A Simple Synthesis of 5-Methoxyindole and 5-Methoxy-2-oxindole

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1-Methoxy- and 1-hydroxy-2-oxindoles rearranged in acidic solution to 5-substituted 2-aminophenylacetic acid derivatives which were cyclized to the corresponding 2-oxindoles with heating. The synthesis of 5-methoxyindole from 5-methoxy-2-oxindole was also described.

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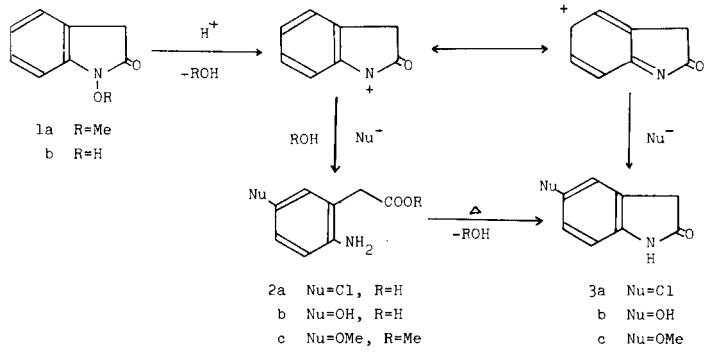
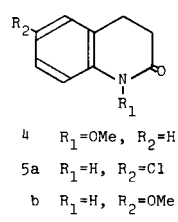
In this article we report a facile synthesis of 5-methoxyindole and 5-methoxy-2-oxindole from 1-methoxy-2-oxindole (**1a**) with acid-catalyzed nucleophilic rearrangements. It was reported that 5-bromo- or 5-chloro-2-oxindole was synthesized from 1-hydroxy-2-oxindole or 1-methoxy-2-oxindole with concentrated hydrobromic acid or hydrochloric acid in poor yield (15% or 18%) [1]. As **1a** and other nitrogen heterocyclic compounds were easily synthesized by the literature methods [2], and also 5-methoxyindole and 5-methoxy-2-oxindole are important precursors for the preparation of the indole alkaloids and medicines, we decided to investigate this reaction deeply. After some trials to improve the yield of 5-chloro-2-oxindole (**3a**), we finally discovered the fact that the amide bond of 2-oxindoles was cleaved under the rearrangement condition to give 2-amino-5-chlorophenylacetic acid (**2a**) which was not extracted and not cyclized with ease. It is worth noting that 10 hours reflux of the aqueous layer neutralized with concentrated ammonium hydroxide to about *p*H 5 is necessary to complete the cyclization. Consequently, the yield of **3a** was raised from 18% to 70%. The synthesis of 5-methoxy-2-oxindole (**3c**) was attempted by a similar procedure [3] and **1a** was treated with refluxing methanol containing few drops of concentrated sulfuric acid. Intermediary methyl 2-amino-5-methoxyphenyl acetate (**2c**) was isolated and converted to 5-methoxy-2-oxindole (**3c**) in 70% yield by refluxing in xylene for 7 hours or in 72% yield by refluxing in benzene containing silica gel for 2 hours [4]. From 1-hydroxy-2-oxindole (**1b**) the same results were obtained. Accordingly, the following mechanism is assumed.

Conversion of **3c** to 5-methoxyindole was accomplished by the chlorination of **3c** with triphenylphosphine-carbon tetrachloride in acetonitrile [5] followed by the catalytic reduction of a chlorine atom in 66% total yield. 2-Chloroindoles bearing no substituents on the benzene ring were easily prepared from the corresponding 2-oxindoles and phosphoryl chloride by heating [6]; however, this method was unsuccessful for the chlorination of **3c**.

Chart 1





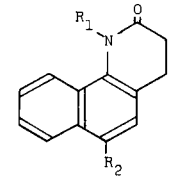
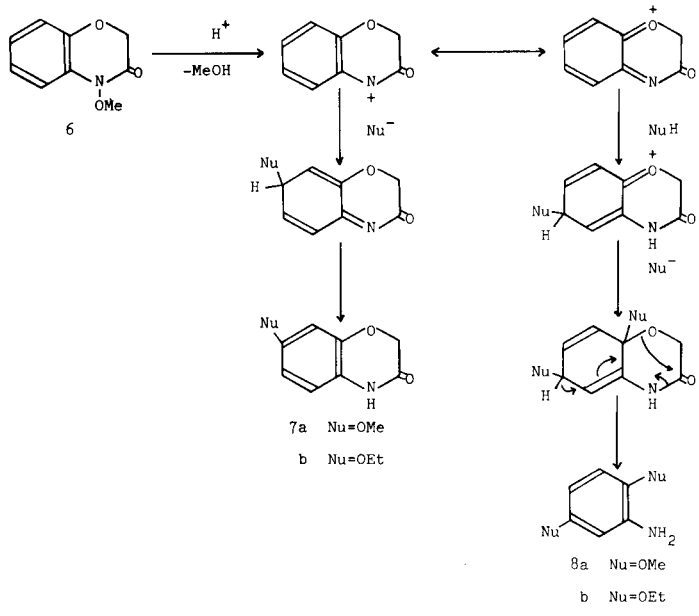


