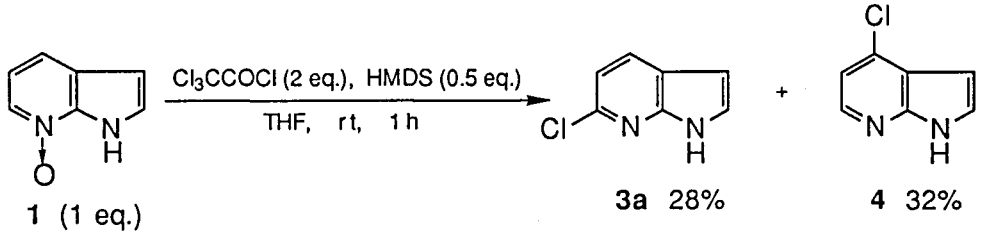
b) Solutions of benzoyl bromide and HMDS in benzene were added dropwise simultaneously to a solution of 7-azaindole *N*-oxide in benzene.

recovered as hydrogen halide salt in Reissert-Henze type reactions, trapping of proton is considered to be one of the important factors to get better yields. HMDS is expected to be a good trapping agent of hydrogen halide resulted by acylation at *N*-1. While the other organic bases form ammonium salts which may serve as proton donors, HMDS generates ammonia upon contact with hydrogen halide.

$$\text{HMDS} + 2\,\text{HX} \longrightarrow 2\,\text{Me}_3\text{Si-X} + \text{NH}_3$$

In this reaction, change of the solvent from tetrahydrofuran to benzene caused no significant effect (runs 2 and 3, or 7 and 8). Benzoyl chloride could be also used instead of the chlorocarbonate to give 1-benzoyl analog **2b** (runs 10 and 11), where the chlorination reaction was effectively assisted by HMDS which approximately doubled the yield (run 11) as compared with Et_3N. When benzoyl bromide was employed (runs 12 and 13), 6-bromination successfully occurred and 1-benzoyl-6-bromo-7-azaindole (**2c**) was obtained according to a modified reaction procedure (footnote b) of Table 1).[7]

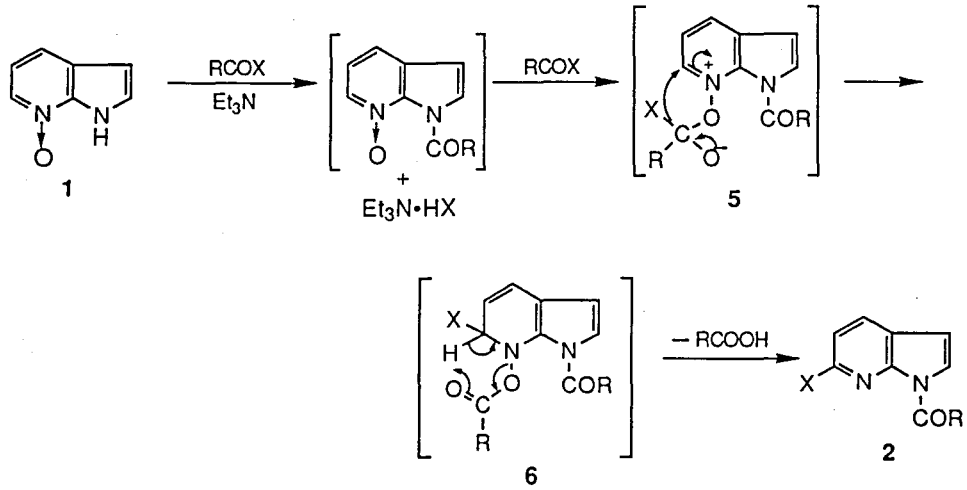
When trichloroacetyl chloride was employed as an acid halide, both 6-chloro-7-azaindole and the 4-chloro isomer were obtained in 28 % and 32 % yields, respectively.



Chlorination of pyridine itself is successfully carried out by the reaction of its *N*-oxide with $POCl_3$ or SO_2Cl_2,[8] but this type of reaction did not occur with acid halides, showing clear contrast to that of 7-azaindole. We tested 2-aminopyridine as a model of 7-azaindole, but halogenated product was not obtained by the reaction of 2-aminopyridine *N*-oxide[9] with methyl chloroformate.

A plausible reaction path is assumed as followes. The pyridinium salt **5** was formed by acylation and addition with two moles of an acid halide. Intramolecular nucleophilic attack of the chloride ion to the 6-position of the intermediate **5** gave 1,2-dihydropyridine intermediate **6**. Intramolecular

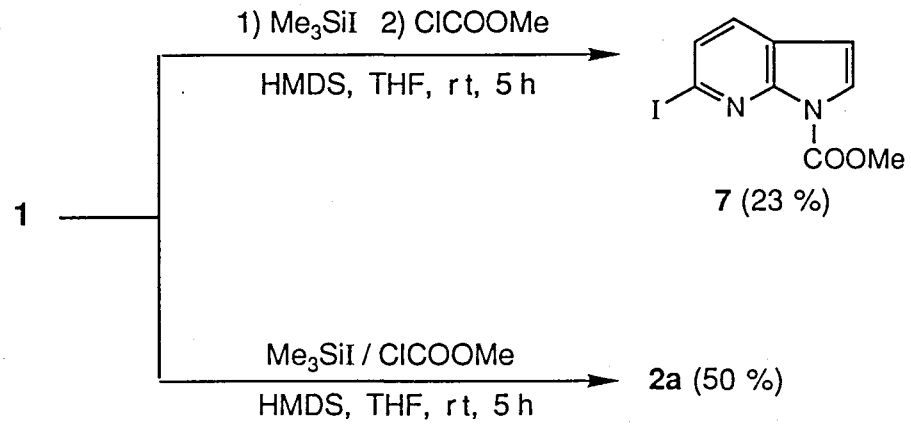
decarboxylation and successive aromatization occurred to afford the 6-halogenated product. If the addition and the elimination would not proceed intramolecularly, it was considered that the improvement of the yield would be expected by adding silver nitrate or bases. Nevertheless no effect was observed for these additives, which well supported this intramolecular mechanism.



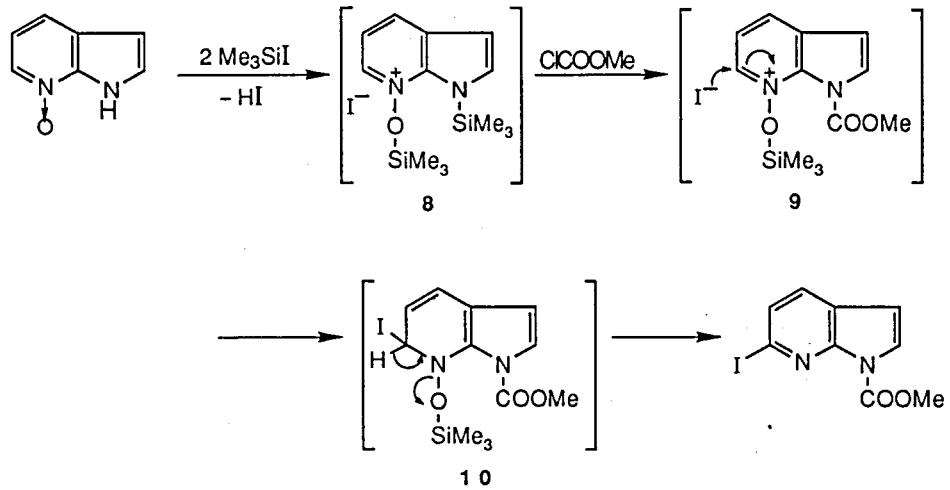
b) Iodination of 7-azaindole

Introduction of other functional groups to pyridine ring of 7-azaindole was also attempted. Since silicon has a strong affinity toward oxygen, reactions of 7-azaindole *N*-oxide with silicon reagents were investigated. Iodination of 7-azaindole was performed with trimethylsilyl iodide, whereas two different procedures gave rise to different products. When trimethylsilyl iodide was added to a solution of 7-azaindole *N*-oxide and HMDS in tetrahydrofuran prior to addition of methyl chloroformate, 6-iodo-1-methoxycarbonyl-7-azaindole (**7**) was obtained in 27 % yield. On the other hand, a solution of trimethylsilyl iodide and methyl chloroformate in tetrahydrofufan was added dropwise to a solution of the *N*-oxide and HMDS in tetrahydrofuran to afford only the chlorinated product **2a**.

Reissert-Henze type iodination reaction like this has not been reported even for pyridine itself.[10)]



Presumable mechanism of the iodination is as follows. Two molecules of trimethylsilyl iodide reacted with 7-azaindole *N*-oxide to give siloxypyridinium salt **8**. Formation of the salt **8** was confirmed by monitoring the reaction by ^{1}H-



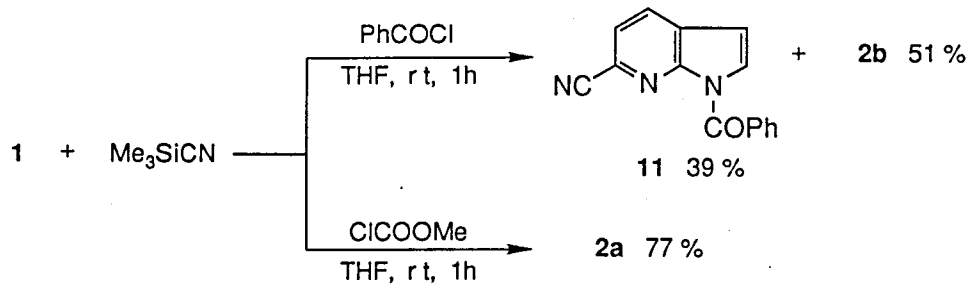
NMR spectroscopy. This pyridinium ring was not attacked by iodide ion, but methoxycarbonylation of N-1 by adding methyl chloroformate caused addition of

iodide ion onto the 6-position. Furthermore, silanol was eliminated from 1,2-dihydropyridine intermediate **10** to give the product.

c) Cyanation and thiocyanation of 7-azaindole

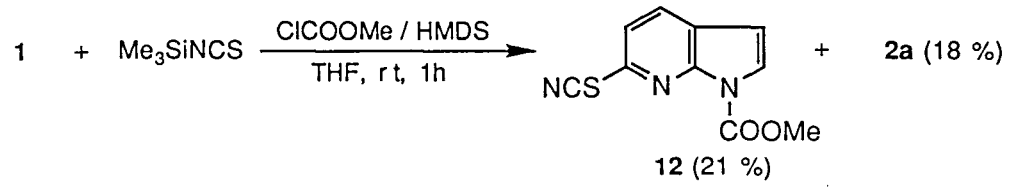
Pyridine *N*-oxide can be converted to 2- or 4-cyanopyridine by the reaction with trimethylsilyl cyanide[11] or diethyl phosphorocyanide[12] and by alkylation[13] or acylation[14] and subsequent treatment with aqueous alkali cyanide. Though 7-azaindole *N*-oxide was heated with trimethylsilyl cyanide in refluxing tetrahydrofuran, the starting materials were recovered.

Addition of benzoyl chloride to this system accelerated the substitution by cyanide ion and the reaction at room temperature gave considerable amount of 1-benzoyl-6-cyano-7-azaindole (**11**) along with the chlorinated derivative **2b**. The substitution occurred selectively at 6-position similarly to halogenation. Interestingly, in the case of using methyl chloroformate as the acylating agent, cyanation did not proceed at all and only 1-methoxycarbonyl-6-chloro-7-azaindole (**2a**) was isolated.

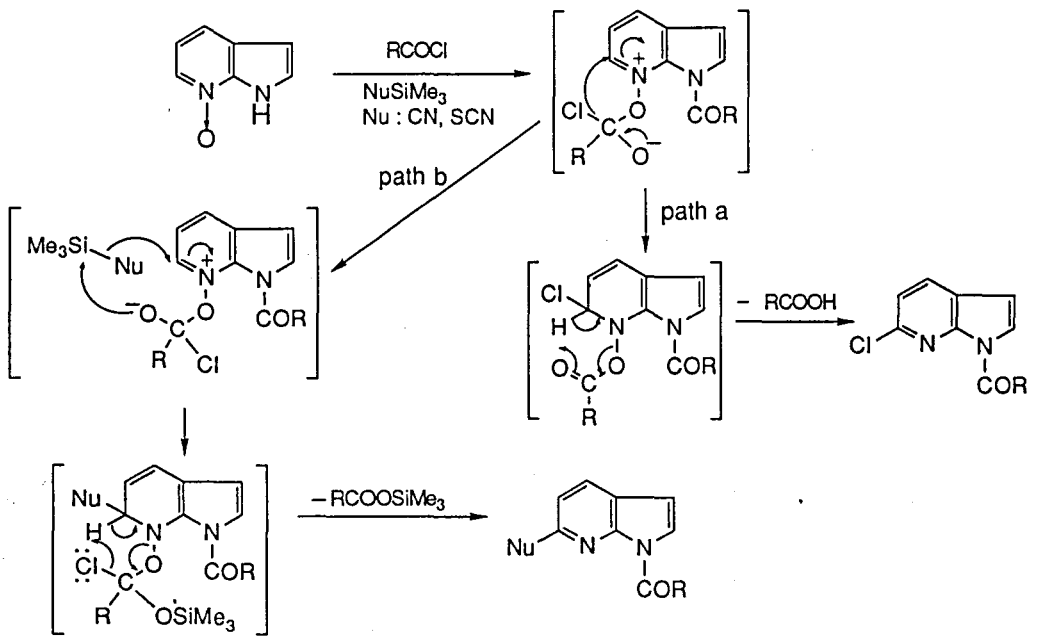


As the silyl cyanide acted as a cyanation reagent, another silyl derivative was studied to introduce thiocyanato group. Trimethylsilyl isothiocyanate was allowed to react with 7-azaindole *N*-oxide in a similar manner as the cyanation reaction and 1-methoxycarbonyl-6-thiocyanato-7-azaindole (**12**) was obtained. No isothiocyanato derivative was isolated in the reaction. Preparation of thiocyanato-

or isothiocyanatopyridine[15] by direct substitution of the ring has never been known.



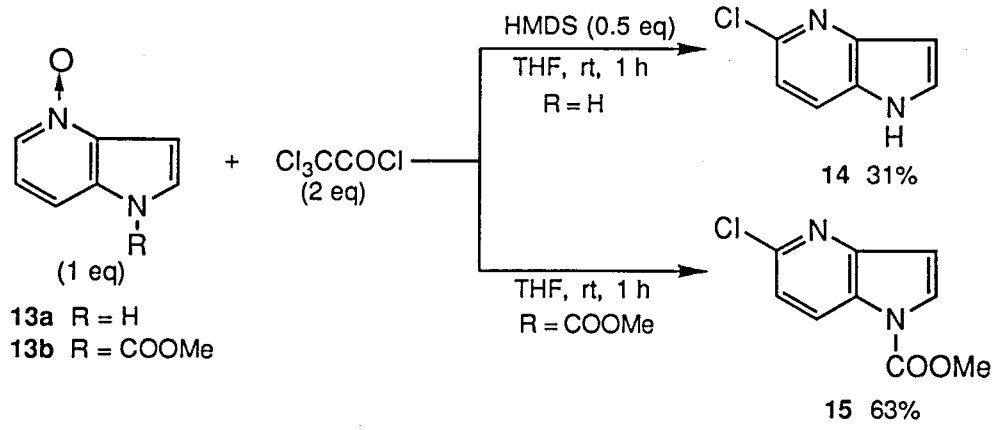
The possible reaction path of the cyanation or thiocyanation of 7-azaindole is given below. As both products were accompanied by chlorinated compounds, paths a and b are considered to be competing in these reactions. Path a is the aforementioned intramolecular chlorination route. But, in path b, oxygen anion of the pyridinium salt attacks the silicon reagents and generated nucleophiles attack at the 6-position intramolecularly. In the last step, the products were given upon elimination of silyl ester.



