

A New Synthesis of 5-Hydroxytryptamine (Serotonin)

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Methoxylation of the 5-position of indoles and indolines was investigated. Treatment of 5-bromo-indoles and indolines with cuprous iodide and sodium methoxide in methanol/dimethylformamide afforded the corresponding methoxy compounds. This methoxylation reaction was applied to the new synthesis of serotonin.

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There are many indole derivatives bearing hydroxyl or methoxyl groups on the benzene ring and they often have potent physiological activities. Synthesis of these compounds usually start from indoles having an oxygen function at the desired position of the indole ring. We intended to establish a new preparative method for hydroxy- or methoxy-indoles by the introduction of an oxygen function after synthesis of the indole ring.

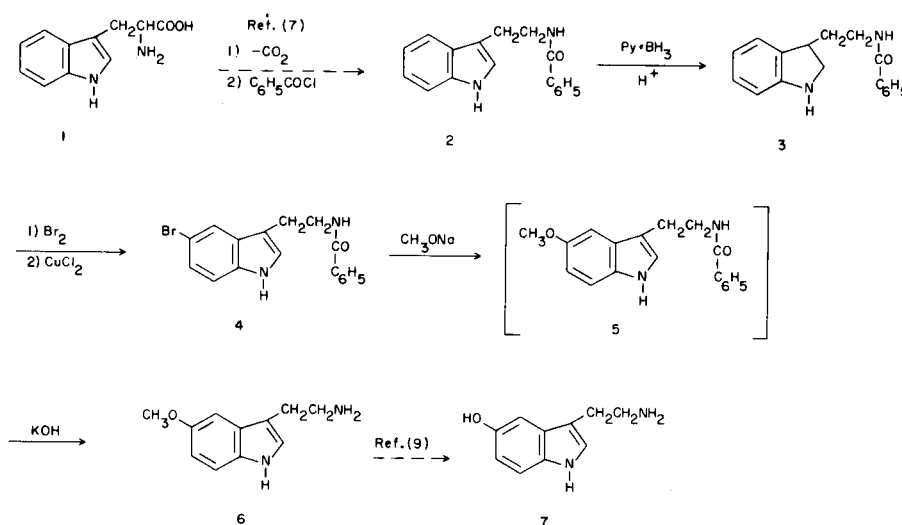
In the previous reports (1), we described the reduction of indoles to indolines with pyridine-borane and, in the present work, we attempted the synthesis of 5-hydroxytryptamine by the use of this reduction reaction, although several other methods for the synthesis of 5-hydroxytryptamine have already been described (2).

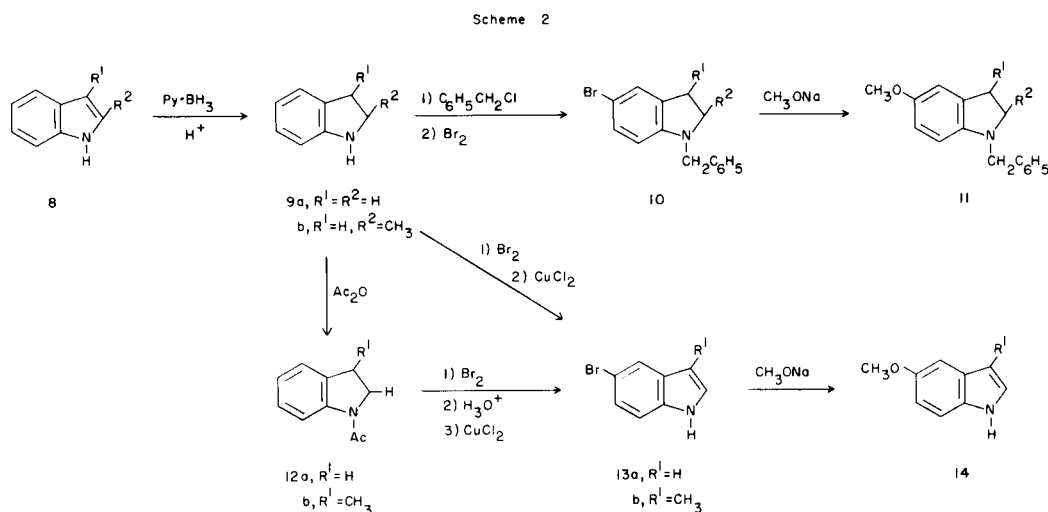
The synthetic strategy was planned as shown in Scheme 1. As the direct halogenation or methoxylation at the 5-position of the indole ring is impossible, bromination was carried out on 2,3-dihydroindoles (9), which were easily prepared by our method (1). The key step of this synthesis should be the substitution of the bromine atom with the methoxyl group.