Chart 2



3,4-Dihydro-1-methoxycarbostyril (**4**) rearranged in aqueous hydrochloric acid or in refluxing methanol containing few drops of concentrated sulfuric acid to give 6-chloro-3,4-dihydrocarbostyril (**5a**) or 3,4-dihydro-6-methoxycarbostyril (**5b**) without detectable cleavage of the amide bond. The mechanism of the rearrangement of **4** is supposed to be the same as that of the rearrangement of 3,4-dihydro-1-hydroxycarbostyrils which appeared in the literature [3].

From 4-methoxy-2*H*-1,4-benzoxazin-3-one (**6**), 2,5-dimethoxyaniline (**8a**) was obtained in 37% yield in addition to 7-methoxy-2*H*-1,4-benzoxazin-3-one (**7a**). The assumed mechanism is illustrated in Chart 2.

This methoxylation was applicable to other nitrogen heterocyclic compounds having *N*-methoxyamide function and 3,4-dihydro-1-methoxybenzo[*h*]carbostyril (**9**) was converted to 3,4-dihydro-6-methoxybenzo[*h*]carbostyril (**10**) in 63% yield under similar reaction conditions.

EXPERIMENTAL

The melting points were determined on Yanako micro melting point apparatus and are uncorrected. The mass spectra were measured with a JEOL DX-300 mass spectrometer. The nmr spectra were measured with a JEOL JNM-GX 270 FT spectrometer (270 MHz) using TMS as an internal standard. The ir spectra were measured with a JASCO IR810 spectrometer. The elemental analyses were performed on a Yanako MT-3.

5-Chloro-2-oxindole (**3a**) and 7-Chloro-2-oxindole (**11**).

A mixture of **1a** (300 mg, 1.84 mmoles) and concentrated hydrochloric acid (15 ml) was stirred for 1.5 hours at 60°. The reaction mixture was extracted with chloroform (15 ml x 8). The combined chloroform layer was washed with 5% sodium bicarbonate solution (30 ml), brine (20 ml x 2), dried (sodium sulfate) and concentrated. The residue was purified by column chromatography over silica gel using benzene-ethyl acetate (5:1, v:v) as eluent to give **3a** (51 mg, 17%) and **11** (11 mg, 3.6%). The aqueous layer was neutralized with concentrated ammonium hydroxide to about *p*H 5, then refluxed for 10 hours, and extracted with ethyl acetate (15 ml x 4). The combined organic layer was washed with brine (20 ml x 2), dried (sodium sulfate) and concentrated. The residue was purified as described above to give **3a** (164 mg, 53%), which was recrystallized from methanol, mp 194-196°, (lit [1] mp 195-196°) and **11** (11 mg, 3.6%), which was recrystallized from methanol, mp 213-217°, (lit [7] mp 215-217°).

5-Methoxy-2-oxindole (**3c**).

A mixture of **1a** (400 mg, 2.45 mmoles) and concentrated sulfuric acid (1.24 g, 12.3 mmoles), and methanol (20 ml) was stirred under reflux for 1 hour. The reaction mixture was concentrated to *ca.* 5 ml and neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate (20 ml x 4). The combined organic layer was washed with brine (20 ml x 2), dried (sodium sulfate) and concentrated. The residue, silica gel (15 g) and benzene (60 ml) were mixed and stirred under reflux for 2 hours. The silica gel was filtered off and washed with ethyl acetate. After removal of the solvent the residue was purified by column chromatography over silica gel using benzene-ethyl acetate (5:1, v:v) as eluent to give **3c** (289 mg, 72%), which was recrystallized from ethanol, mp 156-157°, (lit [8] mp 153-154°).

5-Hydroxy-2-oxindole (**3b**).