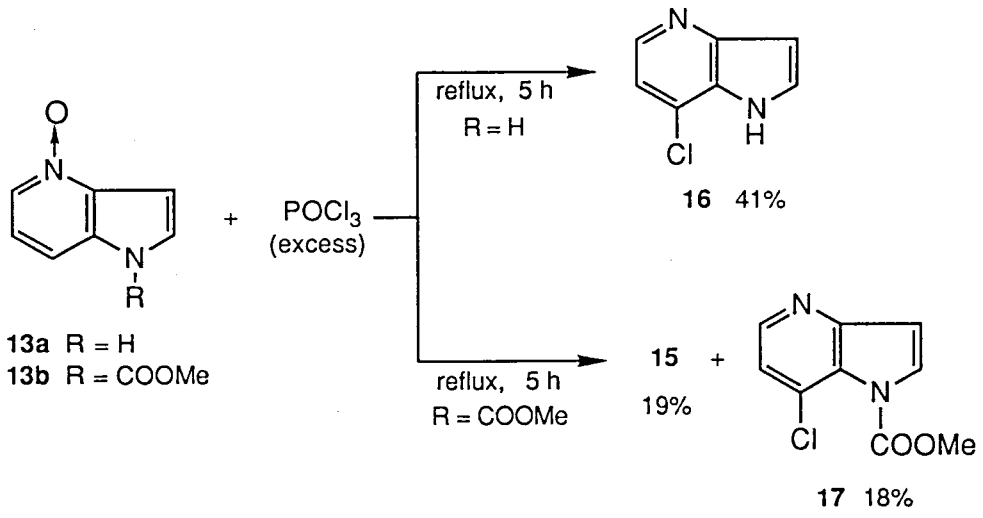
2-2-2. Regioselective functionalization of 4-azaindole via its *N*-oxide

a) Chlorination of 4-azaindole

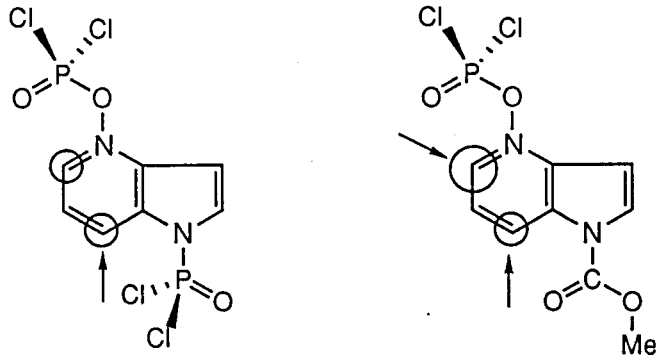
In contrast to 7-azaindole, the regioselective functionalization of the pyridine ring of 4-azaindole has not been known. Though the aforementioned chlorination method of 7-azaindole was applied to 4-azaindole *N*-oxide, the reaction did not proceed at all. Therefore 4-azaindole *N*-oxide was reacted with trichloroacetyl chloride which has stronger electron-withdrawing group than methyl chloroformate or benzoyl chloride. As a result of this reaction, the chlorine atom was introduced regioselectively to 5-position of 4-azaindole. Replacement of *N*-1 hydrogen with methoxycarbonyl group doubled the yield of 5-chlorination. But the reason for this change in yield is not clear at the moment.



On the other hand, the chlorination proceeded at 7-position when 4-azaindole *N*-oxide was treated with phosphorus oxychloride. Regioselectivity in chlorination of 4-azaindole was lost in the reaction 1-methoxycarbonyl-4-azaindole *N*-oxide with phosphorus oxychloride which gave 5-chlorinated 4-azaindole **15** and 7-chlorinated isomer **17** in 1 : 1 ratio.



Molecular orbital calculation (PM3) could explain these phenomena successfully. Two reaction intermediates A and B were calculated to get insight into the reaction mechanism.

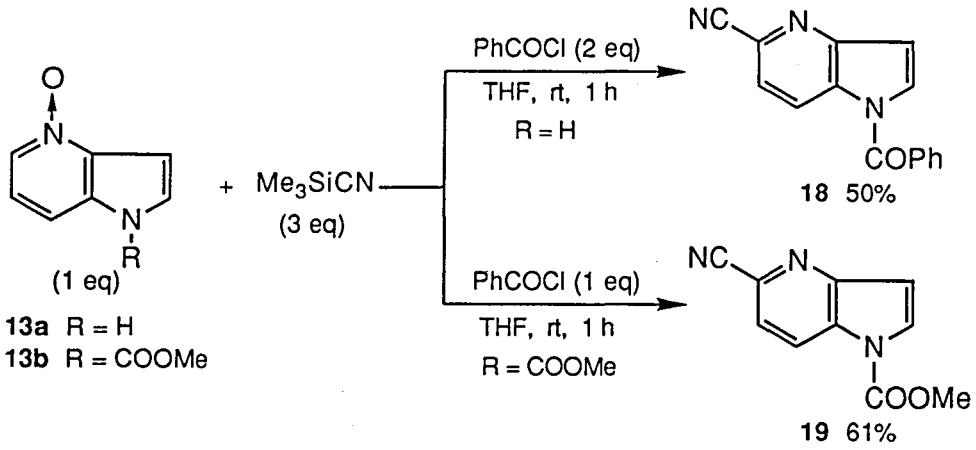


In the case of A, the eigenvalues of C-5 and C-7 of LUMO are almost same in scale (shown as circles in the above structure) and they suggest that susceptibility toward nucleophilic attack at C-5 is not different from that at C-7. However, orientations of two P=O bonds in the intermediate become significant. In other words, approach of a nucleophile to 5-position suffers from larger

electrostatic repulsion between the oxygen than that to 7-position. Thus the nucleophilic attack of chloride ion occurs predominantly at 7-position. In the case of B, it is considered that the electrostatic repulsions are sterically the same situation both at C-5 and C-7 positions. Since the eigenvalue of C-5 of LUMO is larger than that of C-7, the chlorinated product at 5-position is obtained exclusively.

b) Cyanation of 4-azaindole

It turned out that the cyanation method of 7-azaindole could be applied also to 4-azaindole *N*-oxide. Though the chlorinated product was obtained in the cyanation of 7-azaindole, only cyanation reaction proceeded in this case to give better yields.



2-2-3. Regioselectivity in chlorination of azaindoles

The regioselectivity in chlorination of 7- and 4-azaindoles is summarized in Table 2.

Table 2 Regioselectivity in Chlorination of Azaindoles

RCl	7-azaindole		4-azaindole	
	6-	4-	5-	7-
MeOCOCl, PhCOCl	Cl	—	—	—
Cl_3CCOCl	Cl (50)[a]	Cl (50)[a]	Cl	—
$POCl_3$ (1-COOMe)			Cl (50)[a]	Cl (50)[a]
$POCl_3$	—	Cl	—	Cl

a) Numbers in parentheses indicate ratio of regioisomers.

The position of chlorination changed to γ-position of the pyridine ring from α-position with increase in the electron-withdrawing nature of R. This tendency was observed for the both azaindoles, but the chlorination of 4-azaindole needs stronger electron-withdrawing ability of R than that for chlorination of 7-azaindole.

2-3. Experimental

General

Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. Ir spectra were taken on a Hitachi 270-30 infrared spectrometer. ^1H and ^{13}C NMR were recorded on a JEOL JMN-FX-90Q spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained by electron impact (EI) on a Shimadzu GCMS-QP2000 or a JEOL JMS-DX303 mass spectrometer.

6-Chloro-1-methoxycarbonylpyrrolo[2,3-*b*]pyridine (2a)

To a solution of 7-azaindole *N*-oxide[6] (**1** : 134 mg, 1.0 mmol) and HMDS (161 mg, 1.0 mmol) in THF (10 ml) was added dropwise methyl chloroformate (236

mg, 2.5 mmol) under nitrogen atmosphere at room temperature. After stirring for one hour at the same temperature, the solvent was removed and the reaction mixture was washed with saturated $NaHCO_3$ aq. (10 ml x 3), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography on a silica gel column (eluted with hexane/EtOAc = 9/1) to give **2a** (139 mg, 66 %) as colorless plates : mp 118-119 °C; IR (KBr) 1744 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 4.11 (3H, s, COOMe), 6.56 (1H, d, *J* = 4.2 Hz, H-3), 7.23 (1H, d, *J* = 8.1 Hz, H-5), 7.73 (1H, d, *J* = 4.2 Hz, H-2), 7.83 (1H, d, *J* = 8.1 Hz, H-4); MS (DEI) *m/z* (relative intensity) 212 (M^++ 2, 35), 210 (M^+, 100); Found: C, 51.34; H, 3.37; N, 13.26; Cl, 16.67%. Calcd for $C_9H_7ClN_2O_2$: C, 51.32; H, 3.36; N,13.30; Cl,16.83.

1-Benzoyl-6-chloropyrrolo[2,3-*b*]pyridine (2b)

Following the procedure for **2a**, the reaction of 7-azaindole *N*-oxide (**1** : 134 mg, 1.0 mmol), HMDS (81 mg, 0.5 mmol), and benzoyl chloride (281 mg, 2.0 mmol) afforded **2b** (154 mg, 60 %) as colorless needles : mp 128-130 °C; IR (KBr) 1712 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 6.63 (1H, d, *J* = 4.2 Hz, H-3), 7.21 (1H, d, *J* = 8.2 Hz, H-5), 7.5-8.0 (7H, m, Ph, H-2, H-4); MS (DEI) *m/z* (relative intensity) 258 (M^++ 2, 6), 256 (M^+, 17), 105 ($PhCO^+$, 100); Found: C, 65.27; H, 3.44; N, 10,88; Cl, 13.59 %. Calcd for $C_{14}H_9ClN_2O$: C, 65.51; H, 3.53; N, 10.92; Cl, 13.81.

1-Benzoyl-6-bromopyrrolo[2,3-*b*]pyridine (2c)

Solutions of benzoyl bromide (463 mg, 2.5 mmol) in 10 ml of benzene and HMDS (162 mg, 1.0 mmol) in 10 ml of benzene were added dropwise to a solution of 7-azaindole *N*-oxide (**1** : 134 mg, 1.0 mmol) in 20 ml of benzene over one hour under nitrogen atmosphere at room temperature. The mixture was stirred at the same temperature for another hour and the reaction mixture was washed with saturated $NaHCO_3$ aq. (30 ml x 3), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography on a silica gel column (eluted with hexane/ EtOAc = 9/1) to give **2c** (172 mg, 57 %) as colorless plates : mp 133-134 °C; IR (KBr) 1714 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 6.62 (1H, d, *J* = 4.2 Hz, H-3), 7.33

(1H, d, J = 8.1 Hz, H-5) 7.4-8.0 (7H, m, Ph, H-2, H-4); MS (DEI) *m/z* (relative intensity) 303 (M^++ 2, 2), 301 (M^+,3), 105 ($PhCO^+$, 100); Found: C, 56.01; H, 3.02; N, 9.30; Br, 26.72 %. Calcd for $C_{14}H_9BrN_2O$: C, 55.84; H, 3.01; N, 9.31; Br, 26.53.

6-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine (3a)

6-Chloro-1-methoxycarbonyl-7-azaindole (**2a**: 211 mg, 1.0 mmol) or 1-benzoyl-6-chloro-7-azaindole (**2b**: 257 mg, 1.0 mmol) was dissolved in MeOH (30 ml) and 1*N* NaOH (10 ml). After stirring for 24 h at room temperature, MeOH was removed and the residue was exracted with $CHCl_3$ (20 ml x 3), dried ($MgSO_4$) and concentrated in vacuo to give **3a** (152 mg, 100 %) as colorless needles : mp 170-171 °C (lit.[5] mp 170-171 °C); IR (KBr) 3038 (NH) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 6.50 (1H, dd, J = 2,0, 4.0 Hz, H-3), 7.10 (1H, d, J = 8.0 Hz, H-5), 7.30 (1H, dd, J = 4.0, 4.0 Hz, H-2), 7.88 (1H, d, J = 8.0 Hz, H-4), 11.0-11.5 (1H, br,H-1); MS (DEI) *m/z* (relative intensity) 154 (M^++ 2, 35), 152 (M^+, 100), 117 (M^+ - Cl, 47).

6-Bromo-1*H*-pyrrolo[2,3-*b*]pyridne (3b)

Following the procedure for **3a**, 1-benzoyl-6-bromo-7-azaindole (**2c**: 301 mg, 1.0 mmol) was treated with base to afford **3b** (195 mg, 99 %) as colorless needles : mp 192-193 °C; IR (KBr) 3042 (NH) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 6.50 (1H, dd, J = 1.9, 3.7 Hz, H-3), 7.33 (1H, d, J = 8.3 Hz, H-5), 7.42 (1H, dd, J = 3.7, 3.7 Hz, H-2), 7.84 (1H, d, J = 8.3 Hz, H-4), 11.0-12.0 (1H, br, H-1); MS (DEI) *m/z* (relative intensity) 199 (M^++ 2, 5.2), 197 (M^+, 8.1), 117 (M^+ -Br, 100); Found: C, 42.49; H, 2.38; N, 14.17; Br, 40.64. Calcd for $C_7H_5BrN_2$: C, 42.67; H, 2.56; N, 14.22; Br, 40.55.

4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine (4)

Following the procedure for **2a**, the reaction of **1** (134 mg, 1.0 mmol), HMDS (81 mg, 0.5 mmol), and trichloroacetyl chloride (364 mg, 2.0 mmol) afforded **3a** (43 mg, 28 %) and **4** (49 mg, 32 %) : mp 170-171 °C for **3a**, 176-177 °C for **4** (Lit.[5] mp 175-176.5 °C); 1H-NMR ($CDCl_3$) δ = 6.61 (1H, d, J = 3.4 Hz, H-3), 7.15 (1H, d, J = 5.7 Hz, H-5), 7.42 (1H, d, J = 3,4Hz, H-2), 8.24 (1H, d, J = 5.7 Hz, H-6); MS (DEI) *m/z* (relative intnsity) 154 (M^+ +2, 33), 152 (M^+, 100).

6-Iodo-1-methoxycarbonylpyrrolo[2,3-*b*]pyridine (7)

Trimethylsilyl iodide (600 mg, 3.0 mmol) was added to a solution of 7-azaindole *N*-oxide (**1** : 134 mg, 1.0 mmol) and HMDS (161 mg, 1.0 mmol) in THF (10 ml) under nitrogen atmosphere at room temperature. Then methyl chloroformate (189 mg, 2.0 mmol) was added dropwise to the above solution. After stirring for 5 h at room temperature, the solvent was removed and the reaction mixture was washed with saturated $NaHCO_3$ aq. (10 ml x 3), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography on silica gel using hexane/EtOAc = 9 /1 as an eluent to give **7** (69 mg, 23 %) as colorless needles : mp 140-142 °C; IR (KBr) 1732 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 4.09 (3H, s, COOMe), 6.52 (1H, d, J = 4.0 Hz, H-3), 7.52 (1H, d, J = 8.8 Hz, H-5), 7.64 (1H, d, J = 8.8 Hz, H-9), 7.67 (1H, d, J = 4.0 Hz, H-2); Found: *m/z* 301.9552. Calcd for $C_9H_7IN_2O_2$: M, 301.9554.

Alternatively, a solution of trimethylsilyl iodide (600 mg, 3.0 mmol) and methyl chloroformate (189 mg, 2.0 mg) in THF (5 ml) was added dropwise to a solution of 7-azaindole *N*-oxide (**1** : 134 mg, 1.0 mmol) and HMDS in THF (5 ml) under nitrogen atmosphere at room temperature over one hour. After stirring for 4 h at the same temperature, the solvent was removed and the reaction mixture was washed with saturated $NaHCO_3$ aq. (10 ml x 3), dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography on a silica gel column using hexane/EtOAc = 9/1 as an eluent to give **2a** as colorless needles; yield: 80.3 mg (27 %) : mp 140-141 °C.

