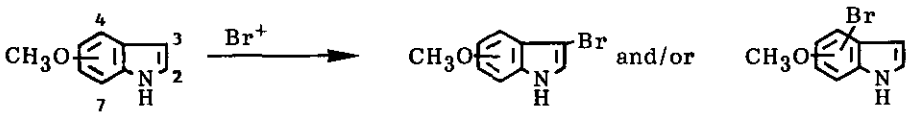
REGIOSELECTIVE BROMINATION OF METHOXY DERIVATIVES OF ETHYL INDOLE-2-CARBOXYLATE [SYNTHETIC STUDIES OF INDOLES AND RELATED COMPOUNDS. XXX[1]]

Masanobu Tani, Hiroyo Ikegami, Mayumi Tashiro, Tetsuji Hiura, Hiroko Tsukioka, Chiaki Kaneko, Toshiko Notoya, Mikiko Shimizu, Masahiko Uchida, Yoshiyuki Aida, Yuusaku Yokoyama, and Yasuoki Murakami*

School of Pharmaceutical Sciences, Toho University,
2-2-1, Miyama, Funabashi, Chiba 274, Japan

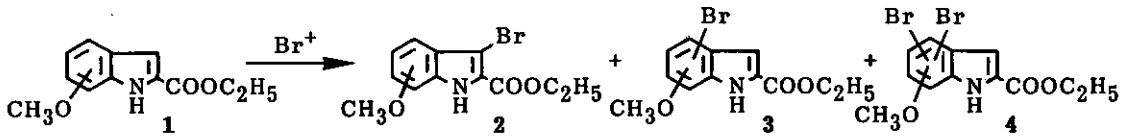
Abstract - Bromination of ethyl methoxyindole-2-carboxylates (**1**) with bromine in acetic acid proceeded on the benzene moiety of **1**, whereas the reaction of **1** with pyridinium bromide perbromide in pyridine or N-bromosuccinimide in dimethylformamide gave ethyl 3-bromo-methoxyindole-2-carboxylates (**2**).

Bromination is one of the fundamental reactions in indole chemistry. Although, bromination usually proceeds at the C_3-position,[2] situation is not the same in methoxyindoles as shown in Scheme 1, because electron-donating group on benzene moiety tends to direct the bromine toward the benzene moiety. Indeed, bromination of ethyl 5-methoxyindole-2-carboxylate (**1b**) with bromine in acetic acid was reported to occur[3] on the C_4-position rather than the C_3-position. In other words C_3-bromination is not easy in methoxyindoles in usual cases, although the C_3-bromination



Scheme 1

Table I. Results for Bromination of Methoxyindoles (1)



Entry	(series)	Starting Material (1)	Reagent	Reaction Conditions	Products (%) 3-Br (2)	Other Mono-Br-(3)	Di-Br- (4)
1	(a)	4-CH_3O- (1a)	A	5°C,108 min	0%	7-Br(58%)	5,7-di-Br(20%)
			B	0°C, 22 min	76%	(0%)	3,7-di-Br(14%)
			C	0°C, 30 min	70%	(0%)	3,7-di-Br(12%)
2	(b)	5-CH_3O- (1b)	A	r.t., 1 h	2%	4-Br(78%)	3,4-di-Br(17%) 3,6-di-Br(2%)
			B	0°C, 37 min	88%	(0%)	---
			C	0°C, 30 min	94%	(0%)	---
3	(c)	6-CH_3O- (1c)	A*,4	r.t., 20 min	13%	5-Br(26%) 7-Br(13%)	3,5-di-Br(8%) 3,7-di-Br(13%)
			B	0°C, 30 min	83%	(0%)	---
			C	0°C,110 min	93%	(0%)	---
4	(d)	7-CH_3O- (1d)	A	r.t., 36 min	0%	4-Br(84%)	---
			B	0°C, 30 min	88%	(0%)	3,4-di-Br(5%)
			C	0°C, 30 min	87%	(0%)	3,4-di-Br(10%)
5	(e)	4,7-di-CH_3O-(1e)	A	r.t., 40 min	<1%	5-Br(62%) 6-Br(4%)	3,5-di-Br(31%)
			B	r.t., 2 h	97%	(0%)	---
6	(f)	4,6-di-CH_3O-(1f)	B*	60°C, 30 min	4%	7-Br(25%)	3,7-di-Br(4%)
7	(g)	7-TsO- (1g)	A	15°C, 10 min	96%	(0%)	---
			B	0°C, 10 min	98	(0%)	---

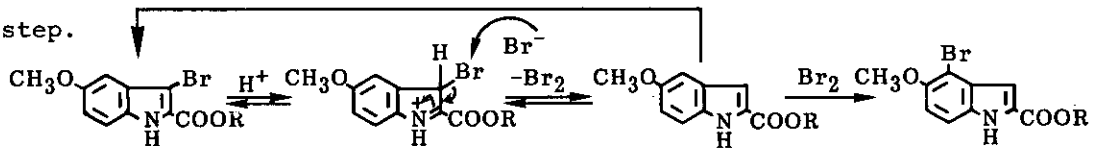
Reagent; A:Br_2 in AcOH, B:Pyridinium bromide perbromide in pyridine, C:NBS in DMF

r.t.;room temterature

*) Starting material was recovered; (c):16%, (f):21%.

becomes necessary sometimes. We report now a regioselective bromination of methoxy derivatives of ethyl indole-2-carboxylate.

