Yasuhiro Tanoue,[a]* Yousuke Ikoma,[a] Norihisa Kai,[a] and Takeshi Nagai[b]

[a]Department of Food Science and Technology, National Fisheries University, Nagatahonmachi, Shimonoseki 759-6595, Japan
[b]Department of Food Science and Technology, Tokyo University of Agriculture, Abashiri, Hokkaido 099-2493, Japan
*E-mail: tanoue@fish-u.ac.jp

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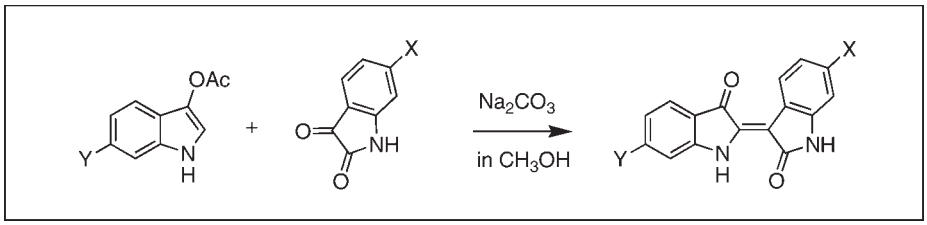

The synthesis of halogenoindirubins was attempted. The reaction of 3-acetoxy-6-bromoindole (**5**) with 6-bromoisation (**10**) in methanol with Na_2CO_3 produced 6-bromo-6′-fluoroindirubin (**11**) in 80% yield. Its structure determination was mainly undertaken using ^{1}H NMR spectroscopy. A similar reaction gave 6′-bromoindirubin (**12**) and 6-bromoindirubin (**3**) in moderate yields.

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INTRODUCTION

Tyrian purple, royal purple, and ancient purple are all synonyms for a dye of molluscan origin and were used as valuable purple dyes of garments for ancient exalted persons such as princes and nobles in the districts along the Mediterranean [1,2]. The precursors of Tyrian purple are contained in the hypobranchial glands of various species of gastropods from the families Muricidae and Thaidinae, and converted into Tyrian purple by the action of sunlight and purpurase [3,4]. In 1909, Friedländer isolated 1.4 g of the dye from 12,000 specimens of the gastropod *Murex brandaris* and identified it as 6,6′-dibromoindigo (**1**) [5].

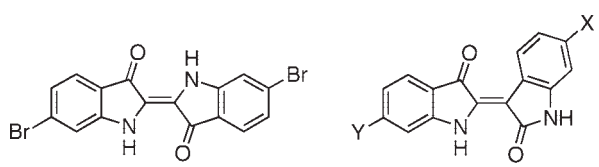
We have already reported that **1** is easily obtained in three steps by the reactions of the commercially available 6-bromoindole [6]. The hypobranchial glands aforementioned contain 6,6′-dibromoindirubin (**2**) and 6-bromo-indiubin (**3**) as minor components [7–10]. Their compounds have become of interest from the standpoint of glycogen synthase kinase (GSK)-3-selective inhibitors [10]. In addition, indirubin (**4**) exhibits strong antitumor [11] and potent aryl hydrocarbon ligand activities [12]. Synthesis of the bromoindirubins has been already reported [13].

The reaction of 3-acetoxy-6-fluoroindole (**5**) with isatin (**6**) produced 6′-fluoroindirubin (**7**). On the basis of this result, we have already revised the synthetic scheme of **2** reported by Cooksey [14]. The revised synthetic scheme is applicable for the syntheses of halogenoindirubins.

The present article describes the syntheses of the halogenoindirubins (Fig. 1).