1-Benzoyl-6-cyanopyrrolo[2,3-*b*]pyridine (11)

To a solution of 7-azaindole *N*-oxide (**1** : 134 mg, 1.0 mmol) and trimethylsilyl cyanide (298 mg, 3.0 mmol) in THF (10 ml) was added dropwise benzoyl chloride (281 mg, 2.0 mmol) under nitrogen atmosphere at room temperature. After stirring for one hour at the same temperature, the solvent was removed and the reaction mixture was washed with saturated $NaHCO_3$ aq.

(10 ml x 3), dried ($MgSO_4$) and concentrated in vacuo. The crude product was separated by chromatography on a silica gel column using hexane/EtOAc = 9/1 to give **2b** as colorless plates; yield: 131 mg (51 %); mp 128-130 °C and hexane/EtOAc = 7/3 to give **11** (96 mg, 39 %) as colorless needles : mp 179-181 °C; IR (KBr) 2236 (CN), 1714 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 6.76 (1H, d, *J* = 4.0 Hz, H-3), 7.4-8.2 (8H, m, Ph, H-2, H-4, H-5); MS (DEI) *m/z* (relative intensity) 247 (M^+, 8), 105 ($PhCO^+$, 100); Found: C, 72.85; H. 3.56; N, 17.00. Calcd for $C_{15}H_9N_3O$: C, 72.86; H, 3.67; N, 17.00.

1-Methoxycarbonyl-6-thiocyanatopyrrolo[2,3-*b*]pyridine (12)

Following the procedure for **7**, the reaction of 7-azaindole *N*-oxide (**1** : 134 mg, 1.0 mmol), HMDS (161 mg, 1.0 mmol), trimethylsilyl isothiocyatnate (394 mg, 3.0 mmol) and methyl chloroformate (189 mg, 2.0 mmol) afforded **2a** as colorless plates; yield: 38 mg (18 %) and hexane/EtOAc = 6 /4 to give **12** (49 mg, 21 %) as colorless needles : mp 125-127 °C; IR (KBr) 2168 (-SCN), 1740 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 4.12 (3H, s, COOMe), 6.60 (1H, d, *J* = 4.2 Hz, H-3), 7.48 (1H, d, *J* = 8.2 Hz, H-5), 7.70 (1H, d, *J* = 4.2 Hz, H-2), 7.95 (1H, d, *J* = 8.2 Hz, H-4); MS (DEI) *m/z* (relative intensity) 233 (M^+, 100), 188 (M^+- COOH, 38), 162 (M^+ - COOH - CN, 22); Found: C, 51.50; H, 2.72; N, 17.79; S, 13.53. Calcd for $C_{10}H_7N_3O_2S$: C, 51.49; H ,3.02; N, 18.02; S, 13.75.

1*H*-pyrrolo[3,2-*b*]pyridine *N*-oxide (13a)

To a solution of 1*H*-pyrrolo[3,2-*b*]pyridine (4-azaindole) (1.18 g, 10 mmol) in 1,2-dimethoxyethane (DME) (20 ml) was added dropwise 85 % m-chloroperoxybenzoic acid (4.3 g, 20 mmol) for 2 h at room tempetature. After stirring for 24 h at the same temperature, the solvent was removed and the residue was washed with ether several times to give **13a** (1.11 g, 83 %) as pale brown powder : mp 210-212 °C; IR (KBr) 1244 (N-O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 6.7-6.9 (1H, m, H-3), 7.04 (1H, dd, *J* = 6.5, 8.6 Hz, H-6), 7.3-7.5 (1H, m. H-2), 7.57

(1H, d, J = 8.6 Hz, H-7), 8.15 (1H, d. J = 6.5 Hz, H-5), 11.0-11.5 (1H, brs, H-1); MS (EI) *m/z* (relative intensity) 134 (M^+, 100), 118 (M^+ -O, 90).

1-Metoxycarbonyl-pyrrolo[3,2-*b*]pyridine *N*-oxide (13b)

Following the procedure for **2a**, the reaction of 4-azaindole *N*-oxide (**13a**: 134 mg, 1.0 mmol), HMDS (81 mg, 0.5 mmol), and methyl chloroformate (189 mg, 2.0 mmol) afforded **13b** (148 mg, 98 %) as colorless plates : mp 140-141 °C (dec.); IR (KBr) 1762 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 4.02 (3H, s, COOMe), 7.02 (1H, d, J = 4.0 Hz, H-2), 8.02 (1H, d, J = 8.5 Hz, H-7), 8.17 (1H, d, J = 6.3 Hz, H-5); MS (DEI) *m/z* (relative intensity) 192 (M^+, 11), 176 (M^+ -O, 100).

5-Chloro-1*H*-pyrrolo[3,2-*b*]pyridine (14)

Following the procedure for **2a**, the reaction of **13a** (134 mg, 1.0 mmol), HMDS (81 mg, 0.5 mmol), and trichloroacetyl chloride (364 mg, 2.0 mmol) afforded **14** (47 mg, 31 %) as colorless needles : ^{1}H-NMR (CD_3OD) δ = 6.53 (1H, d, J = 3.2 Hz, H-3), 7.14 (1H, d, J = 8.5 Hz, H-6), 7.60 (1H, d, J = 3.2 Hz, H-2), 7.82 (1H, d, J = 8.5 Hz, H-7); MS (DEI) *m/z* (relative intensity) 154 (M^+ +2, 32), 152 (M^+, 100).

5-Chloro-1-methoxycarbonyl-pyrrolo[3,2-*b*]pyridine (15)

Following the procedure for **2a**, the reaction of **13b** (192 mg, 1.0 mmol), and trichloroacetyl chloride (364 mg, 2.0 mmol) afforded **15** (135 mg, 63 %) as colorless needles : ^{1}H-NMR ($CDCl_3$) δ = 4.09 (3H, s, COOMe), 6.54 (1H, d, J = 3.7 Hz, H-3), 7.25 (1H, d, J = 8.8 Hz, H-6), 7.83 (1H, d, J = 3.7 Hz, H-2), 8.35 (1H, d, J = 8.8 Hz, H-7); MS (DEI) *m/z* (relative intensity) 212 (M^+ +2, 33), 210 (M^+, 99), 167 (M^+ +2 -COOH, 11), 165 (M^+ -COOH, 33).

7-Chloro-1*H*-pyrrolo[3,2-*b*]pyridine (16)

The solution of 4-azaindole *N*-oxide (**13a**: 134 mg, 1.0 mmol) in phosphorus oxychloride (10 ml) was gently refluxed for 5 h. phosphorus oxychloride was then distilled off under reduced pressure, and water (6 ml) was added to the cooled residue. The solution was basified with sodium carbonate, and after 1 h the precipitate was filtered off. This solid was washed with ether to give **16** (63 mg, 41

%) : ^{1}H-NMR (CD_3OD) δ = 6.71 (1H, d, *J* = 3.2 Hz, H-3), 7.28 (1H, d, *J* = 5.1 Hz, H-6), 7.69 (1H, d, *J* = 3.2 Hz, H-2), 8.27 (1H, d, *J* = 5.1 Hz, H-4); MS (DEI) *m/z* (relative intensity) 154 (M^+ +2, 33), 152 (M^+, 100), 117 (M^+ -Cl, 75).

7-Chloro-1-methoxycarbonyl-pyrrolo[3,2-*b*]pyridine (17)

Following the procedure for **16**, the reaction of **13b** (192 mg, 1.0 mmol) and phosphorus oxychloride (10 ml) afforded **16** (39 mg, 19 %) and **17** (38 mg, 18 %) : ^{1}H-NMR ($CDCl_3$) δ = 4.07 (3H, s, COOMe), 6.83 (1H, d, *J* = 3.9 Hz, H-3), 7.28 (1H, d, *J* = 5.4 Hz, H-6), 7.88 (1H, d, *J* = 3.9 Hz, H-2), 8.40 (1H, d, *J* = 5.4 Hz, H-5); MS (DEI) *m/z* (relative intensity) 212 (M^+ +2, 26), 210 (M^+, 82), 167 (M^+ +2 -COOH, 29), 165 (M^+ -COOH, 84).

1-Benzoyl-5-cyano-pyrrolo[3,2-*b*]pyridine (18)

Following the procedure for **11**, the reaction of **13a** (134 mg, 1.0 mmol), trimethylsilyl cyanide (298 mg, 3.0 mmol), and benzoyl chloride (281 mg, 2.0 mmol) afforded **18** (124 mg, 56 %) : IR (KBr) 2228 (CN), 1700 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 6.88 (1H, d, *J* = 4.0 Hz, H-3), 7.4-7.9 (7H, m, Ph, H-2, H-6), 8.70 (1H, d, *J* = 8.3 Hz, H-7).

5-Chloro-1-methoxycarbonyl-pyrrolo[3,2-*b*]pyridine (19)

Following the procedure for **11**, the reaction of **13b** (192 mg, 1.0 mmol), trimethylsilyl cyanide (298 mg, 3.0 mmol), and benzoyl chloride (281 mg, 2.0 mmol) afforded **19** (298 mg, 61 %) : IR (KBr) 2236 (CN), 1758 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ = 4.12 (3H, s, COOMe), 6.88 (1H, d, *J* = 3.9 Hz, H-3), 7.65 (1H, d, *J* = 8.4 Hz, H-6), 8.00 (1H, d, *J* = 3.9 Hz, H-2), 8.53 (1H, d, *J* = 8.4 Hz, H-5); MS (DEI) *m/z* (relative intensity) 201 (M^+, 100), 156 (M^+ -COOH, 57).

2-4. References

1) V. Levacher, R. Benoit, J. Duflos, G. Dupas, J. Bourguignon, and G. Queguiner, *Tetrahedron*, **47**, 429 (1991); J. Catalan, L. G. de Paz, M. Yanez, F.

Amat-Guerri, R. Houriet, E. Rdli, R. Zehringer, P. Oelhafen, R. W. Taft, F. Anvia, and J. H. Qian, *J. Am. Chem. Soc.*, **110**, 2699 (1988).

2) G. W. Gribble, "Advances in Heterocyclic Natural Product Synthesis", ed by W. H. Pearson, JAI press, London (1990), Vol. 1, pp 43-94.

3) L. N. Yakhontov and A. A. Prokopov, *Russian Chemical Revew*, **49**, 428 (1980).

4) T. V. Sycheva, L. V. Ershov, V. A. Azimov, S. D. Yuzhakov, L. N. Yakhontov, *Khim.- Farm. Zhu.* **20**, 281 (1985); *Russ. Chem.-Pharm. J.* **23**, 166 (1987).
T. V. Sycheva, L. N. Yakhontov, *Khim. Geterotsikl. Soedin.* **1985**, 646;
Chem, Heterocycl. Compds. **19**, 68 (1985).

5) B. A. J. Clark, J. Parrick, *J. Chem. Soc. Perkin Trans. 1* **1974**, 2270.

6) S. W. Schneller, J-K. Luo, *J. Org. Chem.* **45**, 4050 (1980).

7) When the reaction was carried out similarly to that with methyl chloroformate, the yield of the 6-bromo derivative **2c** was low and a considerable amount of 1-benzoyl-6-benzoyloxy-7-azaindole was isolated.

8) E. F. V. Scriven, in "Comprehensive Heterocyclic Chemistry", ed. by A. R. Katritzky, Pergamon Press, Oxford, **1984**, Vol. 2, p. 216.

9) R. Adams, S. Miyano, *J. Am. Chem. Soc.* **76**, 2785 (1954).

10) J. Verbeek, L. Brandsma, *J. Org. Chem.* **49**, 3857 (1984).

11) H. Vorbruggen, K. Krolikiewicz, *Synthesis* **1983**, 316.

12) S. Harusawa, Y. Hamada, T. Shiori, *Heterocycles* **15**, 981 (1981).

13) T. Okamoto, H. Tani,*Chem. Pharm. Bull.* **7**, 130, 930 (1959).
F. Feely, E. M. Beavers, *J. Am. Chem. Soc.* **81**, 4004 (1959).

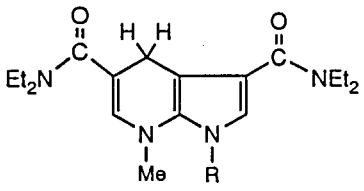
14) M. Henze, *Ber. Dtsch. Chem. Ges.* **69**, 1566 (1936).

15) A. E. S. Fairfull, D. A. Peak, *J. Chem. Soc.* **1955**, 796.
D. J. Le Count, D. J. Dewsbury, W. Grundy, *Synthesis* **1977**, 582.
O-E. Schultz, K. K. Gauri, *Arch. Pharm. (Weinheim)*, **295**, 146 (1962).

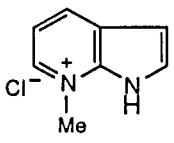
CHAPTER 3. SYNTHESIS OF FUNCTIONALIZED 7-AZAINDOLES

3-1. Introduction

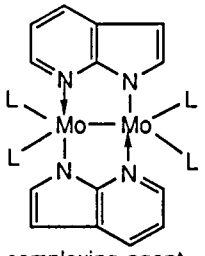
7-Azaindole derivatives have been drawing much attention in physicochemical and biochemical studies because of their characteristic condensed ring systems. In fact, 7-azaindole derivatives are applied to an NADH model,[1] biologically active substances,[2] complexing agents and so on.[3] Some examples of them are shown below. Thus, in this chapter, the functionalization of 7-azaindole directing toward functional materials is investigated.



NADH model
V. Levacher (1991)



azaanalog of indole alkaloid antidepressant
US PAT. (1968)



complexing agent
F. A. Cotton (1978)

As azaindoles contain a basic nitrogen atom of the pyridine ring and an acidic hydrogen atom of the pyridine ring, they readily form complexes with metals[3] and may be applicable also to molecular recognition agents. Furthermore, it will be interesting to synthesize polymers containing 7-azaindole rings, which are hitherto unknown, directing toward materials science. Hence, it is of great importance to functionalize the azaindole ring for development of new or improved properties. Nevertheless, synthesis of functionalized azaindoles has been studied to very limited extent.

First of all, the synthesis of 7-azaindole derivatives as chelating agents and their basic applications are studied. Secondly, the synthesis of polymers containing 7-azaindole rings and some of their biological and physicochemical properties are investigated. In addition to these studies, the possibility of application of azaindole derivatives to nonlinear optical materials is described.