Introduction of Methoxyl Group into Indoles and Indolines.

As the direct methoxylation of the indole ring is difficult, we attempted the substitution of a halogen atom with a methoxyl group. In connection with this synthetic work, we also attempted the synthesis of 5-methoxy- or 5-hydroxy-2,3-dihydroindoles, which have biological significance and are also often quite difficult to prepare. 5-Bromoindolines, which are the precursors of the corresponding methoxyl derivatives, were prepared by the bromination of indolines (9) (3). At first, we employed the copper-catalysed conversion of 1-benzyl-5-bromoindoline (10a) to the corresponding methoxyl compound (11a) by following the published procedure (4) in which *p*-anisidine was obtained from *p*-bromoaniline in 50% yield. Even though the refluxing (160-180°) in collidine/methanol was prolonged to 24 hours, 10a was recovered in 78% yield, with a small amount of the methoxyl compound (11a) (yield, 5%). After some trials failed, we applied the method of the methoxylation of 1,3,5-tribromobenzene reported by KcKillop, *et al.* (5),

Scheme 1





to the methoxylation of the indole and indoline rings.

Treatment of **10a** with excess of sodium methoxide in methanol/dimethylformamide and in the presence of a 0.5 molar equivalent of cuprous iodide resulted in the formation of **11a** in 53% yield. In the case of methoxylation of 5-bromoindoline, 5-methoxyindole (**14a**) was obtained from the tarry residue in 32% yield, probably due to the instability of the indoline ring to oxidation. This instability may be increased by the introduction of the methoxyl group into the benzene ring because 5-methoxyindolines are more darkly colored than the corresponding non-substituted indolines on exposure to air. For the smooth reaction, bromoindoles (**13**) and 1-benzyl-bromoindolines (**10**) are recommended as the starting compounds. The results are presented in Table I.

Although Oishi, *et al.* (3), reported an elegant methoxylation of 3,3-disubstituted indolines, aiming at the methoxylation of indole alkaloids, they used chromium hexacarbonyl and a crown ether, which are not suitable for a large scale preparation. Therefore, this simple and inexpensive procedure will offer a general method for methoxylation at the 5-position of the indole and indoline rings.

Synthesis of 5-Methoxytryptamine (6).

As the methoxylation of indoles has been successfully established, the synthesis of serotonin was carried out as shown in Scheme 1. Although we used the commercially available tryptamine as the starting material, tryptamine synthesized by the decarboxylation of DL-tryptophan (7) will be usable for a large scale preparation, since DL-tryptophan is inexpensive and readily available. We believe that this will be better than other synthetic methods, such as Fischer's indole synthesis (8) and subsequent introduction of the side chain into the 3-

position of the indole ring. The compound **4** was converted to 5-methoxytryptamine (**6**) in 58% yield. Recrystallization from ethanol gave the pure material, m.p. 118-120°, which was identified by the mixture melting point test with an authentic sample purchased from a commercial source. As the demethylation of **6** was reported in the literature (9), the new synthetic route to serotonin was thus established.

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), JNM-C-60HL; gas chromatography, Shimadzu GC-4BM.

Materials.

5-Bromoindoline, **10a**, and 3-bromocarbazole were synthesized by the reported methods cited in Table II. 5-Bromoindoline was also prepared by the acid hydrolysis (3-4% hydrochloric acid, 1.75 hour reflux) of 1-acetyl-5-bromoindoline, m.p. 118-119° [lit. (3b) m.p. 118-119°], prepared by the reported procedure (3b). Compound **10b** and 1-benzyl-6-bromo-1,2,3,4-tetrahydroquinoline were prepared in a similar manner as **10a**. The physical constants of the starting materials and products are summarized in Table II. Tryptamine hydrochloride was purchased from Tokyo Kasei Kogyo Co.