RESULTS AND DISCUSSION

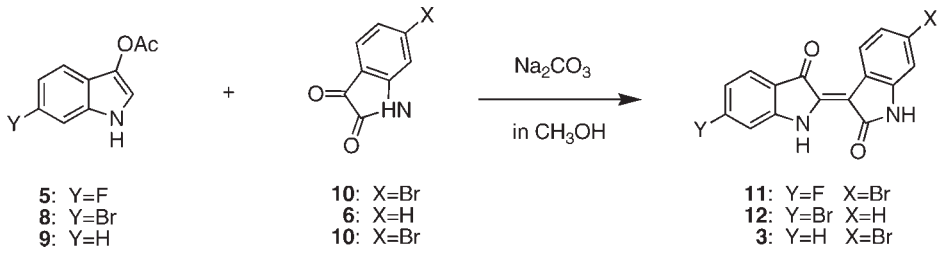
We have already reported that the 3-acetoxy-halogenoindoles are obtained in two steps by the reactions of the commercially available haloindoles. Iodination of the haloindoles, followed by acetoxylation with silver acetate in acetic acid, afforded 3-acetoxy-6-halogenoindole [15]. The reaction of 3-acetoxy-6-fluoroindole (**5**) with 6-bromoisatin (**10**) was carried out in methanol with Na_2CO_3 at room temperature. The structure of the product (**11**) was based on the ^{1}H NMR spectral data and MS spectral data. The H-4 signal ($\delta = 8.67$) showed a remarkable downfield shifts relative to the H-4′ signal ($\delta = 7.74$). The absorption of H-4′ is split by H-5′ ($J_{4'\text{-}5'} = 8.5$ Hz) and F-6′ ($J_{4'\text{-}F} = 5.5$ Hz). Unfortunately, the ^{13}C NMR spectra could not be measured, because **11** was



1 **2**: X=Y=Br
3: X=Br, Y=H
4: X=Y=H

Figure 1. Structures of the indigo and the indirubin families.

Scheme 1. Synthesis of the halogenoindirubins.



5: Y=F
8: Y=Br
9: Y=H

10: X=Br
6: X=H
10: X=Br

11: Y=F X=Br
12: Y=Br X=H
3: Y=H X=Br

only slightly soluble in dimethyl sulfoxide. The mass spectrum of **11** clearly exhibited a molecular ion peak at *m*/*z* 358 (Scheme 1).

The treatment of 3-acetoxy-6-bromoindole (**8**) with **6** gave 6′-bromoindirubin (**12**) in 81% yield. On the other hand, the reaction of 3-acetoxyindole (**9**) [16] with 6-bromoisatin (**10**) afforded 6-bromoindirubin (**3**) in 85% yield.

The ^{1}H NMR spectra of **12** and **3** are shown in Figures 2 and 3 for direct comparison. In general, the signal of the ortho positional proton of Br is observed more downfield than that of the benzene ring proton. The H-5′ ($\delta = 7.15$) and H-7′ ($\delta = 7.66$) signals of **12** showed a downfield shift relative to those of H-5′ ($\delta = 7.03$) and H-7′ ($\delta = 7.42$) of **3**. Similarly, the H-5 ($\delta = 7.21$) and H-7 ($\delta = 7.04$) signals of **3** appeared as a downfield shift compared to those of H-5 ($\delta = 7.00$) and H-7 ($\delta = 6.89$) of **12**.

EXPERIMENTAL

The ^{1}H NMR and ^{13}C NMR spectra were obtained using a JEOL JNM-A500 (500 MHz) spectrometer in dimethyl sulfoxide-d_6 at room temperature. The chemical shifts are given in ppm relative to tetramethylsilane as the 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 (hot-plate type). For the preparative column chromatography, Wakogel C-200 silica gel was used. Indole, 6-fluoroindole, 6-bromoisatin, and isatin were purchased from Tokyo Kasei Kogyo (Tokyo, Japan).

