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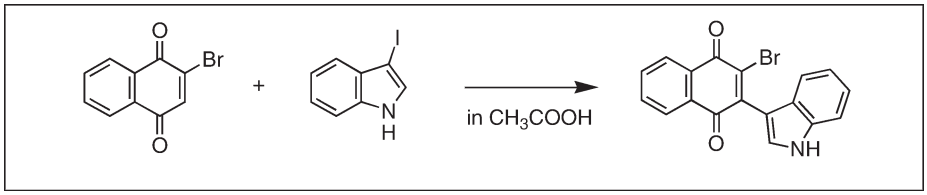

The usefulness of 3-iodoindole available for introduction of an indole unit is presented. The reaction of 3-iodoindole with 2-bromo(or methyl)-1,4-naphthoquinone in acetic acid gave 2-bromo(or methyl)-3-(3-indolyl)-1,4-naphthoquinone. On the other hand, the reaction of 3-iodoindole with 2-bromo-1,4-naphthoquinone in the presence of cesium carbonate in acetonitrile produced 2-(1-indolyl-3-iodo)-1,4-naphthoquinone.

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INTRODUCTION

An indole unit naturally occurs in indole alkaloids and many of the naturally occurring compounds have physiologically important activities [1]. Some reports have appeared concerning the reaction of indoles with the 1,4-naphthoquinones. For example, Bu'Lock and Mason [2] reported that the reaction of indole (**1**) with 1,4-naphthoquinone (**2**) gave 2-(3-indolyl)-1,4-naphthoquinone (**3**) in acetic acid at room temperature for 7 days without describing the yield. Prota and coworkers [3] found that the reaction of **1** with **2** afforded **3** in acidic ethanol at room temperature for 1 h in the moderate yield.

In previous articles [4,5], we reported the syntheses of Tyrian purple (**4**) (Fig. 1) [6] and its related compounds using 3-iodoindoles. Moreover, we have revealed the usefulness of 3- iodoindoles available for introduction of an indole unit [7]. The 3-iodoindole compounds are labile, therefore, not commercially available. However, the compounds are easily synthesized from the corresponding indoles. This article describes the reaction of 3-iodoindole with 1,4-naphthquinones.

RESULTS AND DISCUSSION

The reaction of 3-iodoindole (**5**) with 2-bromo-1,4-naphthoquinone (**6**) in acetic acid at room temperature for 3 days gave the 2-bromo-3-(3-indolyl)-1,4-naphthoquinone (**7**) in 72% yield. The mass spectrum of the product (**7**) exhibits the molecular ion peak at *m*/*z* 351 and 353 in the ratio of 1 to 1. The ^{1}H NMR spectrum of **7** shows a doublet peak (J = 2.8 Hz) at δ = 8.24 due to H-2′.

On the other hand, the same reaction was carried out in the presence of cesium carbonate in acetonitrile at room temperature for 1 day to give 2-(1-indoly-3-iodo)-1,4-naphthoquinone (**8**) in 19% yield with **7** in 5% yield (Scheme 1). The structure of the product (**8**) was mainly based on the NMR spectral data and MS spectral data. The ^{1}H NMR spectrum shows signals at δ = 7.17 (singlet) and 7.68 (singlet) due to H-3 and H-2′, respectively. The ^{13}C NMR spectrum shows a signal at δ = 64.28 due to C-I. The mass spectrum clearly exhibits a molecular ion peak at *m*/*z* 399.

We have already reported the reaction of **5** with **2** in acetic acid at 90°C for 40 min to give **3** in 74% yield [7]. The same reaction was carried out in the presence

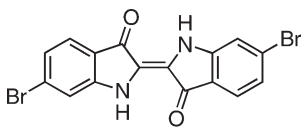

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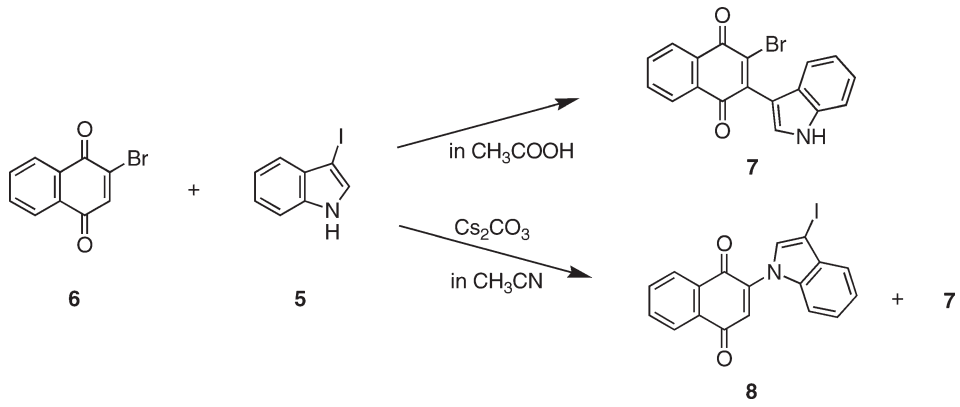
Figure 1. Tyrian purple.