A mixture of **1a** (300 mg, 1.84 mmoles) and 1*N* sulfuric acid (30 ml) was stirred under reflux for 30 minutes. The reaction mixture was neutralized with concentrated ammonium hydroxide to *p*H 5 and extracted with ethyl acetate (20 ml x 6). The combined organic layer was washed with brine (30 ml x 2), dried (sodium sulfate) and concentrated. The residue was purified by column chromatography over silica gel using benzene-ethyl acetate (3:1 next 1:1, v:v) as eluent to give **3b** (156 mg, 57%). The aqueous layer was refluxed for 10 hours, and extracted with ethyl acetate (20 ml x 4). The combined organic layer was washed with brine (30 ml x 2), dried (sodium sulfate) and concentrated. The residue was purified as above described to give **3b** (18 mg, 7%), which was recrystallized from water, mp 266-268° dec, (lit [8] mp 265-266° dec).

6-Chloro-3,4-dihydrocarbostyril (**5a**), 8-Chloro-3,4-dihydro-6-hydroxycarbostyril (**13**) and 3,4-Dihydro-6-hydroxycarbostyril (**12**).

A mixture of **4** (266 mg, 1.50 mmoles) and 1*N* hydrochloric acid (27 ml) was stirred under reflux for 30 minutes. The reaction mixture was neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate (15 ml x 4). The combined organic layer was washed with brine (20 ml x 2), dried (sodium sulfate) and concentrated. The residue was purified by column chromatography over silica gel using benzene-ethyl acetate (5:1 next 1:1, v:v) as eluent to give **13** (15 mg, 5.5%), which was recrystallized from water, mp 103-106°, (lit [9] mp 106°), **5a** (85 mg, 31%), which was recrystallized from methanol, mp 162-165°, (lit [9] mp 167-168° and **12** (61 mg, 25%), which was recrystallized from water, mp 238-239°, (lit [9] mp 237-238°).

3,4-Dihydro-6-methoxycarbostyril (**5b**).

A mixture of **4** (222 mg, 1.25 mmoles), concentrated sulfuric acid (614 mg, 6.25 mmoles) and methanol (11 ml) was stirred under reflux for 3 hours. The reaction mixture was concentrated to *ca.* 5 ml and neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate (15 ml x 4). The combined organic layer was washed with brine (20 ml x 2), dried (sodium sulfate) and concentrated. The residue was purified by column chromatography over silica gel using dichloromethane-methanol (20:1, v:v) as eluent to give **5b** (157 mg, 71%), which was recrystallized from benzene-hexane, mp 142-143°; ir (potassium bromide): 3200, 1680, 1510, 1385, 1245, 1035, 810 cm^{-1}; ^1H nmr (acetone-d_6): δ 2.47 (t, 2H, J = 7.5 Hz, CH_2), 2.91 (t, 2H, J = 7.5 Hz, CH_2), 3.75 (s, 3H, OCH_3), 6.73 (dd, 1H, J = 2.8, 8.4 Hz, H-7), 6.79 (d, 1H, J = 2.8 Hz, H-5), 6.86 (d, 1H, J = 8.4 Hz, H-8), 9.13 (br s, 1H, NH); ms: m/z (relative intensity) 177 (M^+, 100), 162 (53).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.82; H, 6.28; N, 7.89.

7-Methoxy-2*H*-1,4-benzoxazin-3-one (**7a**) and 2,5-Dimethoxyaniline (**8a**).

A mixture of **6** (300 mg, 1.67 mmoles), concentrated sulfuric acid (846 mg, 8.35 mmoles) and methanol (15 ml) was stirred under reflux for 20 minutes. The reaction mixture was concentrated to *ca.* 5 ml and neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate (15 ml x 4). The combined organic layer was washed with brine (20 ml x 2), dried (sodium sulfate) and concentrated. The residue was purified by column chromatography over silica gel using benzene-ethyl acetate (3:1, v:v) as eluent to give **8a** (96 mg, 38%), which was recrystallized from hexane, mp 81°, (lit [10] mp 80°); ^1H nmr (deuteriochloroform): δ 3.72 (s, 3H, OCH_3), 3.76 (br s, 2H, NH_2), 3.79 (s, 3H, OCH_3), 6.24 (dd, 1H, J = 2.8, 8.7 Hz, H-4), 6.32 (d, 1H, J = 2.8 Hz, H-6), 6.69 (d, 1H, J = 8.7 Hz, H-3) and **7a** (122 mg, 41%), which was recrystallized from chloroform-hexane, mp 161-162°, (lit [11] mp 160-161°).

