

# Synthesis of 6-Methoxyindoles and Indolines. Regioselective C-6 Bromination of Indolines and Subsequent Nucleophilic Substitution with a Methoxyl Group

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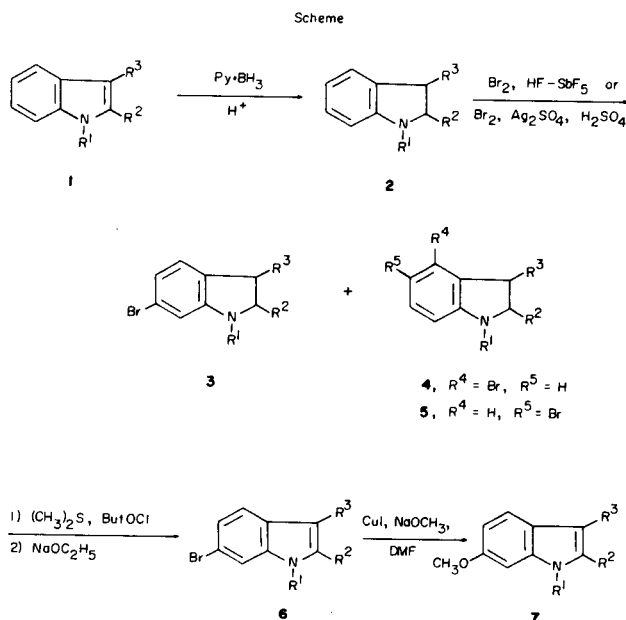
Regioselective bromination of the 6-position of indolines was investigated. Treatment of indolines with bromine in sulfuric acid in the presence of silver sulfate or with bromine in superacid afforded the 6-bromoindolines, which were converted to 6-methoxyindolines and indoles.

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Synthesis of 6-hydroxy or methoxyindoles usually starts from benzene derivatives having an oxygen function at the desired position of the benzene ring. However, sometimes it is difficult to prepare the starting benzene derivatives having substituents at the desired positions. We now intended to use indoles as starting materials and to introduce a methoxyl group into the C-6 position of the indoles. Previously we reported the synthesis of 5-methoxyindoles from 5-bromoindoles by the substitution of a bromine atom with a methoxyl group (1). This method has now been extended to the synthesis of 6-methoxyindoles. Direct C-6 bromination of indoles is difficult and is successful only when indoles have appropriate substituents at suitable positions (2). Thus, the key step of this synthesis should be the regioselective C-6 bromination of indolines as shown in Scheme.

### C-6 Bromination of Indolines with Bromine in 97% Sulfuric Acid in the Presence of Silver Sulfate.

Bromination of indolines in neutral or acidic condition usually occurs at the position *para* to the amino group. For direct introduction of a bromine atom *meta* to an amino group, the method for cationoid bromination of aromatic compounds in sulfuric acid in the presence of silver sulfate has been utilized (3). In a similar manner as above a Russian group published C-6 bromination of 2,3-dimethylindoline in sulfuric acid in the presence of silver sulfate with



bromine to give the corresponding 6-bromo compound in 50% yield (4), and this is the only single case hitherto reported, to our knowledge, concerning C-6 bromination of indolines. Thus we have attempted first detailed studies of the scope and limitation of this reaction on other indolines. The results are summarized in Table I.

Table I

Synthesis of Bromoindolines (3 and 4) with Bromine in Sulfuric Acid in the Presence of Silver Sulfate

Compound No.	R <sup>1</sup> , R <sup>2</sup> , R <sup>3</sup>	Time (hours)	Yield (%) of 3 and 4	Ratio (a) 3:4
2a	R <sup>1</sup> = R <sup>2</sup> = R <sup>3</sup> = H	1	60	11:1
2b	R <sup>1</sup> = CH <sub>3</sub> , R <sup>2</sup> = R <sup>3</sup> = H	1	69	11:1
2c	R <sup>1</sup> = R <sup>2</sup> = H, R <sup>3</sup> = CH <sub>3</sub>	1	46 (2) (b)	16:1
2d	R <sup>1</sup> = H, R <sup>2</sup> = R <sup>3</sup> = (CH <sub>2</sub> ) <sub>4</sub>	3.5	60	41:1
2e	R <sup>1</sup> = R <sup>2</sup> = H, R <sup>3</sup> = (CH <sub>2</sub> ) <sub>2</sub> NHAc	2	42	—
2f	R <sup>1</sup> = R <sup>2</sup> = H, R <sup>3</sup> = (CH <sub>2</sub> ) <sub>2</sub> NHCOC(CH <sub>3</sub> ) <sub>3</sub>	2	30	—

(a) Determined by glc (10% SE-30, 2 m). (b) Yield of 5c.