At first the 5-methoxyindole (**1b**) was treated with bromine in acetic acid (Reagent A). This reaction gave the 4-bromoindole (**3b**) mainly, accompanied with the 3,4- (**4b-1**) and 3,6-dibromoindole (**4b-2**) as by-products, as shown in Entry 2 in Table I. The formation of **3b** with this reagent had been expected by the result of Kruse.[3] They proposed the mechanism that kinetically introduced C_3-bromine atom rearranged to the C_4-position moderately activated by the C_5-methoxy group, as it was reversible in the presence of bromide ion in acidic media. This can be visualized as in Scheme 2. The generation of C_3-protonated intermediate (**5**) is the key step.



Scheme 2 R=C_2H_5

This mechanism suggests that the 3-bromoindole could be prepared in non-acidic media or under the condition in the absence of bromide ion. Thus, the reaction with pyridinium bromide perbromide in pyridine (Reagent B) was found to give only the 3-bromoindole (**2b**), which was stable under this non-acidic condition. The reaction with N-bromosuccinimide (NBS) in dimethylformamide (DMF) (Reagent C) gave the same result with that of Reagent B. These results develop a good method for preparation of 3-bromo-methoxyindole.

Thus, several other methoxyindoles (**1a,c,d**) and dimethoxyindoles (**1e,f**) were treated with 1.1-1.3 equivalents of these three kinds of brominating reagents. The results are shown in Table I.

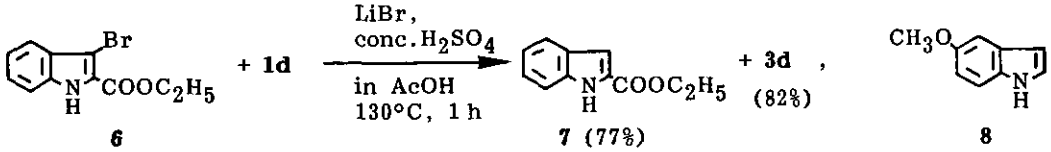
Structure determination of brominated products from monomethoxyindoles (**1a-d**) was made without difficulty by means of ^{1}H-nmr spectroscopy. The C_3-bromine was easily identified by disappearance of C_3-H of **1**, which generally appeared as a doublet with a small coupling constant and changed to a singlet on addition of D_2O. The position of bromine substituted on the benzene moiety was determined by means of coupling pattern of re-

mained two protons and/or NOE technique. On the other hand, the position of bromine on the benzene moiety of dimethoxyindoles (**1e and 1f**) could not be identified till the shift reagent [tris(dipivaloylmethanato)europium][Eu(dpm)$_3$] was used in ^{1}H-nmr measurement.[5]

Reagent A gave generally the product brominated on benzene moiety with high regioselectivity in every case of methoxyindoles except for the 6-methoxyindole (**1c**). The brominated position was ortho- or para-position of methoxy group, probably via the same bromine rearrangement found in the 5-methoxyindole (**1b**). Only the 6-methoxyindole (**1c**) did not show high regioselectivity. Reagents B and C gave generally 3-bromoindole very cleanly as well as the 5-methoxyindole (**1b**) except for the 4,6-dimethoxyindole (**1f**). The latter indole (**1f**) did not give selectively the 3-bromoindole (**2f**) even with Reagent B. The unoccupied C_5- and C_7-positions of **1f** are too electron-enriched by two methoxy groups to undergo bromination regioselectively at the C_3-position. On the other hand bromination of the 7-tosyloxyindole (**1g**), whose benzene moiety is deactivated occurred only at the C_3-position even with Reagent A. In some cases was obtained dibromoindole (**4**), which should be formed by further bromination of corresponding monobromoindole (**2** or **3**). The formation of these by-products (**4**) would be decreased by precise optimization of reaction conditions.

