

Synthesis of *o*-(2-Indolyl)benzoic Acids from Indole

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Synopsis. Treatment of 6*H*-isoindolo[2,1-*a*]indol-6-ones with potassium *t*-butoxide/*t*-butyl alcohol containing a small amount of water at 82° afforded *o*-(2-indolyl)benzoic acids in good yields.

Some 2-arylindoles often have potent physiological activities. However, little attention has been paid to the preparation of some 2-(*o*-substituted phenyl)indoles, such as *o*-(2-indolyl)benzoic acids (**3**), although Pailer *et al.*¹⁾ reported that the reduction of 2-nitrodeoxybenzoin-2'-carboxylic acid afforded *o*-(2-indolyl)benzoic acid (**3a**). On the other hand, we reported the synthesis of 6*H*-isoindolo[2,1-*a*]indol-6-ones (**2**) by the oxidation of 1-arylindoles (**1**) with palladium acetate,²⁾ although **2** was also prepared by the irradiation of 1-(*o*-iodobenzoyl)indole³⁾ or of *N*-(*o*-methylphenyl)-phthalimides.⁴⁾ As a study of the synthetic application of the reaction, we were interested in the synthesis of **3** by hydrolysis of **2**. The results will provide a new route to prepare 2-arylindoles from indole (Scheme 1).

Attempted hydrolysis of 6*H*-isoindolo[2,1-*a*]indol-6-one (**2a**) in the usual conditions (HCl/MeOH+H₂O and NaOH/MeOH+H₂O) was unsuccessful. On the other hand, Gassman *et al.*⁵⁾ previously reported the *t*-BuOK-promoted hydrolysis of amides in diethyl ether containing H₂O. We attempted the hydrolysis of **2** by an application of their method. Treatment of **2a** with *t*-BuOK in *t*-BuOH containing a small amount of H₂O at 82 °C under nitrogen afforded **3a** in 75% yield. Under similar conditions the treatment of **2b** and **2c** with *t*-BuOK gave **3b** (74%) and **3c** (70%), respectively. The structure of **3** was independently confirmed by the elemental analysis, the molecular weight (mass spectroscopy), and NMR and IR data. The physiological activities of **3b** and **3c** were ex-

amined. The compounds **3b** and **3c** exhibit antifungal activities at concentration of 0.1%. The results are listed in Table 1.

Experimental

All the melting points are uncorrected. Elemental analyses were performed by the Analytical Center of Kyoto University. Infrared spectra were recorded with a JASCO IRA-1 spectrometer. Proton magnetic resonance spectra were recorded with a JEOL JNM-60 spectrometer using TMS as the internal reference.

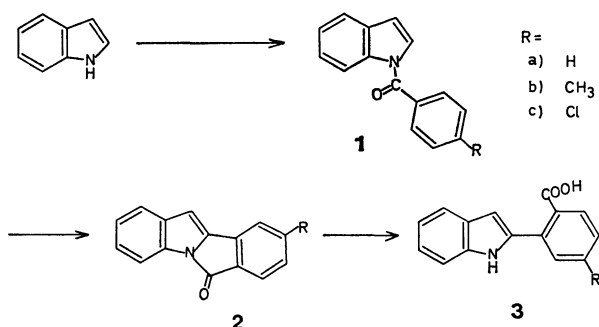
Treatment of 2 with Potassium *t*-Butoxide. The solution of **2** (1.0 mmol) in *t*-BuOH (50 ml) and H₂O (5 ml) containing *t*-BuOK (10.0 mmol) was heated at 82° under nitrogen for 12 h. The reaction mixture was evaporated, diluted with a large amount of water, carefully neutralized with diluted HCl, and extracted with ether. The ether extract was dried with sodium sulfate and evaporated to give a brown semicrystalline residue which was triturated with ether/hexane to give **3**, light brown needles from ether/hexane.

***o*-(2-Indolyl)benzoic Acid (**3a**):** Mp 155–157°, partially decomposed at 128–132° (lit.¹⁾ 159°); IR (Nujol): 3430 (NH), 3200–2250 (COOH), 1680 (COOH) cm⁻¹; NMR (CDCl₃): δ 6.84 (1H, s), 7.12–8.30 (8H, m), 8.60 (1H, broad), 9.42 (1H, broad); Mass (relative intensity, %): 237 (M⁺, 47), 219 (M⁺–H₂O, 100). Found: C, 75.95; H, 4.62; N, 5.74%. Calcd for C₁₅H₁₁NO₂: C, 75.93; H, 4.67; N, 5.90%.

2-(2-Indolyl)-4-methylbenzoic Acid (3b**):** Mp 143–144°, IR (Nujol): 3430 (NH), 3180–2200 (COOH), 1680 (COOH) cm⁻¹; NMR (CDCl₃): δ 2.46 (3H, s), 6.86 (1H, s), 7.21–8.25 (6H, m), 8.12 (1H, d, *J*=9.0 Hz), 8.50 (1H, broad), 9.50 (1H, broad); Mass (relative intensity, %): 251 (M⁺, 42), 233 (M⁺–H₂O, 100). Found: C, 76.49; H, 5.11; N, 5.40%. Calcd for C₁₆H₁₃NO₂: C, 76.47; H, 5.22; N, 5.57%.

2-(2-Indolyl)-4-chlorobenzoic Acid (3c**):** Mp 167–168°; IR (Nujol): 3460 (NH), 3200–2400 (COOH), 1690 (COOH) cm⁻¹; NMR (CDCl₃): δ 6.80 (1H, s), 7.13–8.60 (8H, m), 9.30 (1H, broad); Mass (relative intensity, %): 271 (M⁺, 52), 273 (M⁺+2, 18), 253 (M⁺–H₂O, 100), 255 (M⁺+2–H₂O, 34). Found: C, 66.12; H, 3.58; N, 5.07%. Calcd for C₁₅H₁₀NO₂Cl: C, 66.31; H, 3.71; N, 5.16%.

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Scheme 1.

TABLE 1. ANTIFUNGAL ACTIVITIES OF *o*-(2-INDOLYL)BENZOIC ACIDS **3b** AND **3c**

	<i>Sphaerotheca Fuliginca</i> (Cucumber powdery mildew) (% Inhibition)	<i>Collectotrichum lagenarium</i> (Cucumber anthraenose) (% Inhibition)	<i>Pyricularia oryzae</i> (Rice blast) (% Inhibition)
3b	0	0	94
3c	7	66	100

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