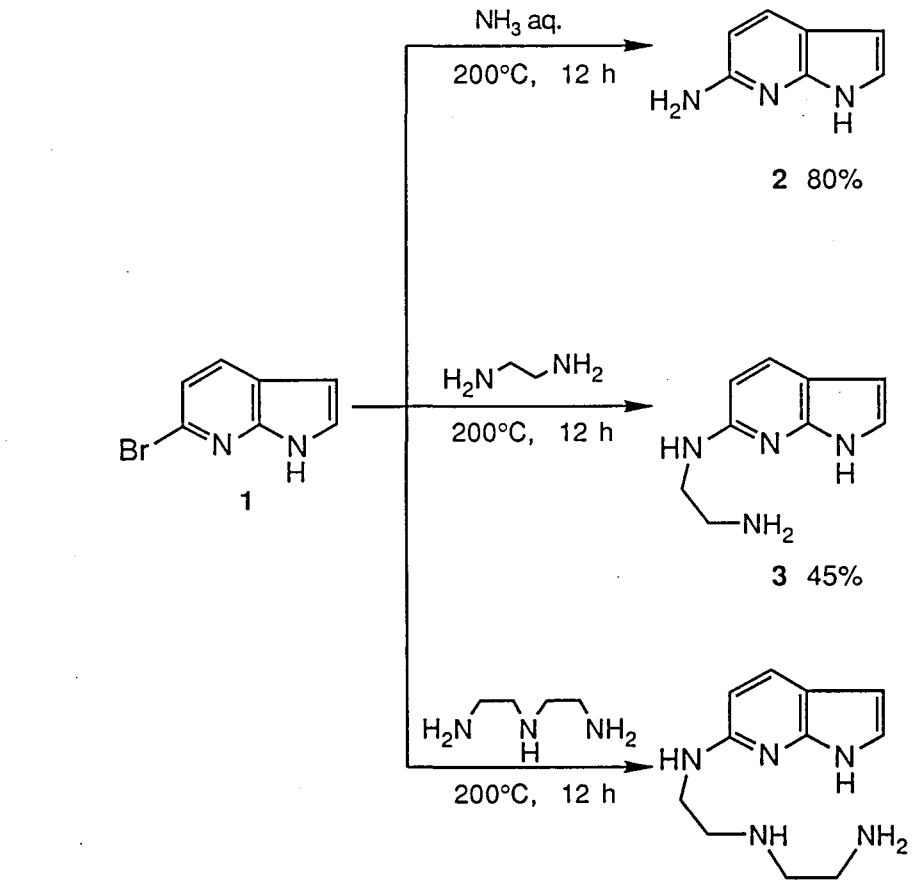
3-2. Results and Discussion

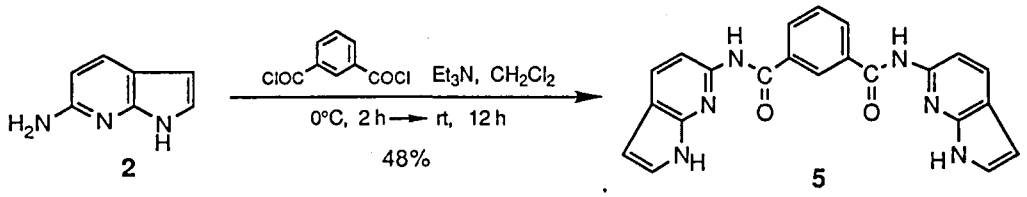
3-2-1. Synthesis of chelating agents containing 7-azaindole

The facile direct introduction of halogen atoms onto 6-position via its *N*-oxide is described in Chapter 2. Although chemical transformation of 6-haloazaindoles has been less studied, they must be useful intermediates for functionalization of 7-azaindole since 2-halopyridines react with various nucleophiles.

Thus 6-bromo-7-azaindole (**1**) was treated with 35% aqueous ammonia solution in a sealed tube at 200 °C for 12 h to give 6-amino-7-azaindole (**2**) in 80% yield. We found that this type of reaction can be applied to synthesis of ethylenediamine and diethylenetriamine derivatives, **3** and **4**, which would be interesting novel multidentate agents. However, 6-chloro-7-azaindole (**2**) was not reactive with the amines under these conditions. The multi-nitrogen compounds **2-4** are expected to be good chelating agents for metals.

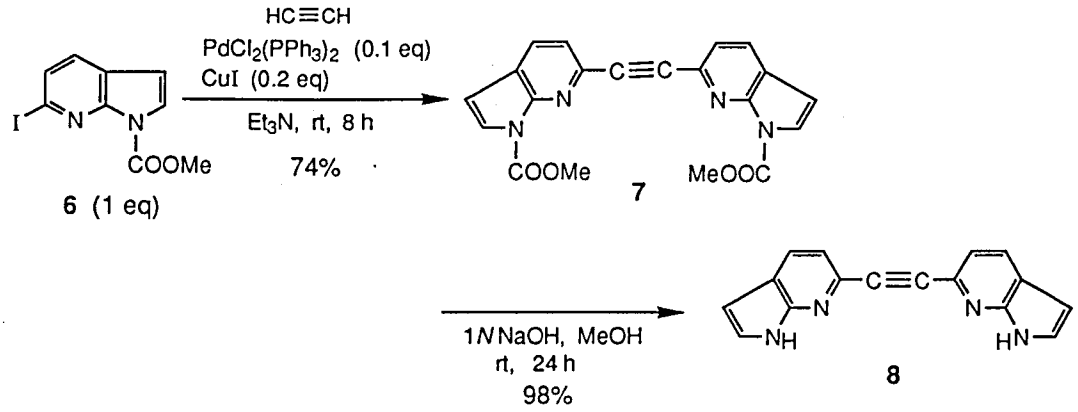
Further treatment of 6-amino-7-azaindole (**2**) with isophthaloyl dichloride in the presence of triethylamine afforded a podant-type chelating agent, *N*,*N*'-bis(1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1,3-benzenedicarboxamide (**5**), in 48% yield.





As another podant-type chelating agent, acetylene disubstituted by 7-azaindole was designed. When gaseous acetylene was reacted with 1-benzoyl-6-bromo-7-azaindole in the presence of palladium/triphenylphosphine complex and

copper(I) iodide, the anticipated diethynylated product was not obtained. But the more active 6-iodo-1-methoxycarbonyl-7-azaindole (**6**) reacted with acetylene[4] in the presence of the same catalyst to give the disubstituted acetylene **7**. Compound **7** was easily deacylated to bis(1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)acetylene (**8**) with methanolic potassium hydroxide. Compounds **5** and **8** are expected to possess molecular recognition ability since they have several sites for hydrogen bonding.



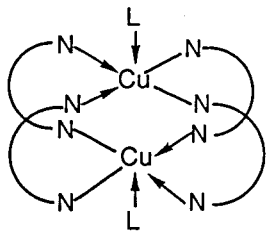
3-2-2. Catalytic oxygenation reaction with the Cu-7-azaindole complex

The chemical function of metal complexes containing 7-azaindole as ligands has rarely been known. So it was attempted to apply this type of complex to organic synthesis.

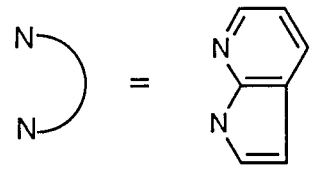
The oxygenation of the α-carbon of ethers using metal or metal oxides has been widely studied.[5] For examples, metal oxides in higher oxidation states, such as ruthenium tetraoxide,[6] chromium trioxide[7] and permanganate,[8] are among the few stoichiometric oxidants that are effective for the selective oxygenation of primary ethers to esters. Attempts to make the above oxidation catalytic by using periodate or hypochlorite ions are also reported.[9] Whereas, it is

unknown that the oxygenation of ethers to esters proceeds catalytically by using a metal complex and molecular oxygen.

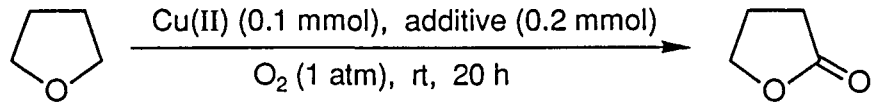
Since the two nitrogen atoms in 7-azaindole are favorably located on the same side, various binuclear metal complexes are easily formed. Among them, the copper(II) complex **9** has the most interesting structure. Because the copper bonds to two pyrrole nitrogens and coordinates to two pyridine nitrogens, this complex is regarded as a sort of model compound of porphyrin.



Cu complex **9**



L = DMSO

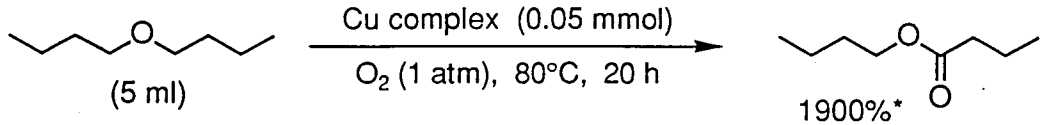


(5 ml)

run	Cu(II)	additive	yield (%)*
1	Cu complex	——	492
2	$Cu(OAc)_2 \cdot H_2O$	——	0
3	$Cu(OAc)_2 \cdot H_2O$	pyridine	10
4	$Cu(OAc)_2 \cdot H_2O$	2,2'-dipyridyl	21
5	$Cu(OAc)_2 \cdot H_2O$	4-azaindole	0
6	$Cu(OAc)_2 \cdot H_2O$	7-azaindole	470

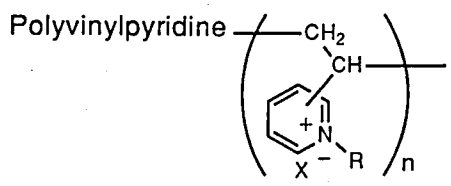
* based on Cu

Thus, we attempted the oxygenation reaction using the complex **9** under oxygen. The Cu complex **9** was reacted with tetrahydrofuran under oxygen atmosphere to give γ-butyrolactone, whose yield was 492 % based on copper to show this reaction proceeded catalytically. The reaction did not proceed when copper(II) acetate monohydrate was used instead of the complex **9**. Though pyridine, 2,2'-dipyridyl or 4-azaindole was added to this system (run 2), oxygenation reaction was not catalyzed. 7-Azaindole-$Cu(OAc)_2 \cdot H_2O$ mixture system (run 6) showed the same effect as the complex **9**. Furthermore, it turned out that this complex could be applied to an acyclic ether.

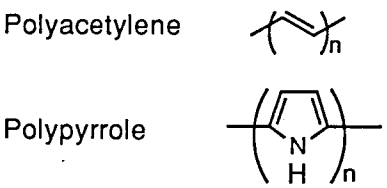


3-2-3. Synthesis of polymers containing 7-azaindoles

Polymers containing heterocyclic compounds have been extensively studied as functional materials. For instance, quaternary polyvinylpyridine is utilyzed as a virus adsorvent.[10] Polyacetylene and polypyrrole are well known as conducting materials.[11] From these points of view, we may expect some new or advanced functions for the polymers containing azaindole rings.



virus adsorvent

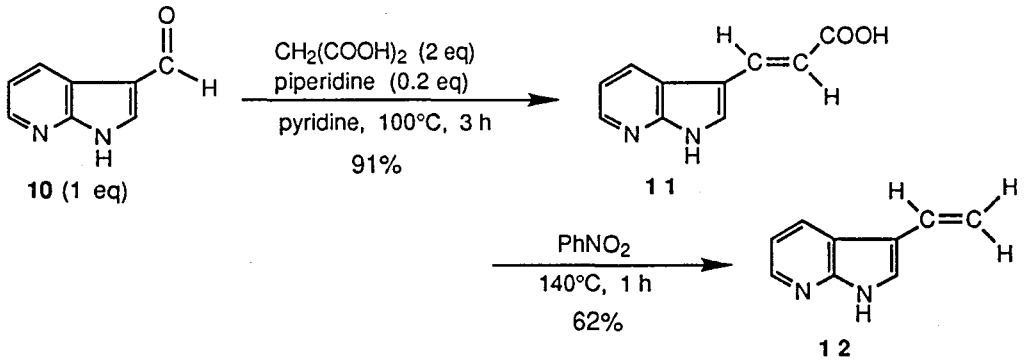


conducting materials

a) Synthesis of monomers : Introduction of unsaturated groups to the azaindole ring

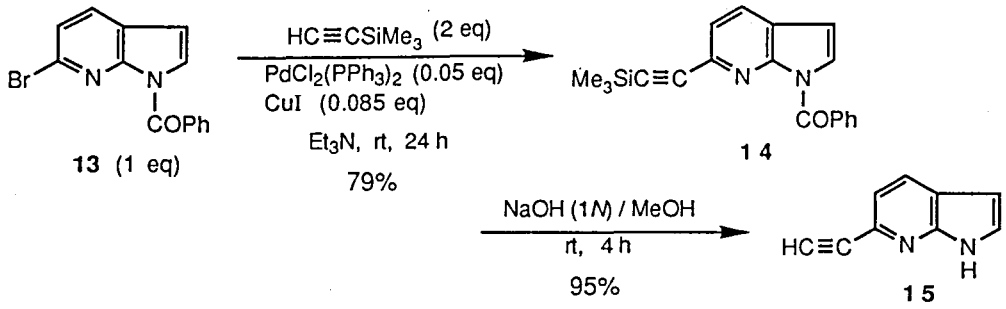
In order to synthesize monomers for 7-azaindole-containing polymers, vinyl and ethynyl groups were introduced to 7-azaindole.

As a precursor of 3-vinylazaindole, 3-formyl-7-azaindole (**10**) was prepared from 7-azaindole by the known procedure.[12] Although Wittig reaction was considered to be a facile method to transform the formyl group of 7-azaindole into vinyl group, this reaction was not appropriate to this compound under conventional reaction conditions using methylenetriphenylphosphorane probably because of acidic hydrogen on the pyrrole nitrogen. When 3-formylazaindole **10** was reacted with malonic acid in the presence of a catalytic amount of piperidine at 100 °C for 3 h, the acrylic acid derivative **11** in *trans*-form was produced in 72% yield. Decarboxylation of the compound **11** easily proceeded by thermal treatment in nitrobenzene to give 3-vinyl-7-azaindole (**12**) in 62% yield.



On the other hand, ethynylation of halogenated aromatic compounds is one of the useful methods in organic synthesis. Palladium-catalyzed cross-coupling reaction of haloarenes with acetylenes[4] was applied to the halogenated azaindoles. 1-Benzoyl-6-bromo-7-azaindole (**13**) reacted with trimethylsilyl-acetylene in the presence of copper(I) iodide and palladium/triphenylphosphine

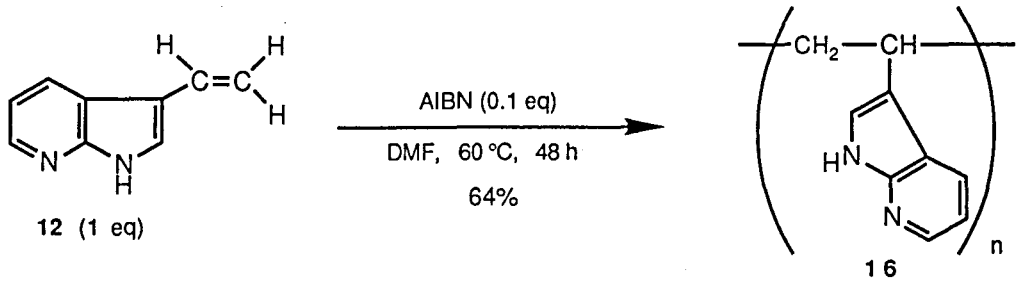
complex to give 1-benzoyl-6-trimethylsilylethynyl-7-azaindole (**14**). Compound **14** was readily desilylated and deacylated to 6-ethynyl-7-azaindole (**15**) by treatment with methanolic sodium hydroxide at room temperature.



13 (1 eq) **14** **15**

b) Polymerization of 3-vinyl-7-azaindole and 6-ethynyl-7-azaindole

3-Vinyl-7-azaindole and 6-ethynyl-7-azaindole did not polymerize on irradiation with γ-ray in DMF solutions. In the case of vinylazaindole **12**, radical polymerization of the vinyl group propagated by using AIBN as an initiator.

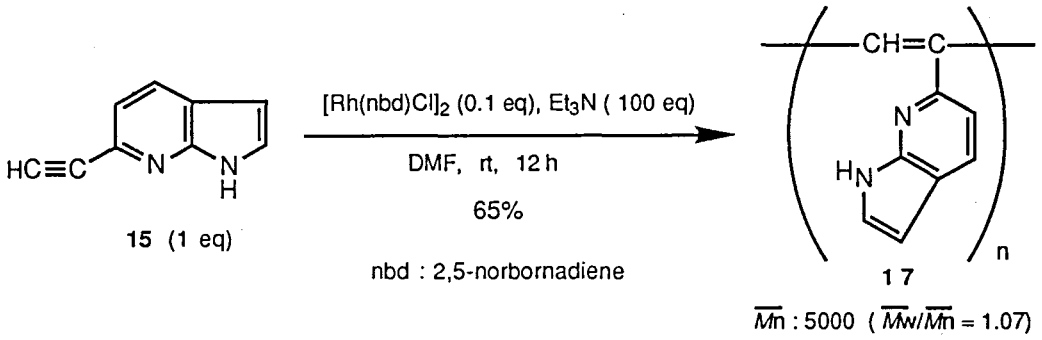


12 (1 eq) **16**

$\overline{Mn}$: 7200 ($\overline{Mw}/\overline{Mn}$ = 1.10)

Recently there has been an extensive interest in the polymerization of acetylenes using transition metal catalysts. Thus we attempted to polymerize the ethynylazaindole **15** by employing Tabata's method[13] for aromatic acetylenes. As

a result, the polymerization of 6-ethynyl-7-azaindole was successfully achieved by a Rh catalyst.