Next, an equimolar mixture of the 3-bromoindole (**6**) and the 7-methoxyindole (**1d**) was treated under heating with concentrated sulfuric acid and lithium bromide in acetic acid to give ethyl indole-2-carboxylate (**7**) (77%) and ethyl 4-bromo-7-methoxyindole-2-carboxylate (**3d**) (82%) (Scheme 3). Together with the result on the reaction of 7-tosyloxyindole (**1g**), this reaction clearly shows that the rearrangement of the bromine atom occurs in intermolecular fashion only when the benzene moiety is activated by methoxy group, and that the mechanism suggested by Kruse[3]

becomes more probable. In addition, the reaction from **6** to **7** suggests a new C_3-debromination procedure.



6 **7** (77%) **8**

Scheme 3

In order to compare with the results on 2-ethoxycarbonyl-methoxyindole (**1**), 5-methoxyindole (**8**) which carries no 2-ethoxycarbonyl group, was treated with Reagent B. The reaction occurred very rapidly and gave probably the corresponding C_3-bromo compound by ^{1}H-nmr spectroscopy. However, the product was too unstable to purify and decomposed gradually, whereas ethyl 3-bromo-methoxyindole-2-carboxylates (**2**) in the present study were very stable under the same treatment. This stability was due to the 2-ethoxycarbonyl group and will be helpful for synthetic work. In this paper we described a synthetic methodology for preparing stable 3-bromo-methoxyindole and a possibility of C_3-debromination. We are now under investigation for the application.

EXPERIMENTAL

All melting points were measured on a micro melting point hot stage apparatus (Yanagimoto) and are uncorrected. Ir spectra were recorded in nujol mulls (unless otherwise stated) on Shimadzu IR-400. ^{1}H-Nmr spectra were recorded in $CDCl_3$ (unless otherwise stated) with JEOL EX-400 (400 MHz) (unless otherwise stated), Hitachi R-900 (90 MHz), and with Hitachi R-24B (60 MHz). In the ^{1}H-nmr spectra, chemical shifts are given in δ-values referred to internal tetramethylsilane, and the assignment of all NH signals was confirmed by the disappearance of their signals after addition of D_2O. Mass spectra were measured by the direct inlet system

on JEOL JMS-D300 and JMS-DX303 spectrometer. For column chromatography, silica gel (Kiesel gel 60, 70-230 mesh, Merch) was used.

Starting Materials.

Ethyl 4- (**1a**), 5- (**1b**), 6- (**1c**), and 7-methoxy-[5] (**1d**), 4,6-dimethoxy-[6] (**1f**), and 7-tosyloxy-[7] (**1g**) indole-2-carboxylate were prepared by the reported methods.

Ethyl 4,7-dimethoxyindole-2-carboxylate (**1e**): A solution of ethyl azidoacetate[8] (25.82 g, 0.20 mol) and 2,5-dimethoxybenzaldehyde (8.31 g, 0.05 mol) in EtOH (100 ml) was added slowly to a solution of NaOEt (prepared from 4.6 g of Na) in EtOH at -20°C and the whole was stirred for 2.35 h at -2 to -4°C. The reaction mixture was poured into large amount of water, and extracted with AcOEt after salting-out. The organic layer was washed with saturated NaCl and dried over $MgSO_4$. The residue obtained by evaporation of solvent was purified by column chromatography over silica gel with AcOEt-hexane by gradient elution to give crystals (14.52 g). Recrystallization from benzene-hexane gave 8.86g (64%) of ethyl 2-azido-3-(2,5-dimethoxyphenyl)acrylate: colorless prisms, mp 84-86.5°C. Anal. Calcd for $C_{13}H_{15}N_3O_4$: C, 56.31, H, 5.45, N, 15.15. Found: C, 56.37, H, 5.46, N, 15.01. Ir ν_{max} cm^{-1}: 2130(N_3), 1710(C=O). ^{1}H-Nmr δ(60 MHz): 1.37(3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.76(6H, s, OCH_3x2), 4.33(2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 6.76(2H, m, C_3 and C_4-H), 7.29(1H, s, Ar-C<u>H</u>=), 7.73(1H, dif. d, J=2.0 Hz, C_6-H). Ms m/z: 277(M^+, 18%), 176(base peak).

A solution of the above azido-acrylate (6.511g, 23.5 mmol) in <u>p</u>-xylene (650 ml) was refluxed[9] for 30 min under Ar atmosphere. After the reaction was over, the reaction mixture was evaporated <u>in vacuo</u>. The residue (5.84 g) was purified by column chromatography over silica gel with AcOEt-hexane by gradient elution to gave ethyl 4,7-dimethoxyindole-2-carboxylate (**1e**)(5.67 g, 97%). Recrystallization from AcOEt-hexane gave colorless needles, mp 127-127.5°C. Anal. Calcd for $C_{13}H_{15}NO_4$: C, 62.64, H, 6.07,

N, 5.62. Found: 62.67, H, 6.11, N, 5.67. Ir ν_{max} cm^{-1}: 3305(NH), 1690 (C=O). ^{1}H-Nmr δ($CDCl_3$, 90 MHz): 1.36(3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.87(6H, s, OCH_3x2), 4.36 (2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 6.32(1H, d, J=8.0 Hz, C_5-H), 6.58(1H, d, J=8.0 Hz, C_6-H), 7.28(1H, d, J=3.0 Hz, C_3-H), 9.03(1H, br s, NH). Ms m/z: 249 (M^+, base peak).