Table II  
Bromination of Indoline (**2a**) with Bromine in the Presence of Fluoroantimonic Acid

Run	Molar Ratio		Temperature (°C)	Time (hours)	Yield (%) of <b>3a</b> and <b>4a</b>
	Br <sub>2</sub> / <b>2a</b>	HF-SbF <sub>5</sub> / <b>2a</b>			
1	0.5	3	-80 to 4	5.5	45 (a)
2	0.7	3	-70 to 6	6	13 (a)
3	0.4	3	20	4	32 (a)
4	0.6	1.5	-15	1	(43) (b)
5	0.6	3	-40	0.5	(32) (c)
					57

(a) The product was contaminated by a dibromo compound. (b) Yield of **5a**. (c) Recovery of **2a**.

6-Bromoindolines **3** were obtained in moderate yields, although gas chromatographic analysis of bromoindolines showed the presence of a small amount of the 4-bromoindolines **4**. In the case of **2c**, 5-bromo-2,3-dihydroskatole (**5c**) was isolated from the reaction mixture as a by-product by silica gel column chromatography [benzene/hexane (1/1) for elution] in low yield, but other 5-bromo compounds could not be detected in the products. For the identification of the products, **3a**, **4a**, **5a**, and **5c** were prepared as authentic samples by another method. Identification of **3a** and **5c** was accomplished by comparison of the spectral data with those of the authentic samples and by the gas chromatographic analysis. Compounds **3b-d** were identified by measurement of the spectral data and **4b-d** were identified by gas chromatograph-mass spectrometric analysis. The physical, spectroscopic and analytical data are recorded in Table V and VI.

C-6 Bromination of Indolines with Bromine in Superacid (HF-SbF<sub>5</sub>).

Although regioselective C-6 bromination of indolines succeeded in moderate yields as is described in the previous section, 97% sulfuric acid is essential as the solvent, which is troublesome in the work-up of the reaction mixture and is not suitable for a large scale preparation. Thus, we next have attempted the same bromination by the use of superacid. At first a number of reaction variables were investigated, *eg.* superacids, molar ratio of superacid and bromine to indoline, solvents, reaction temperature and reaction time. As shown in Table II, the yield of **3a** was highest under the reaction conditions of run 5. C-6 Bromination of several indolines was carried out under these optimum conditions and the results are presented in Table III. The yields of **3** were almost the same as those in the previous experiments but the ratio of **4** to **3** was decreased in the case of 3-substituted indolines and 5-bromo compounds could not be detected in the products. These facts indicate that bromination of indolines is more regioselective in the superacid than in 97% sulfuric acid. Furthermore, this method has the advantage of a short

Table III  
Synthesis of Bromoindolines (**3** and **4**) with Bromine in the Presence of Fluoroantimonic Acid

Compound No.	Yield (%) of <b>3</b> and <b>4</b>	Ratio (b) <b>3:4</b>
<b>2a</b>	57	8:1
<b>2b</b>	64	9:1
<b>2c</b>	49	37:1
<b>2d</b>	58	89:1

(a) Reaction time, 30 minutes. (b) Determined by glc (10% SE-30, 2 m).

reaction time, use of small amounts of acid and easy work-up.

Synthesis of 6-Methoxyindoles.