General procedure for the synthesis of halogenoindirubins. The reaction of 3-acetoxy-6-fluoroindole (**5**) with 6-bromoisatin (**10**) is described as a typical example. A solution of **5** (65 mg, 0.339 mmol) and **10** (77 mg, 0.339 mmol) in methanol (15 mL) was stirred under a nitrogen atmosphere at room temperature for 10 min. To the mixture was added

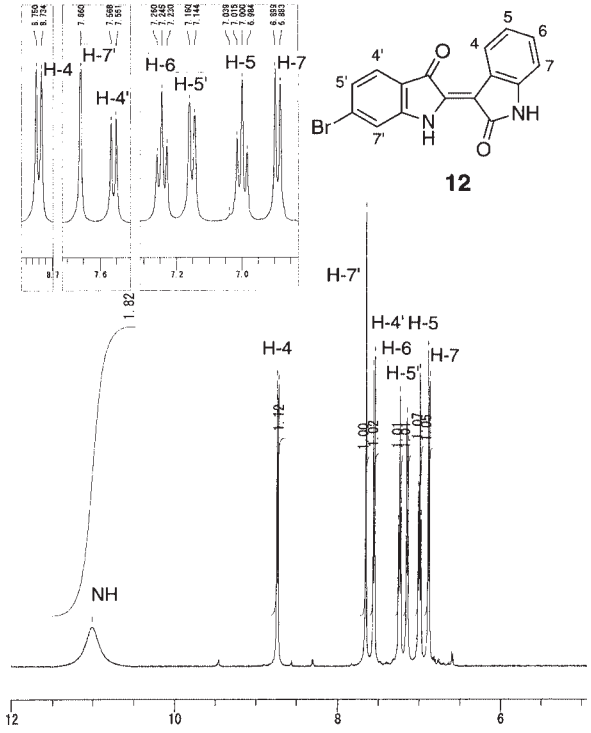


Figure 2. The spectrum of 6′-bromoindirubin (**12**).

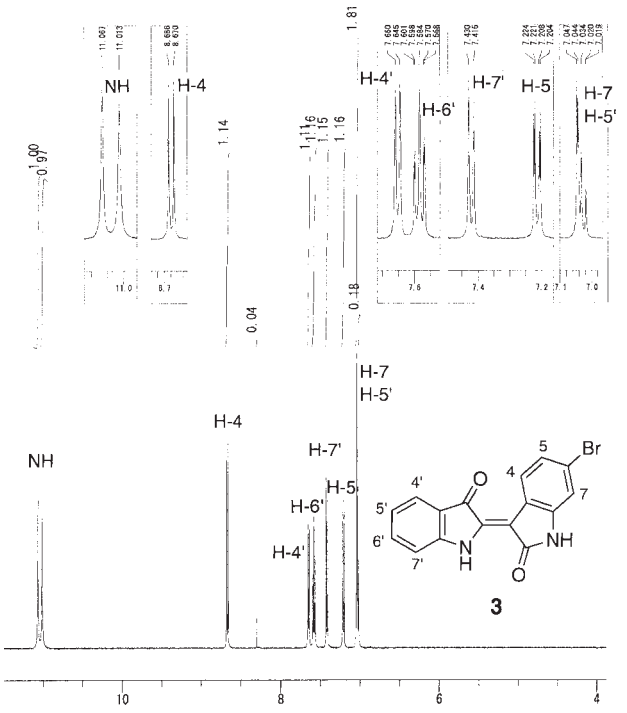


Figure 3. The spectrum of 6-bromoindirubin (**3**).

anhydrous sodium carbonate (86 mg, 0.814 mmol). After the mixture was stirred for 3 h, water was added. The resulting precipitate was collected by filtration, washed with water and aqueous methanol (1:1). The crude product (106 mg) was recrystallized from ethyl acetate to give 6-bromo-6′-fluoroindirubin (**11**) (97 mg, 80% yield) as a red–purple powder, mp > 300°C; ir (potassium bromide): 3300 (NH), 3175 (NH), 1668 (C=O), 1625 (C=O), 1605, 1591, 1451, 1289, 1208, 1129, 1009, 968 cm^{-1}; ^1H NMR (dimethyl sulfoxid-d_6): δ = 6.86 (1H, m, H-5′), 7.11 (1H, d, $J_{7\text{-}5}$ = 2.3 Hz, H-7), 7.20 (1H, dd, $J_{7'\text{-}F}$ = 10, $J_{7'\text{-}5'}$ = 2.5 Hz, H-7′), 7.23 (1H, dd, $J_{5\text{-}4}$ = 8.5, $J_{5\text{-}7}$ = 2.3 Hz, H-5), 7.74 (1H, dd, $J_{4'\text{-}5'}$ = 8.5, $J_{4'\text{-}F}$ = 5.5 Hz, H-4′), 8.67 (1H, d, $J_{4\text{-}5}$ = 8.5 Hz, H-4), 11.05 (1H, s, NH), 11.14 (1H, s, NH); ms (EI): *m*/*z* (relative intensity) 360 (M+2, 99%), 358 (M^+, 100), 332 (21), 330 (21), 223 (62); HRMS(EI) calcd for $C_{16}H_8O_2N_2BrF$, M^+ 357.9753, found 357.9755.