General Procedure for Bromination of Ethyl Methoxyindole-2-carboxylate (1).

1) Bromination with Br_2 in AcOH (Reagent A): A solution of Br_2 (0.66 m mol) in AcOH (0.85 ml) was slowly added to a solution of ethyl methoxyindole-2-carboxylate (1) (0.55 mmol) in AcOH (1.9 ml) and the whole was stired under the reaction conditions shown in Table I. The reaction mixtue was poured into ice-cooled solution of aqueous $Na_2S_2O_3$, and extracted with AcOEt. The organic layer was washed with saturated $NaHCO_3$ and saturated NaCl successively, and dried over anhydrous $MgSO_4$. Evaporation of solvent in vacuo gave crude products. Column chromatography over silica gel with hexane-AcOEt by gradient elution gave pure products, which were recrystallized from appropriate solvent.

2) Bromination with pyridinium bromide perbromide in pyridine (Reagent B): A solution of pyridinium bromide perbromide (1.56 g, 4.88 mmol) in dry pyridine (30 ml) was slowly added to a solution of ethyl methoxyindole-2-carboxylate (1) (4.44 mmol) and the whole was stirred under the conditions shown in Table I. The reaction mixture was poured into ice-water, acidified with 10% HCl, and extracted with AcOEt. The work-up procedure thereafter was the same as described in 1).

3) Bromination with NBS in DMF (Reagent C): A solution of NBS (80 mg, 0.45 mmol) in DMF (1.7 ml) was slowly added to a solution of ethyl methoxyindole-2-carboxylate (1) (0.38 mmol) in DMF (4 ml), and the whole was stirred under the conditions shown in Table I. The reaction mixture was poured into ice-water, and the same work-up as above afforded products.

Identification of the Products Obtained by Bromination.

Ethyl 3-bromo-4-methoxyindole-2-carboxylate (**2a**): Colorless needles, mp 202-203°C from ethyl acetate. Anal. Calcd for $C_{12}H_{12}NO_3Br$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.35; H, 4.06; N. 4.74. Ir ν_{max} cm^{-1}: 3320(NH) 1675(C=O). ^{1}H-Nmr δ: 1.44(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.95(3H, s, OCH_3), 4.44(2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.52(1H, d, J=8.0 Hz, C_5-H), 6.98(1H, d, J=8.0 Hz, C_7-H), 7.24(1H, t, J=8.0 Hz, C_6-H), 9.04(1H, br s, NH). Ms m/z: 299(M^++2, 53%), 297(M^+, 54%), 251(base peak).

Ethyl 7-bromo-4-methoxyindole-2-carboxylate (**3a**): Colorless needles, mp 93-94.5°C from Et_2O-hexane. Anal. Calcd for $C_{12}H_{12}NO_3Br$: C, 48.34, H, 4.06, N, 4.70. Found: C, 48.12, H, 4.05, N, 4.75. Ir ν_{max} cm^{-1}: 3300(NH) 1703(C=O). ^{1}H-Nmr δ(60 MHz, DMSO-d_6): 1.33 (3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.85(3H, s, OCH_3), 4.30 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.48(1H, d, J=8.0 Hz, C_5-H), 7.15(1H, s, C_3-H), 7.35(1H, d, J=8.0 Hz, C_6-H), 11.65(1H, br s, NH). Ms m/z: 299(M^++2, 65%), 297(M^+, 65%), 251(base peak).

Ethyl 5,7-dibromo-4-methoxyindole-2-carboxylate (**4a-1**): Colorless needles, mp 149-152°C from benzene-hexane. High resolution ms calcd for $C_{12}H_{11}NO_3Br_2$: 374.9106. Found: 374.9152. Ir ν_{max} cm^{-1}: 3310(NH), 1715(C=O). ^{1}H-Nmr δ: 1.44(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 4.10(3H, s, OCH_3), 4.44(2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.39(1H, d, J=2.5 Hz, C_3-H), 7.60(1H, s, C_6-H), 8.98 (1H, br s, NH). Ms m/z: 379(M^++4, 40%), 377(M^++2, 81%), 375(M^+, 43%), 331 (base peak).