6-Bromoindolines, thus prepared, were dehydrogenated to 6-bromoindoles (**5**) and they were submitted to the displacement reaction of a bromine atom with a methoxyl group (**1**). The results are summarized in Table IV. As was

Table IV  
Synthesis of 6-Methoxyindoles (**7**)

Compound No.	R <sup>1</sup> , R <sup>2</sup> , R <sup>3</sup>	Time (hours)	Yield (%) of <b>7</b>
<b>6a</b>	R <sup>1</sup> = R <sup>2</sup> = R <sup>3</sup> = H	12	73
<b>6f</b>	R <sup>1</sup> = R <sup>2</sup> = H, R <sup>3</sup> = (CH <sub>2</sub> ) <sub>2</sub> NHCOC(CH <sub>3</sub> ) <sub>3</sub>	8	58
<b>6g</b>	R <sup>1</sup> = CH <sub>3</sub> , R <sup>2</sup> = R <sup>3</sup> = (CH <sub>2</sub> ) <sub>4</sub>	6	80
<b>6h</b>	6-Bromo-9-benzyl-1,2,3,4,4a,9a-hexahydrocarbazole	13	80

expected, the methoxylation reaction proceeded smoothly in both indoles and indolines. Thus, 6-methoxyindoles were synthesized from indoles which had no substituent on the C-6 position. As a bromine atom can be easily displaced with other functional groups by known methods, this procedure will offer a general method for the synthesis of not only 6-methoxyindoles but also other 6-substituted indoles from indoles.

Table V  
 Physical Properties

Compound No.	Mp °C or Bp °C/Torr (a)	Formula	IR cm <sup>-1</sup> (b)	<sup>1</sup> H-NMR (δ) ppm (c)	Mass (M <sup>+</sup> )
<b>3a</b>	116-118/4		1600, 900, 850, 810	2.95 (t, 2H, J = 8 Hz, 3-CH <sub>2</sub> ), 3.57 (t, 2H, J = 8 Hz, 2-CH <sub>2</sub> ), 6.74 (s, 1H, 7-H), 6.81-6.99 (m, 2H, 4 and 5-H)	197
<b>3b</b>	158-161 (d) (Ethanol)	C <sub>15</sub> H <sub>13</sub> BrN <sub>2</sub> O <sub>7</sub>	1600, 880, 830, 790	2.80 (s, 3H, CH <sub>3</sub> ), 2.88 (t, 2H, J = 8 Hz, 3-CH <sub>2</sub> ), 3.35 (t, 2H, J = 8 Hz, 2-CH <sub>2</sub> ), 6.56 (s, 1H, 7-H), 6.74 (dd, 1H, J = 2, 8 Hz, 5-H), 6.90 (d, 1H, J = 8 Hz, 4-H)	211
<b>3c</b>	156-157 (d) (Ethanol)	C <sub>15</sub> H <sub>13</sub> BrN <sub>2</sub> O <sub>7</sub>	1600, 890, 850, 810	1.29 (d, 3H, J = 7 Hz, CH <sub>3</sub> ), 3.04-3.79 (m, 3H, 2 and 3-H), 6.74 (s, 1H, 7-H), 6.83-6.88 (m, 2H, 4 and 5-H)	211
<b>3d</b>	78-79 (Hexane)	C <sub>12</sub> H <sub>14</sub> BrN	1600, 850	1.11-1.92 (m, 8H, 4 × CH <sub>2</sub> ), 3.04 (q, 1H, J = 6 Hz, 4a-H), 3.48-3.85 (m, 1H, 9a-H), 6.78 (s, 1H, 7-H), 6.85-6.98 (m, 2H, 4 and 5-H)	251
<b>3e</b>			3350 (NH), 1670 (C=O), 1600	1.95 (s, 3H, Ac), 1.40-1.95 (m, 2H, CH <sub>2</sub> CH <sub>2</sub> NHAc), 3.08-3.84 (m, 5H, 2 × CH <sub>2</sub> and CH), 5.61 (br s, 1H, NHAc), 6.75 (s, 1H, 7-H), 6.83-7.09 (m, 2H, 4 and 5-H)	282
<b>3f</b>	101-101.5 (Benzene)	C <sub>15</sub> H <sub>21</sub> BrN <sub>2</sub> O	3320, (NH), 1640 (C=O), 1610, 900, 850, 810	1.17 (s, 9H, 3 × CH <sub>3</sub> ), 1.45-2.12 (m, 2H, CH <sub>2</sub> CH <sub>2</sub> NHCO), 3.02-4.07 (m, 5H, 2 × CH <sub>2</sub> and CH), 5.76 (br s, 1H, NHCO), 6.76 (s, 1H, 7-H), 6.78-7.01 (m, 2H, 4 and 5-H)	324
<b>4a</b>	179-180 (d) (Benzene)	C <sub>14</sub> H <sub>11</sub> BrN <sub>2</sub> O <sub>7</sub>	1600, 770	3.05 (t, 2H, J = 8 Hz, 3-CH <sub>2</sub> ), 3.59 (t, 2H, J = 8 Hz, 2-CH <sub>2</sub> ), 6.51 (dd, 1H, J = 2, 8 Hz, 7-H), 6.76-6.88 (m, 2H, 5 and 6-H)	197
<b>6e</b>	131-132 (Ethyl acetate/Hexane)	C <sub>12</sub> H <sub>13</sub> BrN <sub>2</sub> O	3480 (NH), 1670 (C=O)	1.95 (s, 3H, Ac), 2.94 (t, 2H, J = 7 Hz, CH <sub>2</sub> CH <sub>2</sub> NHAc), 3.57 (q, 2H, J = 7 Hz, CH <sub>2</sub> NHAc), 5.51 (br s, 1H, NHAc), 7.02 (d, 1H, J = 2 Hz, 2-H), 7.17-7.54 (m, 3H, arom H), 8.18 (br s, 1H, NH)	280
<b>6f</b>	122-123 (Ethyl acetate)	C <sub>15</sub> H <sub>19</sub> BrN <sub>2</sub> O	3360 (NH), 1610 (C=O), 905, 860, 820	1.13 (s, 9H, 3 × CH <sub>3</sub> ), 2.94 (t, 2H, J = 7 Hz, CH <sub>2</sub> CH <sub>2</sub> NHCO), 3.55 (q, 2H, J = 7 Hz, CH <sub>2</sub> NHCO), 5.71 (br s, 1H, NHCO), 7.00 (s, 1H, 2-H), 7.19-7.54 (m, 3H, arom H), 8.25 (br s, 1H, NH)	322
<b>7f</b>	108-109 (Ethyl acetate)	C <sub>16</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub>	3320 (NH), 1610 (C=O), 840, 830, 820, 780, 700	1.13 (s, 9H, 3 × CH <sub>3</sub> ), 2.90 (t, 2H, J = 7 Hz, CH <sub>2</sub> CH <sub>2</sub> NHCO), 3.50 (t, 2H, J = 7 Hz, CH <sub>2</sub> NHCO), 3.80 (s, 3H, OCH <sub>3</sub> ), 5.80 (br s, 1H, NHCO), 6.62-6.93 (m, 3H, arom H), 7.43 (d, 1H, J = 8 Hz, 4-H), 8.56 (br s 1H, NH)	274