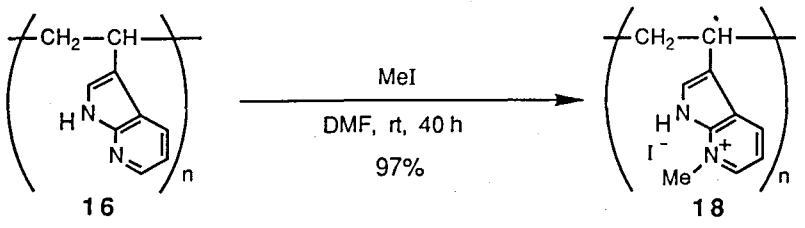


These are not only the first examples of 7-azaindole-containing polyethylene and polyacethylene but also those of azaindole-containing polymers. Though molecular weights of these polymers are low under these polymerization conditions, one of the remarkable features of these polymers is small $\overline{M}w/\overline{M}n$. Especially polyethylene has a very narrow molecular weight distribution. From these results, it is considered that these propagating reactions are living polymerization. However, since the monomers were recovered in the both cases, there remains umbiguity in the present speculation.

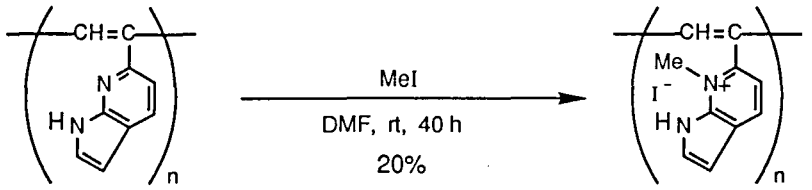
c) Quaternization of the polyethylene and the polyacetylene

As mentioned above, the polymer containing quaternary pyridine has characteristic functions. It was expected that the change of physicochemical properties of azaindole may produce unique functions.

Polyethylene derivative **16** was quaternized quantitatively by iodomethane to give water-soluble polymer. But under such condition, the extent of quaternization of polyacetylene **17** was 20 %.



16 18



17 19

3-2-4. Application of quaternized polymer to functional materials

a) Biological activity

The quaternized polyvinylpyridine is known as a virus adsorvent,[10] but this polymer does not show fungicidal activities. Therefore, we examined the fungicidal activities of the polymer **18** against the several fungi shown below.

In general, it is known that *Escherichia coli* is weaker against a fungicide than *Pseudomonas aeruginosa*. Interestingly, this polymer exhibited fungicidal activity toward *Pseudomonas aeruginosa*, *Pseudomonas fluorescens*, *Staphylococcus aureus* and *Staphylococcus epidermidis*, but it did not show any activity against *Escherichia coli* and *Salmonella typhi*. There is observed an unique selectivity against these fungi for the polymer **18**. Thus it may be expected to develop polymeric fungicides having specific natures.

Table. Fungicidal activity of the quaternized polyvinylazaindole **18**

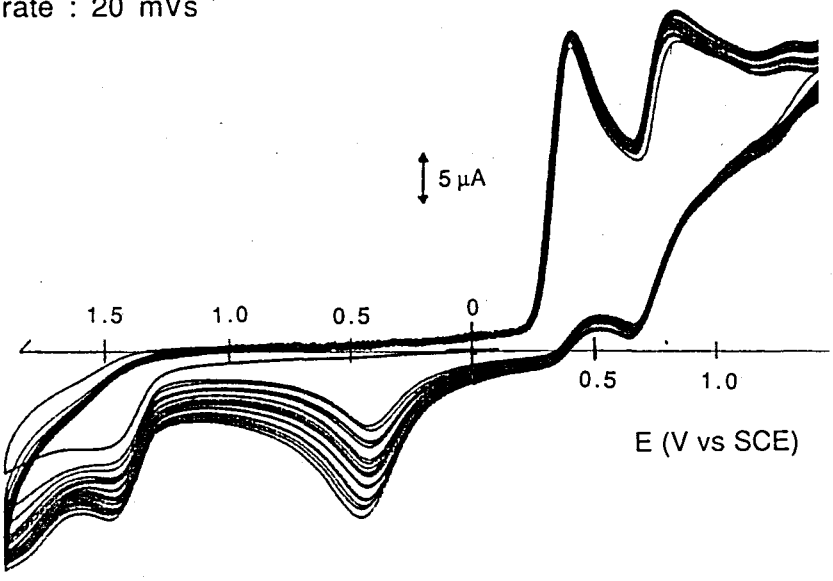
fungi	inhivitory activity	fungi	inhivitory activity
Escherichia coli	—	*Staphylococcus aureus*	+
Salmonella typhi	—	*Staphylococcus epidermidis*	+
		Pseudomonas aeruginosa	+ +
		Pseudomonas fluorescens	+ +

b) Electrochemical property

The increase in polarizabilities of the polymers by quaternization would result in better conducting property.

The cyclic voltammogram of the polymer **18** by repeated potential scans under these conditions is shown below. The several times of scans produce the gradual increase in the current value.

Cyclic voltammograms of polymer **30'** (5×10^{-3} M)
in DMF containing Bu_4NClO_4 (0.1 M)
Sweep rate : 20 mVs^{-1}



This phenomenon was not observed for the polyacetylene derivative **19**. The result supposed that an electrically active substance deposited on the surface of the working electrode. Thus chemical modification of the polymer **18** may be expected to develop a conducting polymer.

3-2-5. Application of azaindole derivatives to second order nonlinear optical materials

Second order nonlinear optical materials have been intensively studied from a viewpoint of the optoelectronic devices.[14] Especially, organic compounds could be one of the most promising candidates for the devices.[15] Second harmonic generation (SHG) needs noncentrosymmetricity of molecular ordering and intramolecular charge transfer system.

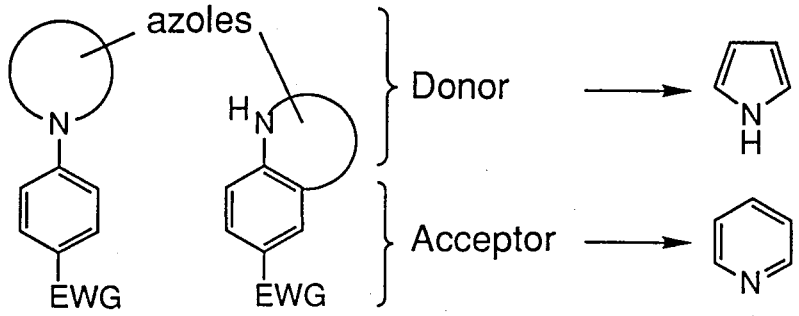
$$p = \mu + \alpha E + \beta EE + \gamma EEE$$

second-order molecular hyperpolarizability (β)

$\Downarrow$

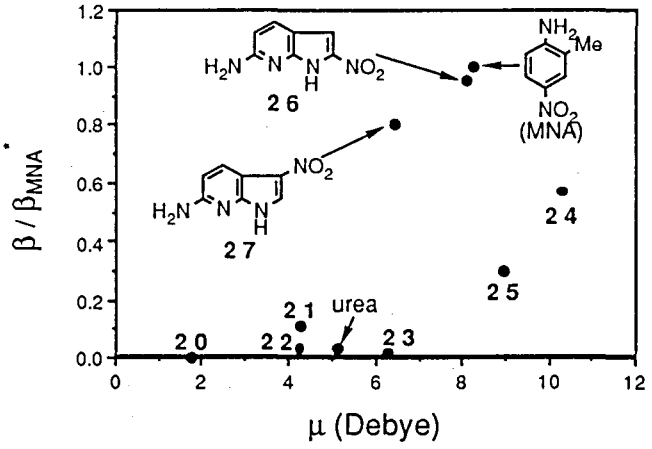
second harmonic generation (SHG)

$$\beta = \frac{3e^2h^2}{2m} \frac{\Delta E \cdot f \cdot \Delta\mu_{ge}}{\{\Delta E^2-(h\omega)^2\}\{\Delta E^2-(2h\omega)^2\}}$$

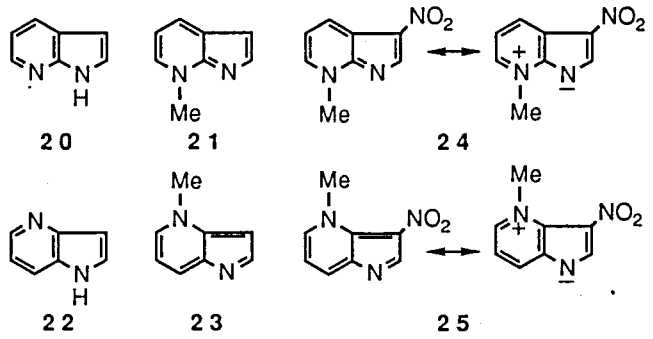


Since azaindole skeleton seems to be the most suitable for these requirements, we calculated the second-order molecular hyperpolarizability (β) and ground-state dipole moment of azaindole derivatives using CPHF method with 6-31G basis set. Figure 1 showed the plots of the calculated ground-state dipole moment versus β(azaindole derivatives) / β(2-methyl-4-nitroaniline). The

Figure 1. Second-Order Molecular Hyperpolarizability (β) versus Dipole Moment Using CPHF Method with 6-31G Basis Set



* $\beta_{MNA} = -8.35 \times 10^{-30}$ (esu)



latter compound, 2-methyl-4-nitroaniline (MNA), is well known for its high SHG activity.[16] It is generally known that the compounds having lower grand-state dipole moment and higher β value are well suited to SHG. To get larger polarization, nitro group was introduced to the compounds **21** and **23** to which nonpolarized resonance structures contribute predominantly as mentioned in Chapter 1. For these nitro compounds **24** and **25**, the betaine structures would be a major contribution of the resonance structures. The calculated β values of the compounds increased as compared with those of compounds **20**, **21**, **22** and **23**, but the values of dipole moment also increased. Therefore, the nitro compounds **24** and **25** are not suitable for SHG. In fact, 3-nitro-7-methyl-7*H*-7-azaindole **24** did not exhibit SHG activity. Then we designed the compounds which have a donor and an acceptor as substituents. 2-Nitro and 3-nitro derivatives (**26** and **27**) of 6-amino-7-azaindole, whose synthetic method was described in the beginning of this chapter, were examined. As the results of the calculation, their β values and dipole moments are comparable to MNA. Though these compounds **26** and **27** have not been synthesized, we would look forward to developing compounds suitable for generation of higher SHG activity.

3-3. Experimental

General

Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. Ir spectra were taken on a Hitachi 270-30 infrared spectrometer. ^{1}H and ^{13}C NMR were recorded on a JEOL JNM-FX-90Q or a JEOL JNM-EX270 spectrometer with TMS(CH_2)SO_3Na (in D_2O) or tetramethylsilane (in the other solvents) as an internal standard. Mass spectra were obtained by electron impact (EI) on a Shimadzu GCMS-QP2000 or a JEOL JMS-DX303 mass spectrometer. GC analyses were performed on a Shimadzu GC-8A instrument and the yield of butyl butylate was determined by GLC (1.5 m 10 %

PEG 20M column 80 °C) with HITACHI D-2500 Chromato-Integrator. Cyclic voltammograms were measured by using a Hokuto Denko HA-301 potentiostat, a GC working electrode, a Pt auxiliary electrode, and an SCE as the reference. The molecular weight distribution of the polymer **16** and **17** was determined by gel permeation chromatography (GPC) using Toyo Soda HLC CP8000 with TSKGEL G2500HXL, and a UV detector operating at 254 nm with DMF as an eluent. Fungicidal activity of azaindoles was evaluated by Sumitomo Chemical Co., Ltd.

6-Amino-1*H*-pyrrolo[2,3-*b*]pyridine (2)

6-Bromo-7-azaindole (**1**: 197 mg, 1.0 mmol) in 35 % aqueous ammonia (10 ml) was sealed in a stainless steel tube and heated at 200 °C for 12 h. Solid potassium carbonate was added to the reaction mixture and extracted with chloroform (20 ml x 3). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The reaction products were separated by thin-layer chromatography with ethyl acetate as an eluent to give **2** (107 mg, 80 %) as pale yellow plates: mp 118-119 °C; IR (KBr) 3436 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 5.0-5.5 (2H, br, NH_2), 6.34 (1H, dd, J = 1.7, 3.7 Hz, H-3), 6.35 (1H, d, J = 8.3 Hz, H-5), 7.0 (1H, dd, J = 2.0, 3.7 Hz, H-2), 7.69 (1H, d, J = 8.3 Hz, H-4), 8.5-9.0 (1H, brs, H-1); MS (EI) m/z (rel intensity) 133 (M^+, 100), 106 (M^+ - HCN, 37); Found: C, 63.08; H, 5.31; N, 31.47%. Calcd for $C_7H_7N_3$: C, 63.14; H, 5.30; N, 31.56%.

***N*-(1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)ethylenediamine (3)**

6-Bromo-7-azaindole (**1**: 197 mg, 1.0 mmol) in ethylenediamine (10 ml) was heated in a sealed tube at 200 °C for 12 h. Excess ethylenediamine was removed and the residue was purified by thin-layer chromatography with ethyl acetate as an eluent to give **3** (80.1 mg, 45 %) as pale yellow plates: mp 133-134 °C; IR (KBr) 3420 (NH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 1.8-2.0 (3H, brs, amino H), 2.99 (2H, t, J = 6.3 Hz, -NHC$\underline{H_2}$-), 3.42 (2H, t, J = 6.3 Hz, -C$\underline{H_2}NH_2$), 6.25 (1H, d, J = 4.0 Hz, H-3), 6.28 (1H, d, J = 8.6 Hz, H-5), 6.93 (1H, d, J = 4.0 Hz, H-2), 7.65 (1H, d, J = 8.6 Hz, H-4);

MS (EI) m/z (rel intensity) 176 (M^+, 20), 146 (M^+ - CH_2NH_2, 100), 117 (M^+ - $NHCH_2CH_2NH_2$, 52); Found: C, 61.58; H, 6.83; N, 31.62%. Calcd for $C_9H_{12}N_4$: C,61.34; H, 6.86; N, 31.79%.

***N*-(1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)diethylenetriamine (4)**

Following the procedure for preparation of **3**, **1** (197 mg, 1.0 mmol) was treated with diethylenetriamine (10 ml) to afford **4** (88.0 mg, 40 %) as yellow oil: IR (KBr) 3296 (NH_2) cm^{-1}; ^1H NMR (CD_3OD) δ = 2.5-3.6 (8H, m, $-CH_2-$ x 4), 6.23 (1H, d, J = 3.4 Hz, H-3), 6.31 (1H, d, J = 8.6 Hz, H-5), 6.92 (1H, d, J = 3.4 Hz, H-2), 7.69 (1H, d, J = 8.6 Hz, H-4); MS (EI) m/z (rel intensity) 219 (M^+, 25), 117 (100); Found: m/z 219.1478. Calcd for $C_{11}H_{17}N_4$: M, 219.1484.