Ethyl 3,7-dibromo-4-methoxyindole-2-carboxylate (**4a-2**): Colorless prisms, mp 137.5-140°C from hexane. Anal. Calcd for $C_{12}H_{11}NO_3Br_2$: C, 38.23, H, 2.94, N,3.72. Found: C, 38.29, H, 2.96, N, 3.72. Ir $\nu_{max}^{CHCl_3}$ cm^{-1}: 3425 (NH), 1695(C=O). ^{1}H-Nmr δ: 1.46(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.94(3H, s, OCH_3), 4.46(2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.45(1H, d, J=8.5 Hz, C_5-H), 7.37 (1H, d, J=8.5 Hz, C_6-H), 8.98(1H, br s, NH). Ms m/z: 379(M^++4, 28%), 377 (M^++2, 56%), 375(M^+, 30%), 331(base peak).

Ethyl 3-bromo-5-methoxyindole-2-carboxylate (**2b**): Colorless needles, mp

157-158.5°C (lit.,[3] 155-157°C) from ethyl acetate-hexane. Anal. Calcd for $C_{12}H_{12}NO_3Br$: C, 48.34, H, 4.06, N, 4.70. Found: C, 48.65, H, 4.12, N, 4.68. Ir ν_{max} cm^{-1}: 3280(NH), 1675(C=O). ^{1}H-Nmr δ: 1.45(3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.89(3H, s, OCH_3), 4.45(2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 7.01(1H, d, J=2.5 Hz, C_4-H), 7.04(1H, dd, J=2.5 and 9.0 Hz, C_6-H), 7.29(1H, d, J= 9.0 Hz, C_7-H), 8.99(1H, br s, NH). Ms m/z: 299(M^++2, 51%), 297(M^+, 51%), 251(base peak).

Ethyl 4-bromo-5-methoxyindole-2-carboxylate (**3b**): Colorless prisms, mp 170-171°C (lit.,[3] 169-170°C and 166-167°C) from EtOH. Anal. Calcd for $C_{12}H_{12}NO_3Br$: C, 48.34, H, 4.06, N, 4.70. Found: C, 48.14, H, 4.10, N, 4.74. Ir ν_{max} cm^{-1}: 3300(NH), 1675(C=O). ^{1}H-Nmr δ: 1.43(3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.94(3H, s, OCH_3), 4.42(2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 7.07(1H, d, J=9.0 Hz, C_6-H), 7.23(1H, dd, J=2.5 and 1.0 Hz, C_3-H), 7.33(1H, dd, J=9.0 and 1.0 Hz, C_7-H), 8.97(1H, br s, NH). Ms m/z: 299(M^++2, 62%), 297(M^+, 63%), 251(base peak).

Ethyl 3,4-dibromo-5-methoxyindole-2-carboxylate (**4b-1**): Colorless needles, mp 173.5-174°C(lit.,[3] 165-166°C) from benzene. Anal. Calcd for $C_{12}H_{11}NO_3Br_2$: C, 38.23, H, 2.94, N, 3.72. Found: C. 38.31, H, 2.93, N, 3.72. Ir ν_{max} cm^{-1}: 3270(NH), 1660(C=O). ^{1}H-Nmr δ: 1.45 (3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.93(3H, s, OCH_3), 7.10(1H, d, J=9.0 Hz, C_6 or C_7-H), 7.33(1H, d, J=9.0 Hz, C_7 or C_6-H), 9.08(1H, br s, NH). Ms m/z: 379(M^++4, 27%), 377(M^++2, 54%), 375(M^+, 28%), 331(base peak).

Ethyl 3,6-dibromo-5-methoxyindole-2-carboxylate (**4b-2**): Colorless needles, mp 218-223°C from ethyl acetate-hexane. High resolution ms Calcd for $C_{12}H_{11}NO_3Br_2$: 374.9106(M^+), 376.9085(M^++2). Found: 374.9186(M^+), 376.9099(M^++ 2). Ir ν_{max} cm^{-1}: 3290(NH), 1680(C=O). ^{1}H-Nmr δ: 1.45(3H, t, J=7.5 Hz, $CH_2\underline{CH_3}$), 3.98(3H, s, OCH_3), 4.45(2H, q, J=7.5 Hz, $O\underline{CH_2}CH_3$), 7.04(1H, s, C_4 or C_7-H), 7.64(1H, s, C_7 or C_4-H), 8.90 (1H, br s, NH). Ms m/z: 379(M^++4, 26%), 377(M^++2, 53%), 375(M^+, 27%), 331 (base peak).