6′-Bromoindirubin (12). This compound was obtained as a brown powder (ethyl acetate), mp > 300°C; ir (potassium bromide): 3330 (NH), 3180 (NH), 1673 (C=O), 1666 (C=O), 1618, 1585, 1444, 1282, 1212, 1008 cm^{-1}; ^1H NMR (dimethyl sulfoxid-d_6): δ = 6.89 (1H, d, $J_{7\text{-}6}$ = 8.0 Hz, H-7), 7.00 (1H, t, *J* = 7.5 Hz, H-5), 7.15 (1H, d, $J_{5'\text{-}4'}$ = 8.0 Hz, H-5′), 7.25 (1H, t, *J* = 7.5 Hz, H-6), 7.56 (1H, d, $J_{4'\text{-}5'}$ = 8.5 Hz, H-4′), 7.66 (1H, s, H-7′), 8.74 (1H, d, $J_{4\text{-}5}$ = 8.0 Hz, H-4), 11.01 (2H, broad, NH); ^{13}C NMR (dimethyl sulfoxide-d_6): δ = 108.13, 110.20, 116.51, 118.54, 121.58, 121.87, 124.61, 125.24, 126.33, 130.25, 131.32, 138.40, 141.46, 153.47, 171.18 (C=O), 187.88 (C=O); MS (EI) *m*/*z* (relative intensity) 342 (M+2, 98%), 340 (M^+, 100), 314 (21), 312 (22), 233 (40), 205 (77), 103 (22); HRMS (EI) calcd for $C_{16}H_9O_2N_2Br$, M^+ 339.9848, found 339.9830.

6-Bromoindirubin (3). This compound was obtained as a brown powder (ethyl acetate), mp > 300°C; ir (potassium bromide): 3310 (NH), 3190 (NH), 1664 (C=O), 1605, 1475, 1302, 1209, 1006 cm^{-1}; ^1H NMR (dimethyl sulfoxid-d_6): δ = 7.03 (1H, m, H-5′), 7.04 (1H, d, $J_{7\text{-}5}$ = 1.5 Hz, H-7), 7.21 (1H, dd, $J_{5\text{-}4}$ = 9.0, $J_{5\text{-}7}$ = 1.5 Hz, H-5), 7.42 (1H, d, $J_{7'\text{-}6'}$ = 7.5 Hz, H-7′), 7.58 (1H, m, H-6′), 7.65 (1H, d, $J_{4'\text{-}5'}$ = 7.5 Hz, H-4′), 8.68 (1H, d, $J_{4\text{-}5}$ = 8.0 Hz, H-4), 11.01 (1H, s, NH), 11.07 (1H, s, NH); ^{13}C NMR (dimethyl sulfoxide-d_6): δ = 105.17, 112.23, 113.56, 118.98, 120.70, 121.33, 121.52, 123.81, 124.42, 125.93, 137.21, 138.83, 142.10, 152.48, 170.69 (C=O), 188.71 (C=O); MS (EI) *m*/*z* (relative intensity), 342 (M+2, 100%), 340 (M^+, 100), 314 (24), 312 (24), 233 (27), 205 (59); HRMS (EI) calcd for $C_{16}H_9O_2N_2Br$, M^+ 339.9848, found 339.9832.

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