***N,N'*-bis(1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)-1,3-benzenedicarboxamide (5)**

To a solution of 6-amino-7-azaindole (**2**: 133 mg, 1 mmol) and triethylamine (400 mg, 4 mmol) in dichloromethane (10 ml) was added dropwise isophthaloyl dichloride (100 mg, 0.5 mmol) in dichloromethane (30 ml) under nitrogen atmosphere at 0 °C over 2 h. After stirring for 12 h at room temperature, the precipitated solid was filtered and extracted with chloroform (20 ml x 3) and saturated $NaHCO_3$ aq. (10 ml x 3). The organic layer was dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by chromatography on a silica gel column eluted with hexane/ethyl acetate (1 : 9) to give **5** (95 mg, 48 %) as colorless plates : mp >300 °C; IR (KBr) 1658 (-NHCO-) cm^{-1}; ^1H NMR (DMSO-d_6) δ = 5.80 (2H, brs, -NHCO- x 2), 6.48 (2H, dd, J = 1.7, 2.9 Hz, H-3' x 2), 7,40 (2H, dd, J = 2.9, 2.9 Hz, H-2' x 2), 7.66 (1H, t, J = 8.0 Hz, H-5), 7.9-8.4 (6H, m, H-4, H-6, H-4' x 2, H-5' x 2), 8.68 (1H, s, H-2); MS (EI) m/z (rel intensity) 396 (M^+, 67), 264 (100); Found: C, 66.90; H, 4.03; N, 20.83%. Calcd for $C_{22}H_{16}N_6O_2$: C, 66.65; H, 4.07; N, 21.20%.

Dimethyl 6,6'-ethynylenebis[1*H*-pyrrolo[2,3-*b*]pyridine-1-carboxylate] (7)

Copper(I) iodide (40 mg, 0.21 mmol) was added to a mixture of bis(triphenylphosphine)palladium(II) chloride (70 mg, 0.1 mmol) and 6-iodo-1-methoxycarbonyl-7-azaindole (**6**: 302 mg, 1.0 mmol) in triethylamine (20 ml) under

nitrogen atmosphere in a flask equipped with a gas inlet tube. A slow current of acetylene was passed through the reaction mixture for 8 h at room temperature. After removal of triethylamine under reduced pressure, 10 ml of water was added to the residue. The reaction mixture was extracted with chloroform (25 ml x 4), dried ($MgSO_4$) and concentrated in vacuo. The crude product was purified by chromatography on a silica gel column eluted with hexane/ethyl acetate (1 : 9) to give **7** (139 mg, 74 %) as colorless plates: mp >300°C; IR (KBr) 1718 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 4.14 (6H, s, -COOMe x 2), 6.60 (2H, d, *J* = 4.2 Hz, H-3 x 2), 7.60 (2H, d, *J* = 8.1 Hz, H-5 x 2), 7.82 (2H, d, *J* = 4.2 Hz, H-2 x 2), 7.90 (2H, d, *J* = 8.1 Hz, H-4 x 2); ^{13}C NMR ($CDCl_3$) δ = 54.5 (OMe), 89.0 (C=C), 105.5 (C-3), 123.3 (C-5), 127.5 (C-2), 128.1 (C-4), 129.3 or 130.2 (C-3a or C-7a), 135.2 (C-6), 151.4 (C=O); MS (EI) *m/z* (rel intensity) 374 (M^+, 28), 330 ($M^+ - CO_2$, 44), 286 ($M^+ - 2CO_2$, 100); Found: C, 64.03; H, 3.42; N, 14.86%. Calcd for $C_{20}H_{14}N_4O_4$: C, 64.17; H, 3.77; N14.97%.

Bis(1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)acetylene (8)

Dimethyl ester (**7**: 187 mg, 0.5 mmol) was dissolved in MeOH (10 ml) and 1 *N* NaOH (15 ml). After stirring for 24 h at room temperature, the reaction mixture was filtered. The solid was washed with water and dried under reduced pressure at 60 °C for 6 h to give **8** (254 mg, 98 %) as pale brown plates: Mp >300 °C; IR (KBr) 3460 (NH) cm^{-1}; ^1H NMR (DMSO-d_6) δ = 6.51 (2H, d, *J* = 3.0 Hz, H-3 x 2), 7.35 (2H, d, *J* = 8.0 Hz, H-4 x 2), 7.59 (2H, d, *J* = 3.0 Hz, H-2 x 2), 8.00 (2H, d, *J* = 8.0 Hz, H-4 x 2); MS (EI) *m/z* (rel intensity) 258 (M^+, 100); Found: C, 74.53; H, 3.99; N, 21.66%. Calcd for $C_{16}H_{10}N_4$: C, 74.40; H, 3.90; N, 21.70%.

Typical procedure oxygenation reaction of ethers

A solution of Cu complex **9** (35.6 mg, 0.05 mmol) in THF was stirred at room temperature under oxygen for 20 h. After removal of THF under reduced pressure, the residue was washed with sat. NH_4Cl aq. (10 ml x 3), dried ($MgSO_4$) and concentrated. The crude product was separated by chromatography on a

silica-gel column eluted with hexane-ethyl acetate (7 : 3) to give γ-butyrolactone (42 mg, 500 % based on Cu). The spectral data were identified with authentic sample.

3-(2-Carboxyethenyl)-1*H*-pyrrolo[2,3-*b*]pyridine (11)

To a solution of 3-formyl-7-azaindole[12] (**10**: 584 mg, 4 mmol) and malonic acid (832 mg, 8 mmol) in pyridine (25 ml) was added piperidine (68 mg, 0.8 mmol) under nitrogen atmosphere. After heating the solution at 100 °C for 3 h, pyridine was removed under reduced pressure. The residue was washed with chloroform and filtered to give crude **11**. The product was purified by recrystallization from THF/hexane to give pure **11** (540 mg, 72 %) as pale yellow plates: mp 189-192 °C; IR (KBr) 1670 (COOH) cm^{-1}; ^1H NMR (DMSO-d_6) δ = 6.36 (1H, d, J = 16.2 Hz, CH=C<u>H</u>COOH), 7.20 (1H, dd, J = 4.8, 7.7 Hz, H-5), 7.79 (1H, d, J = 16.2 Hz, C<u>H</u>=CHCOOH), 8.04 (1H, s, H-2), 8.14 (1H, dd, J = 1.5, 7.7 Hz, H-4), 8.42 (1H, dd, J = 1.5, 4.8 Hz, H-6), 12.0-12.4 (1H, brs, H-1); MS (EI) m/z (rel intensity) 188 (M^+, 100), 171 (M^+ - OH, 42), 144 (M^+ - CO_2, 11); Found: C, 63.95; H, 4.68; N, 14.88%. Calcd for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.87%.

3-Vinyl-1*H*-pyrrolo[2,3-*b*]pyridine (12)

3-(2-Carboxyethenyl)-7-azaindole (**11**: 188 mg, 1.0 mmol) was heated in nitrobenzene at 140 °C for 1 h. After removal of the solvent under reduced pressure, the residue was purified by chromatography on a silica gel column eluted with hexane/ethyl acetate (8 : 2) to give **12** (89 mg, 62 %) as colorless needles: mp 112-115 °C (dec); IR (KBr) 1632 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 5.20 (1H, dd, J = 1.2, 11.0 Hz, =C<u>H</u>H), 5.68 (1H, dd, J = 1.2, 17.6 Hz, =CH<u>H</u>), 6.86 (1H, dd, J = 11.0, 17.6 Hz, C<u>H</u>=CH_2), 7.14 (1H, dd, J = 4.8, 8.1 Hz, H-5), 7.39 (1H, s, H-2), 8.21 (1H, dd, J = 1.5, 8.1 Hz, H-6), 8.34 (1H, dd, J = 1.5, 4.8 Hz, H-6), 10.4-11.0 (1H, brs, H-1); MS (EI) m/z (rel intensity) 145 (M^+ + 1, 28), 144 (M^+, 90), 143 (M^+ - 1, 100); Found: C, 74.91; H, 5.56; N, 19.36%. Calcd for $C_9H_8N_2$: C, 74.97; H, 5.59; N, 19.43%.

1-Benzoyl-6-trimethylsilylethynyl-1*H*-pyrrolo[2,3-*b*]pyridine (14)

To a solution of 1-benzoyl-6-bromo-7-azaindole (**13**: 301 mg, 1.0 mmol), bis(triphenylphosphine)palladium(II) chloride (36 mg, 0.05 mmol) and Copper(I) iodide (16 mg, 0.085 mmol) in triethylamine (25 ml) was added dropwise trimethylsilylacetylene (196 mg, 2.0 mmol) under nitrogen atmosphere at room temperature. After stirring for 24 h at the same temperature, the solvent was removed and the residue was extracted with ether (30 ml x 3), dried ($MgSO_4$) and concentrated in vacuo. The crude product was separated by chromatography on a silica gel column eluted with hexane/ethyl acetate (9 : 1) to give **14** (259 mg, 79 %) as colorless needles: mp 112-113 °C; IR (KBr) 2160 (C=C), 1688 (C=O) cm^{-1}; ^1H MNR ($CDCl_3$) δ = 0.26 (9H, s, $SiMe_3$), 6.62 (1H, d, J = 4.0 Hz, H-3), 7.37 (1H, d, J = 8.0 Hz, H-5), 7.4-8.0 (7H, m, H-2, H-4, Ph); MS (EI) m/z (rel intensity) 319 (M^+ + 1, 3), 318 (M^+, 9), 290 (M^+ - CO, 26), 105 ($PhCO^+$, 100); Found: C, 71.58; H, 5.73; N, 8.69%. Calcd for $C_{19}H_{18}N_2OSi$: C, 71.66; H, 5.70; N, 8.80%.

6-Ethynyl-1*H*-pyrrolo[2,3-*b*]pyridine (15)

1-Benzoyl-6-trimethylsilylethynyl-7-azaindole (**14**: 318 mg, 1.0 mmol) was dissolved in MeOH (10 ml) and 1*N* NaOH (20 ml). After stirring for 4 h at room temperature, MeOH was removed and the residue was extracted with ether (20 ml x 3), dried ($MgSO_4$) and concentrated in vacuo to give **15**. The crude product was subjected to recrystallization from chloroform/ether to give pure **15** (135 mg, 95 %) as colorless needles: mp 176 -177 °C; IR (KBr) 3296 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ = 3.18 (1H, s, -C=CH), 6.53 (1H, d, J = 3.4 Hz, H-3), 7.31 (1H, d, J = 8.1 Hz, H-5), 7.50 (1H, d, J = 3.4 Hz, H-2), 7.93 (1H, d, J = 8.1 Hz, H-4), 11.5-12.3 (1H, brs, NH); MS (EI) m/z (rel intensity) 142 (M^+, 100), 116 (7), 115 (22); Found: C, 76.20; H, 4.32; N, 19.56%. Calcd for $C_9H_6N_2$: C, 76.04; H, 4.25; N,19.71%.

Poly[(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)acetylene] (16)

A solution of 3-vinyl-7-azaindole (**12**: 400 mg, 2.7 mmol) and AIBN (46 mg, 0.27 mmol) in DMF (3.5 ml) was degassed by freeze-drying and stirred at 60 °C for 48 h in a sealed tube. After removal of DMF under reduced pressure, CH_2Cl_2 was

added to the residue. Soluble materials was monomer (132 mg, 34 %) and insoluble solid was washed with ether to give **12** (117.3 mg, 65 %) as pale yellow powder: mp 213 °C (dec); IR (KBr) 1608, 1582, and 1442 cm^{-1}; ^1H NMR (DMSO-d_6) δ = 0.2-2.2 (3H, br, -CH_2-CH-), 6-8 (4H, br, H-2, H-4, H-5, H-6) 11-12 (1H, br, NH).

Poly[(1*H*-pyrrolo[2,3-*b*]pyridin-6-yl)acetylene] (17)

To a solution of [Rh(norbornadiene)Cl]$_2$ (56 mg, 0.127 mmol) and triethylamine (1.3 g, 127 mmol) in DMF (3 ml) was added dropwise 6-ethynyl-7-azaindole (**15**: 180 mg, 1.27 mmol) in DMF (2 ml) under nitrogen atmosphere over 4 h. After stirring for 8 h at the same temperature, the solvent was removed in vacuo and the residue was subjected to reprecipitation from DMF/$CHCl_3$ to give **17** (117.3 mg, 65 %) as dark purple powder: mp >300°C; IR (KBr) 1602, 894, 820 and 726 cm^{-1}; ^1H NMR (DMSO-d_6) δ = 6-7 (2H, m, -C=CH-, H-3), 7-8 (3H, br, H-2, H-4, H-5) 11-12 (1H, br, NH); Found: C, 72.31; H, 4.20; N, 17.73%. Calcd for $C_9H_6N_2$: C, 76.04; H, 4.25; N, 19.71%.

Typical procedure of quaternization reaction of the polymers

To a solution of the polymer (**16**: 144 mg, 1.0 mmol) in DMF (3 ml) was added iodomethame (2.84 g, 20 mmol) under nitrogen atmosphere at room temperature for 40 h. After removal of DMF, the residue was washed with ether to give **18** (277 mg, 97 %) as pale yellow powder: mp 268 °C (dec); IR (KBr) 1628, 1368, 800 and 748 cm^{-1}; ^1H NMR (DMSO-d_6) δ = 0.2-2.2 (3H, br, -CH_2-CH-), 3.8-4.2 (3H, br, Me) 6.0-8.2 (4H, br, H-2, H-4, H-5, H-6) 11.5-12.5 (br, NH). dada for **19**: mp > 300 °C; IR (KBr) 1608, 1388 cm^{-1}; ^1H NMR (DMSO-d_6) δ = 4.0-4.5 (br, Me), 6.0-9.0 (6H, br -C=CH-, H-2, H-3, H-4, H-5), 11-12.5 (br, NH).

7-Methyl-3-nitro-7*H*-pyrrolo[2,3-*b*]pyridine (24)

To a solution of 3-nitro-7-azaindole (210 mg, 1.5 mmol) in DMF (3 ml) was added iodomethane (2.13 g, 1.5 mmol) under nitrogen atmosphere at room temperature for 12 h. After removal of DMF, the residue was washed with ether to give 7-methyl-3-nitro-7-azaindolium iodide (333 mg, 73 %) as pale yellow powder:

mp > 300 °C; IR (KBr) 1638, 816, 726 cm^{-1}, ^1H NMR (D_2O) δ = 4.43 (3H, s, Me), 7.81 (1H, dd, J = 6.0, 8.3 Hz, H-5), 8.59 (1H, d, J = 6.0 Hz, H-6), 8.78 (1H, s, H-2), 9.60 (1H, d, J = 8.3 Hz, H-4); MS (DEI) *m/z* (relative intensity) 178 (M^+, 11), 177 (M^+ -H, 100). To a solution of this pyridinium salt (150 mg, 0.5 mmol) in water (5 ml) was added K_2CO_3. The sat. solution with K_2CO_3 was extracted with CH_2Cl_2 (20 ml x 5), dried (K_2CO_3) and concentrated. The crude product was washed with ether/hexane to give **24** (54 mg, 61 %) as yellow powder: mp 201-203 °C; IR (KBr) 1628, 800. 750 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 4.42 (3H, s, Me), 7.31 (1H, dd, J = 6.3, 7.6 Hz, H-5), 7.87 (1H, d, J = 6.3 Hz, H-6), 8.70 (1H, s, H-2), 8.86 (1H, d, J = 7.6 Hz, H-4); MS (DEI) *m/z* (relative intensity) 178 (M^+, 10), 177 (M^+ -H, 100).

3-4. References

1) V. Levacher, R. Benoit, J. Duflos, G. Dupas, J. Bourguignon, and G. Queguiner, *Tetrahedron*, **47**, 429 (1991).

2) US P 3 777 246 (1968); *Chem. Abds.*, **11** 7131 (1968).

3) F. A. Cotton, D. G. Lay, and M. Millar, *Inorg. Chem.*, **17**, 186 (1978).

4) K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett.*, **1975**, 4467; T. Sakamoto, M. Shiraiwa, Y. Kondo, and H. Yamanaka, *Synthesis*, **1983**, 312.

5) M. Bressan, A. Morvillo, and G. Romanello, *Inorg. Chem.*, **29**, 2976 (1990).

6) L. M. Berkowitz and P. N. Rylander, *J. Am. Chem. Soc.*, **80**, 6682 (1958).

7) I. T. Harrison and S. Harrison, *J. Chem. Soc., Chem. Commun.*, **1966**, 752.

8) H. J. Schmidt and H. J. Schaefer, *Angew, Chem., Int. Ed. Engl.* **18**, 69 (1979).