(a) Recrystallization solvent. (b) Compounds **3a**, **3b**, **3c** and **4a**, neat; **3d**, **3f**, **6f** and **7f**, in nujol; **3e** and **6e** in chloroform. (c) In deuteriochloroform. (d) Picrate.

## EXPERIMENTAL

All melting points and boiling points are uncorrected. The following instruments were used for obtaining physical data: infrared (ir) spectra, Shimadzu IR-400; nmr spectra (tetramethylsilane as an internal standard), JEOL PS-PFT/EC 100; GC-mass spectra and mass spectra, Shimadzu LKB-9000; gas chromatography, Shimadzu GC-4BM.

## Materials.

Compound **2a** was purchased from Tokyo Kasei Kogyo Co. Compound **2b** bp 59-60°/3 torr [lit (6) bp 216°/728 torr] was synthesized by the *N*-methylation of **2a**. Compound **2**, bp 130°/8 torr (Kugelrohr apparatus) [lit (7) bp 231-232°/744 torr], **2e**, mp 91-92° (*Anal.* Calcd. for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O: C, 70.56; H, 7.90; N, 13.72. Found: C, 70.40; H, 7.90; N, 13.52), and **2f**, mp 103-104° (*Anal.* Calcd. for C<sub>15</sub>H<sub>22</sub>N<sub>2</sub>O: C, 73.13; H, 9.00; N, 11.37.