Ethyl 3-bromo-6-methoxyindole-2-carboxylate (**2c**): Colorless prisms, mp

145-147°C from benzene. Anal. Calcd for $C_{12}H_{12}NO_3Br$: C, 48.34, H, 4.06, N, 4.70. Found C, 48.29, H, 4.03, 4.71. Ir ν_{max} cm^{-1}: 3290(NH), 1670 (C=O). ^{1}H-Nmr δ(60 MHz): 1.45(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.81(3H, s, OCH_3), 4.41 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.76(1H, dif. s, C_7-H), 6.83(1H, dd, J=8.0 and 2.0 Hz, C_5-H), 7.48(1H, dif. d, J=8.0 Hz, C_4-H), 9.00(1H, br s, NH). Ms m/z: 299(M^++2, 79%), 297(M^+, 80%), 251(base peak).

Ethyl 5-bromo-6-methoxyindole-2-carboxylate(**3c-1**): Colorless needles, mp 179-180°C from ethyl acetate-hexane. Anal. Calcd for $C_{12}H_{12}NO_3Br$: C, 48.34, H, 4.06, N, 4.70. Found: C, 48.18, C, 4.07, N, 4.77. Ir ν_{max} cm^{-1}: 3360(NH), 1675(C=O). ^{1}H-Nmr δ(60 MHz, DMSO-d_6): 1.31(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.82(3H, s, OCH_3), 4.27(2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.94(1H, s, C_7-H), 6.95(1H, dif. d, J=2.0 Hz, C_3-H), 7.74(1H, s, C_4-H), 11.81(1H, br s, NH). Ms m/z: 299(M^++2, 97%), 297(M^+, 99%), 253(base peak).

Ethyl 7-bromo-6-methoxyindole-2-carboxylate (**3c-2**): Not isolated.[4] ^{1}H-Nmr δ(DMSO-d_6): 1.34(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.90(3H, s, OCH_3), 4.33 (2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 7.04(1H,d, J=9.0 Hz, C_5-H), 7.25(1H, d, J= 2.0 Hz, C_3-H), 7.66(1H, d, J=9.0 Hz, C_4-H), 11.46(1H, br s, NH).

Ethyl 3,5-dibromo-6-methoxyindole-2-carboxylate (**4c-1**): Colorless needles, mp 236.5-238°C from ethyl acetate-hexane. Anal. Calcd for $C_{12}H_{11}NO_3Br_2$: C, 38.23, H, 2.94, N, 3.72. Found: C, 38.02, H, 2.92, N, 3.78. Ir ν_{max} cm^{-1}: 3280(NH), 1665(C=O). ^{1}H-Nmr δ(60 MHz, DMSO-d_6): 1.35(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.85(3H, s, OCH_3), 4.31(2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.93(1H, s, C_7-H), 7.58(1H, s, C_4-H), 12.15(1H, br s, NH). Ms m/z: 379 (M^++4, 39%), 377(M^++2, 79%), 375 (M^+, 41%), 331(base peak).

Ethyl 3,7-dibromo-6-methoxyindole-2-carboxylate (**4c-2**): Colorless needles, mp 118.5-120°C from hexane-ethyl acetate. Anal. Calcd for $C_{12}H_{11}NO_3Br_2$: C, 38.23, H, 2.94, N, 3.72. Found 38.35, H, 2.98, N, 3.75. Ir ν_{max} cm^{-1}: 3250(NH), 1680(C=O). ^{1}H-Nmr δ(60 MHz): 1.43(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.94(3H, s, OCH_3), 4.42(2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.87(1H, d, J=8.0 Hz, C_5-H), 7.49(1H, d, J=8.0 Hz, C_4-H), 8.82(1H, br s, NH). Ms m/z:

379(M^++4, 32%), 377(M^++2, 64%), 375(M^+, 32%), 331(base peak).

Ethyl 3-bromo-7-methoxyindole-2-carboxylate (**2d**): Colorless needles, mp 128-129°C from benzene-hexane. Anal. Calcd for $C_{12}H_{12}NO_3Br$: C, 48.34, H, 4.06, N, 4.70. Found: C, 48.35, H, 4.04, N, 4.59. Ir ν_{max} cm^{-1}: 3280 (NH), 1688(C=O). ^{1}H-Nmr δ: 1.45(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.98(3H, s, OCH_3), 4.45(2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.77(1H, d, J=8.0 Hz, C_6-H), 7.14 (1H, t, J=8.0 Hz, C_5-H), 7.25(1H, d, J=8.0 Hz, C_4-H), 9.14, (1H, br s, NH). Ms m/z: 299(M^++2, 84%), 297(M^+, 85%), 251(base peak).