Synthesis of 5-Bromo- and 5-Bromo-3-methyl-indoles (**13a** and **13b**).

Synthesis of **13a** and **13b** were performed by reference to the reported method (10) as follows. A mixture of 5-bromoindoline (1.31 g., 6.62 mmoles), copper (II) chloride (1.78 g., 13.24 mmoles), and pyridine (56 ml.) was refluxed for 3.5 hours. After evaporation of pyridine, the residue was triturated with benzene and filtered. The combined benzene solution was washed with saturated sodium chloride and dried over anhydrous sodium sulfate. After evaporation of benzene, the residue was submitted to column chromatography over silica gel (Merck, Art. 7734) using benzene/hexane (1/1) for elution to give 0.78 g.

Table I
Synthesis of Methoxy Compounds

Starting Material (SM)	Sodium Methoxide/ SM	Molar Ratio	Cupric Iodide/ SM	Temperature	Reaction Time	Product (Yield, %)
5-Bromoindoline	10		2	120-130	12	14a (32)
10a	5		0.5	120-130	12	11a (53)
10b	5		0.5	120-130	12	11b (60)
13a	10		2	~ 120	6	14a (79)
13b	10		2	120-130	12	14b (44)
3-Bromocarbazole	10		2	120-130	12	3-Methoxycarbazole (69)
1-Benzyl-6-bromo-1,2,3,4-tetrahydroquinoline	4.5		0.5	~ 120	12	1-Benzyl-6-methoxy-1,2,3,4-tetrahydroquinoline (84)

(60%) of **13a**, m.p. 87-88.5°, recrystallized from hexane. Compound **13b** was prepared in a similar manner as **13a**.

General Procedure for Introduction of the Methoxyl Group.

Dimethyl formamide (DMF) (3.5 ml.), copper (I) iodide (644 mg., 3.38 mmoles), and **13a** (331 mg., 1.69 mmoles) were added to absolute methanol (4 ml.) in which metallic sodium (389 mg., 16.9 mmoles) was dissolved. After more DMF (3.5 ml.) was added, the mixture was refluxed (oil bath 120°) for 6 hours in an argon atmosphere. After the reaction was completed, the precipitate was filtered off and the filtrate was evaporated *in vacuo*. To its residue, 2% sodium hydroxide was added, followed by extraction with benzene which was washed with saturated sodium chloride and dried over anhydrous sodium sulfate. After evaporation of benzene, the residue was purified by column chromatography [silica gel, benzene/hexane (2/1) for **14a**; benzene/hexane (1/1) for 1-benzyl-5-methoxy-1,2,3,4-tetrahydroquinoline; benzene/hexane~benzene for **14b** and 3-methoxycarbazole; alumina, benzene/hexane (2/1) for **11a**; benzene/hexane (1/3) for **11b**] to give 196 mg. (79%) of **14a**; m.p. 53-55°, which was recrystallized from cyclohexane to afford colorless needles, m.p. 56-57°.

Synthesis of 5-Bromo-N-benzoyltryptamine (**4**).

To a mixture of acetic acid (50 ml.), concentrated sulfuric acid (0.38 g. in 3 ml. of acetic acid) and **3** (2.0 g., 7.5 mmoles) prepared by the reported method (1), bromine (1.2 g., 7.5 mmoles in 4 ml. of acetic acid) was added, and the solution was stirred for 5 hours at room temperature. After the reaction, acetic acid was evaporated *in vacuo* and 10% sodium hydroxide was added to the residue. The aqueous solution was extracted with ethyl acetate and the extract was washed with saturated sodium chloride and dried over anhydrous sodium sulfate. After evaporation of the ethyl acetate, copper (II) chloride (2.0 g., 14.9 mmoles) was added to the residue which was dissolved in pyridine (60 ml.), and the mixture was refluxed for 3.5 hours. After evaporation of pyridine, the residue was triturated with ethyl acetate and filtered. The combined ethyl acetate solution was washed with saturated sodium chloride and dried over anhydrous sodium sulfate. After evaporation of the ethyl acetate, the residue was submitted to column chromatography using the Lober column [benzene/acetone (6/1) for elution] to give 0.83 g. of **4** (32%) which was recrystallized from ethanol, m.p. 175-176°; ir (nujol): ν 3330, 3220 (NH), 1620 (C=O); nmr ((CD₃)₂SO-d₆): δ 2.83-3.17 (2H, m, CH₂), 3.40-3.77 (2H, m, CH₂), 7.20-8.00 (9H, m, arom H), 8.47-8.80 (1H, br., NH), 10.90-11.17 (1H, br., NH).