Scheme 1



of cesium carbonate in acetonitrile at room temperature for 1 day, but the iodo compound (**8**) was not obtained (Scheme 2).

We next applied the reaction of Scheme 1 to 2-methyl-1,4-naphthoquinone (**9**) (Scheme 3). The treatment of **5** with **9** in acetic acid at room temperature for 4 days gave 2-methyl-3-(3-indolyl)-1,4-naphthoquinone (**10**) in 62% yield.

The structure of the product (**10**) was mainly determined on the basis of the NMR spectral data and MS spectral data. The ^{1}H NMR spectrum shows signals at $\delta = 2.21$ (singlet) and $\delta = 7.43$ (singlet) due to CH_3 and H-2′, respectively. The ^{13}C NMR spectrum shows a signal at $\delta = 15.76$ due to CH_3. The mass spectrum clearly exhibited a molecular ion peak at *m*/*z* 287. The same reaction was carried out in the presence of cesium carbonate in acetonitrile at room temperature for a day, but the compound (**10**) instead of the iodo compound was obtained in 23% yield.

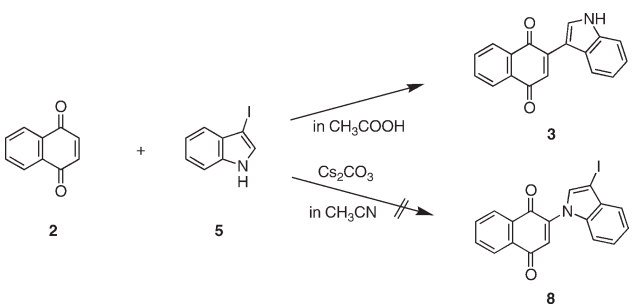
EXPERIMENTAL

The ^{1}H NMR and ^{13}C NMR spectra were obtained using a JEOL JNM-A500 (500 MHz) spectrometer at room temperature. The chemical shifts are given in ppm relative to tetramethylsilane as an internal reference standard. The EI mass spectra were performed using a JEOL JMS-SX 102A mass spectrometer. The infrared spectra were recorded using a Shimadzu IR 470 spectrometer in potassium bromide pellets. The melting points were obtained using a Yanaco MS-S3 micro melting point apparatus (hotplate type). For the preparative column chromatography, Wakogel C-200 silica gel was employed. Thin-layer chromatography (TLC) was accomplished on precoated plates of silica gel 60 $F_{254+366}$ (Merck). 2-Bromo-1,4-naphthquinone and 2-methyl-1,4-naphthoquinone were purchased from Aldrich (USA) and Tokyo Kasei Kogyo Co. (Tokyo, Japan), respectively.

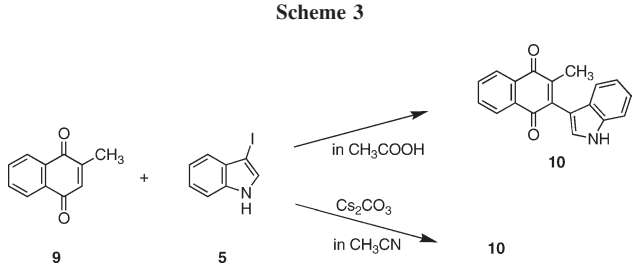
3-Iodoindole (5). 3-Iodoindole was prepared using a modified procedure of Arnold's method [8]. To a solution of indole (**1**) (100 mg, 0.85 mmol) in methanol (10 mL) was added sodium hydroxide (34 mg, 0.85 mmol). After the mixture was stirred at room temperature for 10 min, iodine (217 mg, 0.85 mmol) and an aqueous solution (1 mL) of potassium iodide (142 mg, 0.85 mmol) was added. The mixture was further stirred at room temperature for 10 min and the water was then added. The resulting precipitate was collected by filtration, washed with water, and dried *in vacuo* to obtain **5** (167 mg), which was used for the following reaction without its purification because of its lability.

2-Bromo-3-(3-indolyl)-1,4-naphthoquinone (7). A solution of 3-iodoindole (**5**) (149 mg, 0.61 mmol) and 2-bromo-1,4-naphthoquinone (**6**) (145 mg, 0.61 mmol) in acetic acid (10 mL) was stirred at room temperature for 3 days. After the mixture was concentrated under reduced pressure, the residue was chromatographed on silica gel with chloroform to give **7** (62 mg) in 29% yield with the starting material **6** (86 mg). The yield based on the amount of the consumed quinone was 72%. The product **7** was recrystallized with ethyl acetate–hexane (1:1), mp 202–205°C; ir (potassium bromide): 3335 (NH), 1661, 1588, 1547, 1421, 1269, 745, 717 cm^{-1}; ^{1}H NMR