Ethyl 4-bromo-7-methoxyindole-2-carboxylate (**3d**): Colorless needles, mp 141.5-142.5°C from benzene-hexane. Anal. Calcd for $C_{12}H_{12}NO_3Br$: C, 48.34, H, 4.06, N, 4.70. Found: C, 48.20, H, 3.98, N, 4.67. Ir ν_{max} cm^{-1}: 3300 (NH), 1705(C=O). ^{1}H-Nmr δ: 1.42(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.95(3H, s, OCH_3), 4.42(2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.58(1H, d, J=8.0 Hz, C_6-H), 7.20 (1H, d, J=8.0 Hz, C_5-H), 7.21(1H, d, J=2.0 Hz, C_3-H), 9.17(1H, br s, NH). Ms m/z: 299(M^++2, 98%), 297(M^+, 97%), 253(base peak).

Ethyl 3,4-dibromo-7-methoxyindole-2-carboxylate (**4d**): Colorless needles, mp 155-156°C from benzene-hexane. Anal. Calcd for $C_{12}H_{11}NO_3Br_2$: C, 38.23, H, 2.94, N, 3,72. Found: C, 38.41, H, 2.92, N, 3.75. Ir ν_{max} cm^{-1}: 3270 (NH), 1700(C=O). ^{1}H-Nmr δ: 1.45(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.95(3H, s, OCH_3), 4.46(2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.56(1H, d, J=8.0 Hz, C_6-H), 7.26 (1H, d, J=8.0 Hz, C_5-H), 9.24(1H, br s, NH). Ms m/z: 379(M^++4, 34%), 377 (M^++2, 70%), 375(M^+, 35%), 331 (base peak).

Ethyl 3-bromo-4,7-dimethoxyindole-2-carboxylate (**2e**): Colorless plates, mp 206.5-208°C from $CHCl_3$. Anal. Calcd for $C_{13}H_{14}NO_4Br$: C, 47.58, H, 4.30, N, 4.27. Found: C, 47.70, H, 4.28, N, 4.42. Ir ν_{max} cm^{-1}: 3280(NH), 1680(C=O). ^{1}H-Nmr δ(60 MHz): 1.40(3H, t, J=7.0 Hz, $CH_2C\underline{H}_3$), 3.83(6H, s, OCH_3x2), 4.38(2H, q, J=7.0 Hz, $OC\underline{H}_2CH_3$), 6.27(1H, d, J=8.0 Hz, C_5 or C_6-H), 6.52(1H, d, J=8.0 Hz, C_6 or C_5-H), 9.08(1H, br s, NH). Ms m/z:329 (M^++2, 78%), 327(M^+, 79%), 281(base peak).

Ethyl 5-bromo-4,7-dimethoxyindole-2-carboxylate (**3e-1**): Colorless prisms,

mp 133-136°C from ethyl acetate-hexane. Anal. Calcd for $C_{13}H_{14}NO_4Br$: C, 47.58, H,4.30, N, 4.27. Found: C, 47.72, H, 4.30, N, 4.36. Ir ν_{max} cm^{-1}: 3290 (NH), 1690 (C=O). ^{1}H-Nmr δ(90 MHz): 1.39(3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.91(3H, s, C_7-OCH_3), 3.97(3H, s, C_4-OCH_3), 4.41(2H, q, J=7.0 Hz, $O\underline{CH_2}$-CH_3), 6.77(1H, s, C_6-H), 7.24(1H, d, J=2.0 Hz, C_3-H), 9.10(1H, br s, NH). Ms m/z: 329(M^++2, 99%), 377(M^+, base peak).

Ethyl 6-bromo-4,7-dimethoxyindole-2-carboxylate (**3e-2**): Colorless prisms, mp 106-109°C from ethyl acetate-hexane. Anal. Calcd for $C_{13}H_{14}NO_4Br$: C, 47.58, H, 4.30, N, 4.27. Found: C, 47.36, H, 4.29, N, 4.28. Ir ν_{max} cm^{-1}: 3320(NH), 1685(C=O). ^{1}H-Nmr δ(90 MHz): 1.40(3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.90(3H, s, C_4-OCH_3), 3.93(3H, s, C_7-OCH_3), 4.40(2H, q, J=7.0 Hz, O-$\underline{CH_2}$-CH_3), 6.56(1H, s, C_5-H), 7.27(1H, d, J=2.0 Hz, C_3-H), 9.08(1H, br s, NH). Ms m/z: 329(M^++2, 95%), 327(M^+, base peak).

Ethyl 3,5-dibromo-4,7-dimethoxyindole-2-carboxylate (**4e**): Colorless prisms, mp 148.5-150.5°C from ethyl acetate-hexane. Anal. Calcd for $C_{13}H_{13}NO_4Br_2$: C, 38.36, H, 3.22, N, 3.44. Found: C, 38.37, H, 3,28, N, 3.48. Ir ν_{max} cm^{-1}: 3270(NH), 1685(C=O). ^{1}H-Nmr δ: 1.45(3H, t, J=7.0 Hz, CH_2-$\underline{CH_3}$), 3.93(6H, s, OCH_3x2), 4.45(2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 6.81(1H, s, C_6-H), 9.22(1H, br s, NH). Ms m/z: 409(M^++4, 49%), 407(M^++2, base peak), 405(M^+, 51%).