9) A. B. Smith and R. M. Scarborough, *Synth. Commun.*, **10**, 205 (1980); P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.*, **46**, 3336 (1981).

10) N. Kawabata, T. Hayashi, T. Matsumoto, *Appl. Environ. Microbiol.*, **46**, 203 (1983); N. Kawabata, K. Nakagawa, *J. Microbiol. Methods*, **9**, 337 (1984).

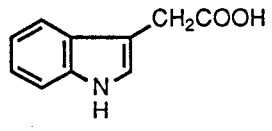
11) H. Shirakawa and S. Ikeda, *Synthetic Metals*, **1**, 175 (1979);
A. F. Diaz and K. K. Kanazawa, *J. Chem. Soc. Chem. Commun.*, **1979**, 635.
12) M. M. Robison and B. L. Robison, *J. Am. Chem. Soc.*, **77**, 457 (1955).
13) M. Tabata, W. Yang, and K. Yokota, *Polymer J.*, **22**, 1105 (1990).
14) G. I. Stegeman, *ACS Symp. Ser.*, **445**, 113 (1991).
15) "Non-Linear Optical Properties of Organic Molecules and Crystals, " ed. by D. S. Chemla and J. Zyss, Academic press, New York (1987), Vol. 1 and 2.
16) G. F. Lipscomb, A. F. Garito, R. S. Narang, *Appl. Phys. Lett.*, **38**, 663 (1981).

CHAPTER 4. APPLICATION OF 7-AZAINDOLE DERIVATIVES AS AGRICULTURAL FUNGICIDES

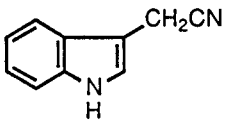
4-1. Introduction

Studies on biological activities of 7-azaindole derivatives have been expanded significantly in recent years,[1] since they are aza-analogs of indole alkaloids. Although biological properties of some azaindoles in animals have been studied, their activities in plants have rarely been investigated.[2] For example, 7-azaindole-3-acetic acid stimulated the vacuolation of the protoplasm from roots. The vacuolation-stimulating effect was parallel to the growth-stimulating effect of the corresponding indole alkaloid.[3] By contrast, 7-azatriptophan inhibits the growth of *Nicotinia tabacum* (tobacco) and *daucus carota* (carrot) cells.[4] These antipodal biological activities of 7-azaindole derivatives stimulated me to investigate 7-azaindole as agrochemicals.

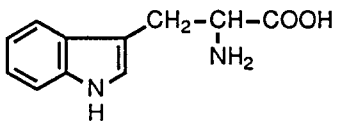
Indole Alkaloids



indole-3-acetic acid

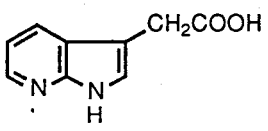


indole-3-acetonitrile

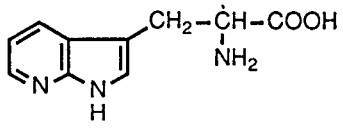


tryptophan

Azaanalogs of Indole Alkaloids



growth stimulant of root protoplasm



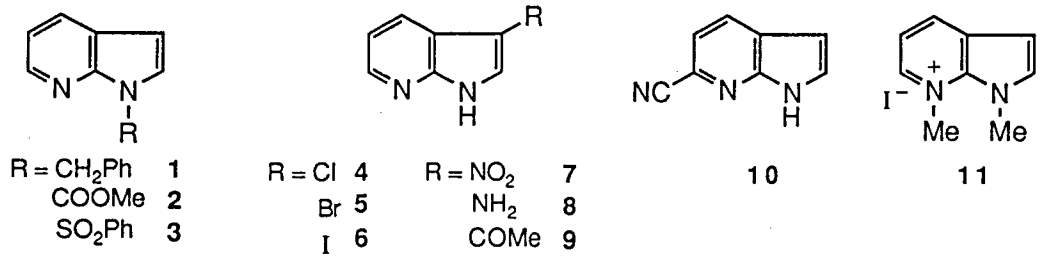
growth inhibitor of tobacco and carrot

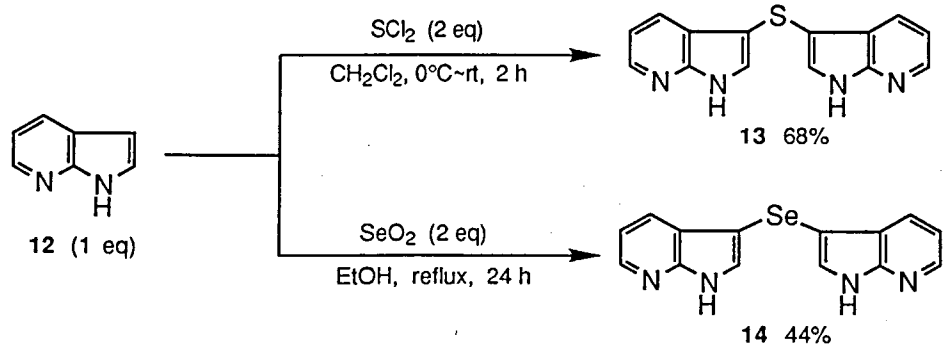
Therefore, we have synthesized some 7-azaindole derivatives in addition to the aforementioned products and tested their biological activities as agricultural fungicides. From the results of the screening, structure-activity correlation was also investigated.

4-2. Results and Discussion

4-2-1. Synthesis of 7-azaindole derivatives

In order to examine structure-activity correlation, several 7-azaindole derivatives, which were 1-substituted **1-3**, 3-substituted **4-9**,[5] 6-substituted **10** and water-soluble pyridinium salt **11**, were prepared in addition to the compounds obtained in Chapters 2 and 3.





For the purpose of wider screening of the fungicidal activity, structurally characteristic compounds, sulfide **13** and selenide **14**,[6] were synthesized by the reaction of 7-azaindole with sulfur dichloride or selenium dioxide, respectively.

4-2-2. Fungicidal activity of 7-azaindole derivatives

Part of the results of the screening for the fungicidal activities against representative fungi for rice, vegitable and fruit are summarized in Table 1. The inhibitory ability *in vivo* or *in vitro* is formulated as shown below, respectively.

In vivo

$$\text{Inhibition (\%)} = \frac{N_N - N_T}{N_N} \times 100$$

N_N = extent of disease of non-treated rice plant

N_T = extent of disease of treated rice plant[a]

a) rice plant was sprayed with a fixed amount of a solution of an azaindole (250 ppm) just after spray of *Pyricularia oryzae*.

In vitro

$$\text{Inhibition (\%)} = \frac{R_N - R_T}{R_N} \times 100$$

R_N = radius of colony of a fungus on non-treated culture medium

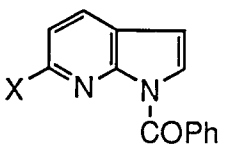
R_T = radius of colony of a fungus on treated culture medium[b]

b) a fungus was planted on culture medium containing an azaindole (50 ppm) and incubated for three days.

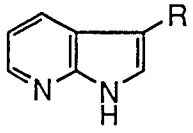
As a result of the screening *in vivo*, a series of the synthesized 7-azaindoles exhibited considerable fungicidal activity toward *Pyricularia oryzae*,

Table.1 Fungicidal Activity of 7-Azaindole Derivatives

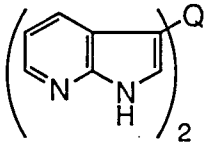
compound	*in vivo* rice blast	*in vitro* rice *Cochliobolus miyabeanus*	rice *Xanthomonas oryzae*	cucumber *Colletotrichum lagenarium*	apple *Alternaria mali*
15	0	58	100	100	29
16	83	57	0	47	46
4	29	100	0	83	87
5	24	100	0	94	90
6	92	100	0	94	97
17	0	76	0	30	62
18	47	90	0	88	66
13	89	77	0	71	60
14	0	57	0	50	24
19	0	17	0	0	15
11	88	30	0	54	9



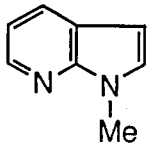
X = Cl **15**
Br **16**



R = Cl **4**
Br **5**
I **6**
$CH=CHCO_2H$ **17**
$CH=CH_2$ **18**



Q = S **13**
Se **14**



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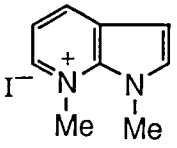


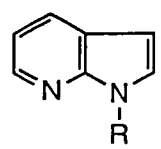
11

which is a fungus of rice blast. 6-Halo-7-azaindole derivatives **15** and **16** showed activity against different fungi. For instance, although 6-chloro derivative **15** is highly effective for rice bacterial leaf blight and cucumber anthracnose *in vitro*, 6-bromo derivative **16** showed considerable effectiveness against rice blast. Among 3-substituted derivatives of 7-azaindole, halogenated compounds **4-6** were good drugs for various fungi and 3-vinyl-7-azaindole **18** had also wide spectra of activity. Since many chalcogen derivatives are known as agrochemicals, the selenide **13** and the sulfide **14** were also tested. Although the sulfide **13** showed fungicidal activity against rice blast and helminthosporium leaf spot, the selenide **14** did not show any activity toward these fungi in spite of our expectation. 1-Methyl-7-azaindole (**19**) did not exhibit any activity, but its pyridinium salt **11** revealed high activity against rice blast.

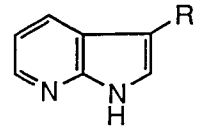
4-2-2. The correlation between several parameters and fungicidal activity of 7-azaindoles against rice blast

In the past decades, correlation between various parameters and biological activities has been drawing much attention in pharmacology and medicinal chemistry.[7,8] There are many physicochemical parameters such as molecular structure,[9] hydrophobicity[10] and conformational details. Recently, besides these parameters, various quantum parameters have been correlated with observed activities of some pharmaceuticals.[11] However, structure-activity correlation employing quantam parameters have rarely been studied in the field of agrochemicals.

From these points of view, we investigated the relation between several parameters of the following mono-substituted 7-azaindole derivatives and the inhibitory activity against rice blast.

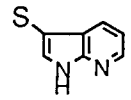
■ 

R= CH_2Ph 1
COOMe 2
SO_2Ph 3

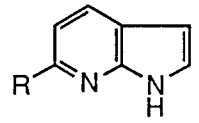
● 

R= Cl 4
Br 5
I 6
NO_2 7
NH_2 8
COMe 9

R= $CH=CH_2$ 18



13

Δ 

R= Br 20
NH_2 21
C≡CH 22
CN 10

To begin with, no correlation was observed between activities and position of a substituent or molecular structure. Secondly, hydrophobic parameter π was adopted. Parameter π derived from partition coefficient is defined as follows.

$$P = \log P_X - \log P_H$$

P_H is the partition coefficient of benzene between 1-octanol and water, and P_X is that for monosubstituted benzene.[12] Figure 1 showed the relation between π value of the substituent of 7-azaindoles and fungicidal activity against rice blast. Though there were a few exceptions, the compounds having π-value larger than 1 exhibit higher activity. But this relation did not always show a good mutual relation.

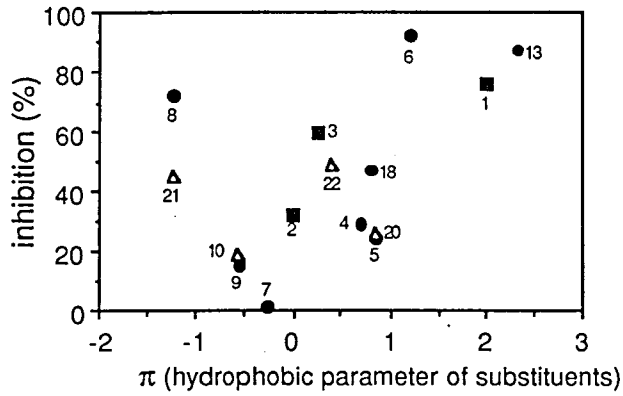


Figure 1. The relation between π value of the substituent of 7-azaindole and fungicidal activity against rice blast

On the other hand, as another parameter, dipole moment of 7-azaindole derived from MO calculation using PM3 was studied. The relation between the calculated dipole moment and the activities is shown Figure 2. But there was no good correlation between them.

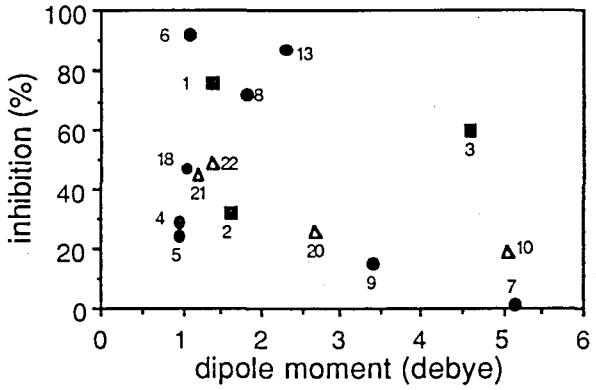


Figure 2. The relation between dipole moment of 7-azaindole and fungicidal activity against rice blast

However, a good mutual relation was observed between the activities and calculated ionization potential. Namely, the activity became higher with decrease in the value of ionization potential in the range of 8~10 eV (Figure 3).

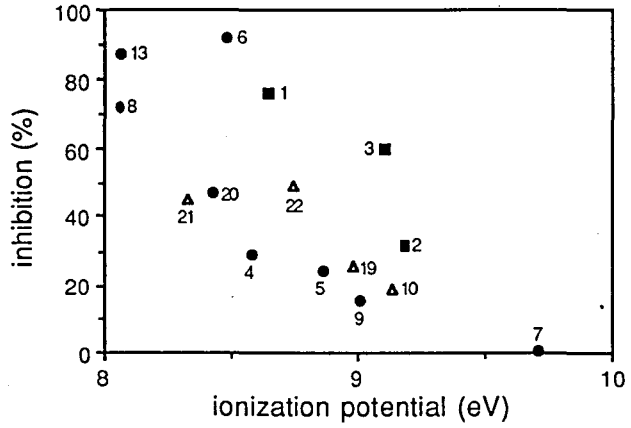


Figure 3. The relation between ionization potential of 7-azaindole and fungicidal activity against rice blast

This result indicates possibility that 7-azaindole derivatives may be involved in an electron transfer process in *pyricularia oryzae* (fungus of rice blast). It could not be concluded that these agricultural fungicides might act in this way in a complex living body. This type of relation between biological activity and ionization potential is rarely known in the field of agrochemicals as mentioned before. We shall be able to have a basic information when agricultural fungicides for rice blast are designed using 7-azaindole as a lead compound. Though several agents against rice blast having a bicyclic structure consists of condensed 5-membered ring and 6-membered ring are known, the detailed mechanisms of action have not been clarified. If the mechanisms of action of these azaindole derivatives made clear, it will be possible to develop the more effective anti-rice blast agent.

4-3. Experimental

General

Melting points were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. Ir spectra were taken on a Hitachi 270-30 infrared spectrometer. ^{1}H and ^{13}C NMR were recorded on a JEOL JNM-FX-90Q or a JEOL JNM-EX270 spectrometer with TMS(CH_2)SO_3Na (D_2O) or tetramethylsilane (in the other solvent) as an internal standard. Mass spectra were obtained by electron impact (EI) on a Shimadzu GCMS-QP2000 or a JEOL JMS-DX303 mass spectrometer. Fungicidal activity of azaindoles was evaluated by Dainippon Ink and Chemicals, Inc.

Preparation of compounds 5-9.

Most of 3-substituted 7-azaindoles have already been prepared. The compounds **5**,[5a] **6**,[5b] **7**,[5c] **8**[5c] and **9**[5d] were synthesized by the known procedures.