Anal. Calcd. for C₁₇H₁₅BrN₂O: C, 59.49; H, 4.41; N, 8.16. Found: C, 59.31; H, 4.51; N, 8.24.

Synthesis of 5-Methoxytryptamine (**6**).

Metallic sodium (482 mg., 21.0 mmoles) was dissolved in absolute methanol (6 ml.), into which nitrogen gas was bubbled, and to this solution, DMF (10 ml.), copper (I) iodide (998 mg., 5.2 mmoles) and **4** (719 mg., 2.1 mmoles) were added. After adding more DMF (10 ml.), the reaction mixture was refluxed for 10 hours (oil bath, 130-140°) in an argon atmosphere. When cooled, the precipitate was filtered with suction, washed with ethyl acetate and the filtrate was extracted with ethyl acetate. The combined ethyl acetate solution was washed with saturated sodium chloride and dried over anhydrous sodium sulfate. After evaporation of the ethyl acetate, the residue was submitted to silica gel column chromatography [benzene/acetone (4/1) for elution] to give a turbid oil (380 mg.), which was

Table II
Physical Constants

Compound No.	B.p. °C/Torr or M.p., °C (a)	Formula or Literature B.p., °C/Torr or M.p., °C	Analysis (%)		
			C	Calcd. (Found) H	N
5-Bromoindoline	132/5	114-114.5/2 (3a)			
10a	212-216/6	174-176/1 (3c)			
10b	143-145 dec (b) (Methanol/Diethyl Ether)	C ₁₆ H ₁₇ BrCl	56.74 (56.56)	5.06 (4.88)	4.14 (4.16)
11a	182-184 dec (b) (Methanol/Diethyl Ether)	183-184 dec (6)			
11b	164-166 dec (b) (Methanol/Diethyl Ether)	C ₁₇ H ₂₀ ClNO	70.46 (70.18)	6.96 (6.72)	4.83 (4.81)
13a	87-88.5 (Hexane)	90-91 (11)			
13b	76-78 (Hexane)	79.5-80.5 (12)			
14a	56-57 (Cyclohexane)	57-57.5 (14)			
14b	64-66 (Ligroin)	66 (15)			
3-Bromocarbazole	195-196 (Methanol)	201 (13)			
3-Methoxycarbazole	149-151 (Methanol)	149-151 (16)			
1-Benzyl-6-bromo-1,2,3,4-tetrahydroquinoline	66-67 (Hexane)	C ₁₆ H ₁₆ BrN	63.59 (63.56)	5.34 (5.33)	4.63 (4.83)
1-Benzyl-6-methoxy-1,2,3,4-tetrahydroquinoline	56-58 (Ligroin)	C ₁₇ H ₁₉ NO	80.57 (80.37)	7.56 (7.40)	5.53 (5.39)

(a) Recrystallization solvents. (b) hydrochloride salt.

hydrolysed with potassium hydroxide [5.7 g. in 50% aqueous methanol (26 ml.)] with refluxing for 27.5 hours. After evaporation of methanol, the aqueous layer was extracted with dichloromethane, which was washed with saturated sodium chloride, and dried over anhydrous sodium sulfate. After evaporation of dichloromethane, **6** was obtained in 58% yield (230 mg.) as crude crystals, which were recrystallized from ethanol m.p. 118-120°; nmr (deuteriochloroform): δ 1.35 (2H, s, NH₂), 2.83-3.25 (4H, m, CH₂CH₂), 3.87 (3H, s, OCH₃), 6.70-7.37 (4H, m, arom H), 8.18-8.63 (1H, br., NH). Identity of **6** was also established by the comparison of its ir spectrum with that of an authentic sample purchased from a commercial source.

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