Ethyl 3-bromo-4,6-dimethoxyindole-2-carboxylate (**2f**): Colorless prisms, mp, 216-219°C from hexane-ethyl acetate. High resolution ms calcd for $C_{13}H_{14}NO_4Br$: 327.0106; Found: 327.0155. Ir ν_{max} cm^{-1}: 3300(NH), 1660 (C=O). ^{1}H-Nmr δ: 1.43(3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.83(3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.41(2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 6.19(1H, d, J=2.0 Hz, C_5 or C_7-H), 6.38(1H, d, J=2.0 Hz, C_7 or C_5-H), 8.84(1H, br s, NH). Ms m/z: 329(M^++2, 71%), 327(M^+, 73%), 281(base peak).

Ethyl 7-bromo-4,6-dimethoxyindole-2-carboxylate (**3f**): Colorless prisms, mp 141.5-144°C from hexane-ethyl acetate. High resolution ms calcd for $C_{13}H_{14}NO_4Br$: 327.0106. Found: 327.0146. Ir ν_{max} cm: 3310(NH), 1685(C=O).

^{1}H-Nmr δ(60 MHz): 1.38(3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.90(6H, s, OCH_3x2), 4.37 (2H, q, J=7.0 Hz, OCH_2CH_3), 6.26(1H, s, C_5-H), 7.24(1H, d, J=2.0 Hz, C_3-H), 8.73(1H, br s, NH). Ms m/z: 329(M^++2, 79%), 327(M^+, 78%), 281 (base peak).

Ethyl 3,7-dibromo-4,6-dimethoxyindole-2-carboxylate (**4f**): Colorless prisms, mp 165-167.5°C from ethyl acetate-hexane. Anal. Calcd for $C_{13}H_{13}NO_4Br_2$: C, 38.36, H, 3.22, N, 3.44. Found: C, 38.58, H, 3.29, N, 3.47. Ir ν_{max} cm^{-1}: 3445(NH), 1690(C=O). ^{1}H-Nmr δ: 1.44(3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 3.97(6H, s, OCH_3x2), 4.44(2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 6.32(1H, s, C_5-H), 8.85(1H, br s, NH). Ms m/z: 409(M^++4, 28%), 407(M^++2, 53%), 405 (M^+, 27%), 361(base peak).

Ethyl 3-bromo-7-(p-toluenesulfonyloxy)indole-2-carboxylate (**2g**): Colorless needles, mp 125-127°C from benzene-hexane. Anal. Calcd for $C_{18}H_{16}NO_5BrS$: C, 49.33, H, 3.68, N, 3.20. Found: C, 49.53, H, 3.70, N, 3.21. Ir ν_{max} cm^{-1}: 3270(NH), 1705(C=O). ^{1}H-Nmr δ: 1.46(3H, t, J=7.0 Hz, $CH_2\underline{CH_3}$), 2.45 (3H, s, $ArCH_3$), 4.46(2H, q, J=7.0 Hz, $O\underline{CH_2}CH_3$), 6.81(1H, d, J=7.5 Hz, C_6-H), 7.05(1H, t, J=7.5 Hz, C_5-H), 7.32(2H, d, J=8.5 Hz, Ar-H), 7.55(1H, d, J=7.5 Hz, C_4-H), 7.73(2H, d, J=8.5 Hz, Ar-H), 9.16(1H, br s, NH). Ms m/z: 439(M^++2, 55%), 437(M^+, 52%), 282(base peak).

The Experiment for Intermolecular Bromine Rearrangement

Ethyl 3-bromoindole-2-carboxylate (**6**) (100 mg, 0.37 mmol), ethyl 7-methoxyindole-2-carboxylate (**1d**) (82 mg, 0.37 mmol), and $LiBr\cdot H_2O$ (39 mg, 0.37 mmol) were added to a solution of 97% H_2SO_4 (43 mg, 0.43 mmol) in AcOH (6 ml). The whole was stirred at 130°C for 1 h. The reaction mixture was poured into ice-water, neutralized with 10% NaOH, and extracted with AcOEt. The organic layer was washed with saturated NaCl, dried over $MgSO_4$, and evaporated to dryness in vacuo. The residue (174 mg) was chromatographed over silica gel with hexane-AcOEt by gradient elution to give ethyl indole-2-carboxylate (**7**) (55 mg, 77% yield based on **6**) and

ethyl 4-bromo-7-methoxyindole-2-carboxylate (**3d**) (91 mg, 82% yield based on **1d**).

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