7-Ethoxy-2*H*-1,4-benzoxazin-3-one (**7b**) and 2,5-Diethoxyaniline (**8b**).

In a similar manner as described above, the following two compounds were obtained from **6** (276 mg, 1.54 mmoles): **8b** (69 mg, 25%), which was recrystallized from hexane, mp 81-82°, (lit [12] mp 84°) and **7b** (135 mg, 45%), which was recrystallized from benzene, mp 163-164°; ir (potassium bromide): 3180-2875, 1680, 1610, 1515, 1170, 810 cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.28 (t, 3H, J = 7.0 Hz, CH_2CH_3), 3.94 (q, 2H, J = 7.0 Hz, CH_2CH_3), 4.52 (s, 2H, CH_2), 6.46-6.57 (m, 2H, H-6 and H-8), 6.79 (d, 1H, J = 8.4 Hz, H-5); ms: m/z (relative intensity) 193 (M^+, 100), 165 (75).

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found; C, 62.34; H, 5.71; N, 7.15.

To confirm the structures of **7a** and **b**, the methyl and ethyl ether bonds were cleaved by aluminum chloride-ethanethiol [13], followed by the acetylation and they were converted to 7-acetoxy-2*H*-1,4-benzoxazin-3-one, which was recrystallized from methanol, mp 223-226°, (lit [11] mp 211-216°); ir (potassium bromide): 3200-2850, 1760, 1690, 1620, 1510, 1220, 830 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.23 (s, 3H, $COCH_3$), 4.59 (s, 2H, CH_2), 6.71 (dd, 1H, J = 2.6, 8.4 Hz, H-6), 6.78 (d, 1H, J = 2.6 Hz, H-8), 6.88 (d, 1H, J = 8.4 Hz, H-5), 10.8 (br s, 1H, NH).

3,4-Dihydro-6-methoxybenzo[*h*]carbostyril (**10**).

A mixture of **9** (320 mg, 1.41 mmoles), concentrated sulfuric acid (712 mg, 7.05 mmoles) and methanol (16 ml) was stirred under reflux for 40 minutes. The reaction mixture was concentrated to *ca.* 5 ml and neutralized with saturated sodium bicarbonate solution and extracted with ethyl acetate (25 ml x 4). The combined organic layer was washed with brine (20 ml x 2), dried (sodium sulfate) and concentrated. Recrystallization of the residue from methanol and subsequent silica gel column chromatography of the mother liquor using benzene-ethyl acetate (3:1, v:v) for elution gave **10** (230 mg, 63%), mp 228-230°; ir (potassium bromide): 3230, 1690, 1490, 1400 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.54 (t, 2H, J = 7.2 Hz, CH_2 partly overlapped with DMSO signals), 3.03 (t, 2H, J = 7.2 Hz, CH_2), 3.94 (s, 3H, OCH_3), 6.88 (s, 1H, H-5), 7.43-7.54 (m, 2H, H-8 and H-9), 8.12 (d, J = 7.9 Hz, H-7 or H-10), 8.25 (d, J = 7.9 Hz, H-7 or H-10), 10.15 (br s, 1H, NH); ms: m/z (relative intensity) 227 (M^+, 87), 212 (100).

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.05; H, 5.80; N, 6.01.

5-Methoxyindole.

Distilled carbon tetrachloride (0.59 ml, 6.1 mmoles) was added to a suspension of **3c** (100 mg, 0.61 mmole) and triphenylphosphine (322 mg, 1.22 mmoles) in dry acetonitrile (8 ml) with stirring at room temperature. The reaction mixture was stirred for 7 hours at 70°. The solvent was concentrated and the residue was purified by short column chromatography over silica gel using benzene as eluent to give 2-chloro-5-methoxyindole (81 mg, 73%). A mixture of 2-chloro-5-methoxyindole (81 mg, 0.45 mmole), 10% palladium-carbon (16 mg) and ethyl acetate (8 ml) was stirred under atmosphere of hydrogen gas at room temperature. The catalyst was removed by filtration and the filtrate was concentrated. The residue was purified by column chromatography over silica gel using benzene as eluent to give 5-methoxyindole (61 mg, 93%, total yield 66%), which was recrystallized from petroleum ether, mp 53-55°, (lit [14] mp 55°).

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