Scheme 2



Scheme 3



($CDCl_3$): δ 7.30 (m, 1H, H-5′), 7.46 (m, 2H, H-6′, 7′), 7.76 (m, 2H, H-4′, 6), 7.99 (m, 1H, H-7), 8.13 (m, 1H, H-8), 8.17 (m, 1H, H-5), 8.24 (d, 1H, J = 2.8 Hz, H-2′), 8.74 (s, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 109.00, 111.92, 113.29, 117.48, 120.44, 121.90, 123.37, 125.89, 126.89, 129.73, 130.98, 132.24, 133.31, 136.32, 142.03, 144.47, 178.39 (C=O), 182.06 (C=O); MS (EI) *m/z* (relative intensity) 353 (M+2, 52%), 351 (M^+, 47), 274 (57), 273 (100), 272 (63), 217 (62), 216 (45), 189 (37); HRMS (EI) calcd. for $C_{18}H_{10}O_2NBr$, M^+ 350.9895, found 350.9884.

2-(1-Indolyl-3-iodo)-1,4-naphthoquinone (8). A mixture of 3-iodoindole (**5**) (142 mg, 0.58 mmol), 2-bromo-1,4-naphthoquinone (**6**) (139 mg, 0.58 mmol), and cesium carbonate (190 mg, 0.58 mmol) in acetonitrile (10 mL) was stirred at room temperature for 1 day. The reaction mixture was filtered and the filtrate was concentrated. The residue was chromatographed on silica gel with chloroform, followed by chromatography of TLC (silica gel; $CHCl_3$: CH_3CN = 20:1) to give **8** (44 mg) in 19% yield along with **7** (11 mg) in 5% yield. The product **8** was recrystallized with ethyl acetate–hexane (3:1), mp 196–198°C; ir (potassium bromide): 1670, 1654, 1609, 1603, 1591, 1573, 1448, 1287, 1204, 732, 717 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 7.17 (s, 1H, H-3), 7.31–7.38 (m, 2H, H-5′, 6′), 7.51 (dd, 1H, J = 1.0, 7.5 Hz, H-7′), 7.56 (dd, 1H, J = 1.0, 7.5 Hz, H-4′), 7.68 (s, 1H, H-2′), 7.80–7.86 (m, 2H, H-6, 7), 7.17 (dd, 1H, J =1.0, 7.5 Hz, H-5), 8.22 (dd, 1H, J = 1.0, 7.5 Hz, H-8); ^{13}C NMR ($CDCl_3$): δ 64.28 (C-I), 112.03, 122.15, 123.10, 124.57, 125.95, 126.28, 127.34, 131.54, 131.77, 132.12, 132.84, 134.04, 134.69, 135.45, 141.95, 181.05 (C=O), 184.32 (C=O); MS (EI) *m/z* (relative intensity) 399 (M^+, 100%), 272 (59), 244 (21), 216 (36), 136 (20); HRMS (EI) calcd. for $C_{18}H_{10}O_2NI$, M^+ 398.9756, found 398.9760.

2-Methyl-3-(3-indolyl)-1,4-naphthoquinone (10). A solution of 3-iodoindole (**5**) (167 mg, 0.69 mmol) and 2-methyl-1,4-naphtoquinone (**9**) (118 mg, 0.69 mmol) in acetic acid (10 mL) was stirred at room temperature for 4 days. After the mixture was concentrated under reduced pressure, the residue was chromatographed on silica gel with chloroform, followed by TLC (silica gel; $CHCl_3$: CH_3CN = 20:1) to give **10** (31 mg) in 16% yield with the starting material **9** (77 mg). The yield based on the amount of the consumed quinone was 62%. The product **10** was recrystallized with ethyl acetate–hexane (2:1), mp 252–254°C; ir (potassium bromide): 3340 (NH), 1653, 1594, 1288, 746, 718 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.21 (s, 3H, CH_3), 7.15–7.18 (m, 1H, H-5′), 7.22–7.26 (m, 1H, H-6′), 7.32 (d, 1H, J = 8.2 Hz, H-7′), 7.43 (s, 1H, H-2′), 7.46 (d, 1H, J = 8.2 Hz, H-4′), 7.74 (m, 2H, H-6, 7), 8.16 (m, 2H, H-5, 8), 9.38 (broad, 1H, NH); ^{13}C NMR ($CDCl_3$): δ 15.76 (CH_3), 108.28, 111.69, 111.74, 120.37, 120.42, 122.30, 126.19, 126.70, 127.22, 132.48, 132.52, 133.46, 133.53, 135.80, 140.43, 143.30,184.76 (C=O), 185.99 (C=O); MS (EI) *m/z* (relative intensity) 287 (M^+, 100%), 270 (56), 230 (16), 154 (10); HRMS (EI) calcd. for $C_{19}H_{13}O_2N$, M^+ 287.0946, found 287.0973.

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