1-Benzyl-pyrrolo[2,3-*b*]pyridine (1)

7-Azaindole (118 mg, 1.0 mmol) in HMPA (3 ml) was added dropwise to the NaH (40 mg, 1.0 mmol) at 0 °C over 30 min under nitrogen atmosphere. After stirring for 3 h at room temperature, benzyl bromide (171 mg, 1.0 mmol) was added. This solution was stirred over night and 3 ml of water was added, extracted with ether (20 ml x 3), washed with water (100 ml x 5). This organic layer was dried ($MgSO_4$) and concentrated in vacuo. The crude product was subjected to recrystallization from hexane to give **1** (173 mg, 83 %) as colorless needles: mp 68-69 °C; ^{1}H-NMR ($CDCl_3$) δ = 5.34 (2H, s, CH_2), 6.35 (1H, d, *J* = 3.4 Hz, H-2), 6.95 (1H, dd, *J* = 4.6 7.8 Hz, H-5), 7.04 (1H, d, *J* = 3.4 Hz, H-2), 7.13 (1H, s, Ph), 7.79 (1H, dd, *J* = 1.5, 7.8 Hz, H-4), 8.24 (1H, dd, *J* = 1.5, 4.6 Hz, H-6); MS (DEI) *m/z* (relative intensity) 208 (M^+, 74), 138 (M^+ -Ph, 29), 91($PhCH^2$, 100).

1-Methoxycarbonyl-pyrrolo[2,3-*b*]pyridine (2)

To a solution of 7-azaindole (118 mg, 1.0 mmol) and triethylamine (303 mg, 3.0 mmol) in benzene (5 ml) was added dropwise metyl chloroformate (920 mg, 10 mmol) under nitrogen atmosphere. After stirring for 24 h, the reaction mixture was extracted with benzene (10 ml x 3), dried ($MgSO_4$), concentrated in vacuo to give **2** (151 mg, 86 %): mp 51-52 °C; ^{1}H-NMR ($CDCl_3$) δ = 4.11 (3H, s, COOMe), 6.57 (1H, d, *J* = 3.9 Hz, H-3), 7.21 (1H, dd, *J* = 5.1, 8.1 Hz, H-5), 7.50 (1H, d, *J* = 3.9 Hz, H-2), 7.89 (1H, d, *J* = 8.1 Hz, H-4), 8.50 (1H, d, *J* = 5.0 Hz, H-6); MS (DEI) *m/z* (relative intensity) 176 (M^+, 58), 131 (M^+ -COOH, 100).

1-Benzensulfonyl-pyrrolo[2,3-*b*]pyridine (3)

To a solution of 7-azaindole (1.18g, 10 mmol) in THF (10 ml) was added dropwise *n*-BuLi (1.6 M in hexane, 7.5 ml, 12 mmol) over 15 min at -72 °C under nitrogen atmosphere. The cooling bath was removed and the solution was stirred for 2 h while warming to 0 °C. After the solution was recooled to -72 °C, benzensulfonyl chloride (2.1 g, 11 mmol) was added over 20 min. The mixture was finally allowed to warm to room temperature and stirred over night. To the reaction mixture 2 % $NaHCO_3$ aq. (20 ml) was added and extracted with ether (30 ml x 3). The organic phase was washed with 2 % $NaHCO_3$ aq. (30 ml), water (50 ml x 2), brine (50 ml x 2) sequentially and dried ($MgSO_4$). Removal of the solvent on the rotary evaporator gave **3** (2.229 g, 86 %): mp 132-133 °C; ^{1}H-NMR ($CDCl_3$) δ = 6.59 (1H, d, *J* = 4.0 Hz, H-3), 7.16 (1H, dd, *J* = 4.9, 8.0 Hz, H-5), 7.3-7.6 (3H, m. *m*-, *p*-Ph), 7.72 (1H, d, *J* = 4.0 Hz, H-2), 7.84 (1H, dd, *J* = 1.5, 8.0 Hz, H-4), 8.0-8.3 (2H, m. *o*-Ph), 8.42 (1H, dd, *J* = 1.5, 4.9 Hz, H-6); MS (DEI) *m/z* (relative intensity) 258 (M^+, 16), 194 ($M^+ - SO_2$, 56), 77 (Ph, 100).

3-Chloro-1*H*-pyrrolo[2,3-*b*]pyridine (4)

A solution of 7-azaindole (118 mg, 1.0 mmol) and *N*-chlorosuccinimide (150 mg, 1.1 mmol) in CCl_4 (20 ml) and $CHCl_3$ (10 ml) was stirred for 4 h at room temperature under nitrogen atmosphere. After removal of solvent, 70 ml of ether was added and washed with sat. $NaHCO_3$ aq. (20 ml x 2), dried ($MgSO_4$) concentrated in vacuo to give **4** (152 mg, 99 %) as colorless powder: mp 169-170 °C; ^{1}H-NMR ($CDCl_3$) δ = 7.19 (1H, dd, *J* = 5.0, 8.0 Hz, H-5), 7.35 (1H, s, H-2), 8.00 (1H, d, *J* = 8.0 Hz, H-5), 8.38 (1H, d, *J* = 5.0 Hz, H-6); MS (DEI) *m/z* (relative intensity) 154 (M^+ +2, 33), 152 (M^+, 100).

6-Cyano-1*H*-pyrrolo[2,3-*b*]pyridine (10)

1-Benzoyl-6-cyano-7-azaindole (247 mg, 1.0 mmol) was dissolved in MeOH (30 ml) and 1*N* NaOH (10 ml). After stirring for 24 h at room temperature, MeOH was removed and the residue was extracted with $CHCl_3$ (20 ml x 3), dried

($MgSO_4$) and concentrated in vacuo to give **10** (109 mg, 76 %) as pale yellow powder: mp 175 177 °C; ^{1}H-NMR ($CDCl_3$) δ = 6.6 6.7 (1H, m, H-3), 7.50 (1H, d, *J* = 8.1 Hz, H-5), 7.5-7.6 (1H, m. H-2), 8.04 (1H, d, *J* = 8.1 Hz, H-4); MS (DEI) *m/z* (relative intensity) 143 (M^+, 100), 116 (M^+ -HCN, 49).

1,7-Dimethyl-7-azaindolium iodide (11)

To a solution of 7-methyl-7*H*-7-azaindole (132 mg, 1.0 mmol) in benzene (3 ml) was added iodomethane (1.42 g, 10 mmol) under nitrogen atmosphere at room temperature. After stirring for 24 h at the same temperature, the precipitated solid was filtered and washed with ether to give **11** (273 mg, 100 %) as colorless powder: mp 285 °C (subl); ^{1}H-NMR (D_2O) δ = 4.26 (1H, s, 1-Me), 4.65 (1H, s, 7-Me), 6.86 (1H, d, *J* = 4.0 Hz, H-3), 7.49 (1H, dd, *J* = 6.3, 8.0 Hz, H-5), 7.51 (1H, d, *J* = 4.0 Hz, H-2), 8.24 (1H, d, *J* = 6.3 Hz, H-6), 8.56 (1H, d, *J* = 8.0 Hz, H-4); MS (DEI) *m/z* (relative intensity) 146 (M^+ -1, 4), 142 (MeI, 100).

3,3'-Thiobis[1*H*-pyrrolo[2,3-*b*]pyridine] (13)

To a solution of 7-azaindole (**12**: 118 mg, 1.0 mmol) in dichloromethane (2 ml) was added dropwise sulfur dichloride (206 mg, 2.0 mmol) in dichloromethane (3 ml) under nitrogen atmosphere at 0 °C over 1 h. After stirring for 1 h at room temperature, the reaction mixture was washed with 1 *N* NaOH (10 ml x 3). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The residue was washed with EtOH, dried in vacuo to give **13** (58.5 mg, 44 %) as yellow plates: mp 252-254 °C (dec); IR (KBr) 3144 (NH), 1590, 1410 and 1284 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ = 7.08 (2H, dd, *J* = 4.8, 7.6 Hz, H-5 x 2), 7.83 (2H, d, *J* = 2.3 Hz, H-2 x 2), 8.08 (2H, dd, *J* = 1.9, 7.6 Hz, H-4 x 2), 8.19 (2H, dd, *J* = 1.9, 4.8 Hz, H-6 x 2), 11.5-12.0 (2H, brs, H-1 x 2); MS (EI) *m/z* (rel intensity) 268 (M^+ + 2, 10), 267 (M^+ + 1, 29), 266 (M^+, 100), 234 (M^+ - S, 32); Found: C, 63.05; H, 3.81; N, 20.76; S, 12.01%. Calcd for $C_{14}H_{10}N_4S$: C, 63.14; H, 3.78; N, 21.04; S, 12.04%.

3,3'-Selenobis[1*H*-pyrrolo[2,3-*b*]pyridine] (14)

7-Azaindole (**12**: 118 mg, 1.0 mmol) and selenium dioxide (222 mg. 2.0 mmol) were heated in EtOH (10 ml) at refluxing temperature for 24 h. The precipitates were filtered off, washed with EtOH, and dried under reduced pressure to give **14** (68.4 mg, 44 %) as pale red powder: mp 245-247 °C; IR (KBr) 3156 (NH) 1420 and 1292 cm^{-1}; ^1H NMR (DMSO-d_6) δ = 7.09 (2H, dd, J = 4.8, 8.1 Hz, H-5 x 2), 7.78 (2H, d, J = 2.1 Hz, H-2 x 2), 8.01 (2H, dd, J = 1.7, 8.1 Hz, H-4 x 2), 8.19 (2H, dd, J = 1.7, 4.8 Hz, H-6 x 2), 11.7-12.0 (2H, brs, H-1 x 2); ^{13}C NMR (DMSO-d_6) δ = 97.3 (C-3), 116.1 (C-5), 121.6 (C-3a), 127.3 (C-2), 131.1 (C-4), 143.9 (C-6), 148.5 (C-7a); MS (EI) m/z (rel intensity) 314 (M^+, 100), 234 (M^+ - Se, 6); Found: C, 53.41; H, 3.01; N, 18.03%. Calcd for $C_{14}H_{10}N_4Se$: C, 53.69; H, 3.22; N, 17.89%.

4-4. References

1) L. N. Yakhontov and A. A. Prokopov, *Russian Chemical Review*, **49**, 428 (1980).

2) R. E. Willete, *Adv. Heterocycl. Chem.*, **9**, 27 (1968).

3) P. E. Pilet and C. R. Hebd, *Seances Acad. Sci., Sev. D*, **273**, 2253 (1971); *Chem. Abs.*, **76**, 95687 (1972).

4) J. M. Widholm, *Biochim. Biophys. Acta*, **261**, 44 (1972).

5) a) M.M. Robison and B. L. Robison, *J. Am, Chem, Soc.*, **78**, 1247 (1956); b) R. Herbert and D. G. Wibberley, *J. Chem. Soc. (C)*, **1969**, 1505; c) M. M. Robison, B. L. Robison, and F. P. Butler, *J. Am, Chem, Soc.*, **81**, 743, (1959); d) C. Galvez and P. Viladoms, *J. Heterocyclic Chem.*, **19**, 665, (1982).

6) J. F. K. Wilshire, *Aust. J. Chem.*, **20**, 359 (1967).

7) C. Hansch, T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).

9) O. Kirino, S. Yamamoto, T. Kato, *Agric. Biol. Chem.*, **44**, 2143 (1980).

10) T. Fujita, *J. Pharm. Sci.*, **72**, 285 (1983); T. Fujita, *Prog. Phys. Org. Chem.*, **14**, 75 (1983).

11) M. Kumber, V. Cusimono, and D. V. S. Sankar, *J. Pharm. Sci.*, **65**, 1014 (1976).

12) T. Fujita, J. Iwasa, and C. Hansch, *J. Am, Chem, Soc.*, **86**, 5175 (1964).

CONCLUSION

In this thesis are studied synthesis and application of functionalized azaindole derivatives which are important key compounds for the development of functional heterocyclic systems containing nitrogen atoms.

In Chapter 1, contribution of resonance structures of 7-methyl-7*H*-7-azaindole and 4-methyl-4*H*-4-azaindole was examined. It was concluded from both multinuclear NMR and MO calculation studies that the contribution of the nonpolarized structure to 7-methyl-7*H*-7-azaindole or 4-methyl-4*H*-4-azaindole is greater than that of the polarized structure. But they have much larger dipole moments than non-functionalized azaindoles. In addition, the electronic natures of pyrrole ring and pyridine ring of these compounds are exchanged compared with those of 7- and 4-azaindoles and the directions of their dipole moments were reversed. Hence, it is expected they would become functional materials or their precursors.

In Chapter 2, functionalization of 7- and 4-azaindoles utilizing Reissert-Henze type reaction was studied. It was found that the direct halogenation (Cl, Br, I), cyanation and thiocyanation of 7-azaindole proceeded regioselectively. Direct regioselective chlorination and cyanation were also successful for 4-azaindole. In chlorination of both 7- and 4-azaindoles, the regioselectivity was controlled by changing chlorination agents as well as acylation agents. Although these reaction conditions should be optimized to get better yields, these functional groups could be converted to very useful functional groups.

In Chapter 3, study was focused on synthesis of 7-azaindole derivatives as chelating agents and polymers containing 7-azaindole rings. It was found that the copper (II) complexed with 7-azaindole catalyzes oxygenation reaction of ethers to esters. Furthermore, it was successful to synthesize the polyethylene and polyacetylene containing 7-azaindoles, which have not been reported.

Especially the quaternized polyvinyl-7-azaindole had a fungicidal activity and showed an unique selectivity against *Staphylococcus aureus* and *Escherichia coli*, and it was clarified that chemical modification of this polymer might be expected to develop a conducting polymer.

In Chapter 4, various 7-azaindole derivatives in addition to the above products were synthesized and their biological activities as agricultural fungicides were tested. These 7-azaindoles showed inhibitory activity against various fungi. Among them, they exhibited considerable fungicidal activity toward *Pyricularia oryzae* (fungus of rice blast) *in vivo*. With these results, a new structure-activity correlation was established. Namely, good mutual correlation was observed between the fungicidal activities against rice blast and calculated ionization potentials of 7-azaindole derivatives.

Most of the functionalized azaindoles obtained in this study are hitherto unknown compounds or those synthesized with much difficultly. The characteristics of azaindole ring are found to be applicable to functional materials in the fields of physicochemical and biochemical studies. Hence, this study would provide useful synthetic methods of azaindoles and applications to functional materials containing azaindole skeleton.

LIST OF PUBLICATIONS

(1) Regioselective Functionalization of 1*H*-Pyrrolo[2,3-*b*]pyridine via Its *N*-Oxide
S. Minakata, M. Komatsu, and Y. Ohshiro
Synthesis, **1992**, 661-663.

(2) Functionalization of 1*H*-Pyrrolo[2,3-*b*]pyridine
S. Minakata, S. Itoh, M. Komatsu, and Y. Ohshiro
Bull. Chem. Soc. Jpn., **65**, 2992-2997 (1992).

(3) Multinuclear NMR and *Ab Initio* MO studies of 7-Methyl-7*H*-pyrrolo[2,3-*b*]pyridine and Related Compounds
S. Minakata, S. Itoh, M. Komatsu, Y. Ohshiro, and Y. Ohshiro
J. Phys. Org. Chem., in press.

(4) Oxygenation Reaction of Ethers Catalyzed by 7-Azaindole-Cu(II) Complex
S. Minakata, S. Itoh, M. Komatsu, and Y. Ohshiro
in preparation.

(5) Functionalized 7-Azaindoles as Agricultural Fungicides : Correlation between Inhibitory Activity against Fungus of rice blast and Ionization potential
S. Minakata, S. Itoh, M. Komatsu, and Y. Ohshiro
in preparation.

SUPPLEMENTARY PAPERS

(1) A Novel Ethynylation of Pyridine by Reissert-Henze Type Reaction
N. Nishiwaki, S. Minakata, M. Komatsu, and Y. Ohshiro
Chem. Lett., **1989**, 773-776.

(2) Syntheses of Bicyclic Pyridine Derivatives from 3-Substituted 2-(Phenylethynyl)pyridines
N. Nishiwaki, S. Minakata, M. Komatsu, and Y. Ohshiro
SYNLETT, **1990**, 273-275.

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