Table VI  
Elemental Analyses

Compound No.	Formula	Analysis		
		C	H	N
<b>3b</b>	C <sub>12</sub> H <sub>13</sub> BrN <sub>4</sub> O <sub>7</sub> (a)	40.84	2.97	12.70
		(41.09)	(3.05)	(12.73)
<b>3c</b>	C <sub>15</sub> H <sub>13</sub> BrN <sub>4</sub> O <sub>7</sub> (a)	40.84	2.97	12.70
		(41.07)	(3.12)	(12.63)
<b>3d</b>	C <sub>12</sub> H <sub>14</sub> BrN	57.16	5.60	5.56
		(57.02)	(5.46)	(5.42)
<b>3f</b>	C <sub>13</sub> H <sub>21</sub> BrN <sub>2</sub> O	55.39	6.51	8.61
		(55.61)	(6.79)	(8.53)
<b>4a</b>	C <sub>14</sub> H <sub>11</sub> BrN <sub>4</sub> O <sub>7</sub> (a)	39.36	2.60	13.11
		(39.42)	(2.80)	(12.99)
<b>6e</b>	C <sub>12</sub> H <sub>13</sub> BrN <sub>2</sub> O	51.26	4.66	9.77
		(51.13)	(4.43)	(9.81)
<b>6f</b>	C <sub>15</sub> H <sub>15</sub> BrN <sub>2</sub> O	55.74	5.92	8.67
		(55.47)	(5.63)	(8.67)
<b>7f</b>	C <sub>16</sub> H <sub>22</sub> N <sub>2</sub> O <sub>2</sub>	70.04	8.08	10.21
		(70.07)	(7.98)	(10.35)

(a) Picrate.

Found: C, 72.92; H, 9.26; N, 11.22), were prepared by literature methods (8). Reduction of 1,2,3,4-tetrahydrocarbazole with pyridine-borane gave *cis*-1,2,3,4,4a,9a-hexahydrocarbazole (**2d**), mp 96-98° [lit (9) mp 99°]. Sulfuric acid and cuprous iodide were purchased from Wako Pure Chemical Industries, Ltd. Fluoroantimonic acid was purchased from Aldrich Chemical Company, Inc.

General Procedure for Bromination in 97% Sulfuric Acid in the Presence of Silver Sulfate.

Bromine (0.13 ml, 2.52 mmoles) was added to a mixture of 97% sulfuric acid (3 ml), silver sulfate (393 mg, 1.26 mmoles), and indoline (**2a**) (300 mg, 2.52 mmoles), and the mixture was vigorously stirred for 30 minutes at room temperature. After most of bromine had disappeared, the mixture was poured into cold water, made alkaline by 20% aqueous potassium hydroxide and filtered. The filtrate was washed with benzene. The aqueous layer was extracted with benzene (60 ml) and the combined organic layer was washed with brine, dried (sodium sulfate) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (benzene for elution) to give 298 mg of a yellow solid (60% yield)

which was the mixture of **3a** and **4a** (**3a:4a** = 11:1). **3a** and **4a** could not be separated by either chromatography or distillation (bp 116-118°/4 torr), but after the dehydrogenation of the mixture to indoles, they were easily separated by silica gel column chromatography [benzene-hexane (1:1) for elution]. Gas chromatographic conditions are as follows: glass column (2 m); 10% SE-30 on Chromosorb W (60-80 mesh); temperature, 160°; carrier gas, nitrogen at a flow rate of 50 ml/minute.

General Procedure for Bromination in the Presence of Fluoroantimonic Acid.

Fluoroantimonic acid (HF-SbF<sub>5</sub>) (1:1) 1.8 g, 7.6 mmoles) was added to a solution of **2a** (300 mg, 2.52 mmoles) in dichloromethane (10 ml) in an argon atmosphere at -40°. After 5 minutes stirring, bromine (0.08 ml, 1.51 mmoles) was added and stirred at -40° for 30 minutes. The reaction mixture was poured into 10% sodium hydroxide (12 ml) and the solution was extracted with ether (60 ml). Insoluble materials were filtered off and the filtrate was washed with ether. The combined organic layer was washed with brine, dried (sodium sulfate) and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (benzene for elution) to give 286 mg of a yellow solid (57% yield) which was the mixture of **3a** and **4a** (**3a:4a** = 8:1).

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