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

Toshio ITAHARA

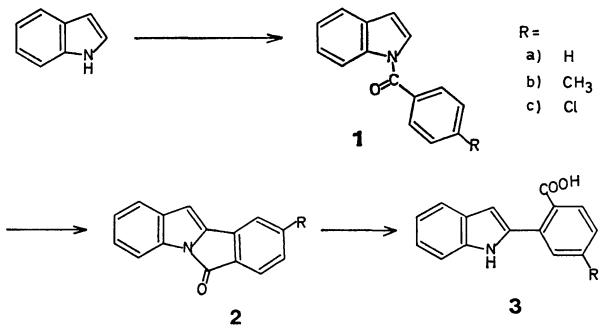
Institute of Chemistry, College of Liberal Arts, Kagoshima University, Kagoshima 890

(Received June 13, 1980)

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*-isoindole[2,1-*a*]indol-6-ones (**2**) by the oxidation of 1-aroylindoles (**1**) with palladium acetate,[2] although **2** was also prepared by the irradiation of 1-(*o*-iodobenzoyl)indole[3] 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+H_2O and NaOH/MeOH+H_2O) was unsuccessful. On the other hand, Gassman *et al.*[5] previously reported the *t*-BuOK-promoted hydrolysis of amides in diethyl ether containing H_2O. 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 H_2O 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 specroscopy), and NMR and IR data. The physiological activities of **3b** and **3c** were examined. The compounds **3b** and **3c** exhibit antifungal activities at concentration of 0.1%. The results are listed in Table 1.



Scheme 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 H_2O (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 ($CDCl_3$): 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^+-H_2O, 100). Found: C, 75.95; H, 4.62; N, 5.74%. Calcd for $C_{15}H_{11}NO_2$: 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 ($CDCl_3$): 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^+-H_2O, 100). Found: C, 76.49; H, 5.11; N, 5.40%. Calcd for $C_{16}H_{13}NO_2$: 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 ($CDCl_3$): 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^+-H_2O, 100), 255 (M^++2−H_2O, 34). Found: C, 66.12; H, 3.58; N, 5.07%. Calcd for $C_{15}H_{10}NO_2Cl$: C, 66.31; H, 3.71; N, 5.16%.

The author wishes to thank Professor Tsunao Hase and Mr. Tetsuo Iwagawa of Kagoshima University (Faculty of Science) for mass spectrometric analyses and Dr. Masaaki Takami of Kuraray Co., Ltd., for biological assays.

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

	Sphaerotheca Fuliginca (Cucumber powdery mildew) (% Inhibition)	*Collectotrichum lagenarium* (Cucumber anthraenose) (% Inhibition)	*Pyricularia oryzoe* (Rice blast) (% Inhibition)
3b	0	0	94
3c	7	66	100

References

1) M. Pailer, A. Schleppnik, and A. Meller, *Mh. Chem.*, **96**, 1695 (1965).
2) T. Itahara, *Synthesis*, **1979**, 151.
3) W. Carruthers and E. Evans, *J. Chem. Soc., Perkin Trans. 1*, **1974**, 1523.
4) Y. Kanaoka and K. Koyama, *Tetrahedron Lett.*, **1972**, 4517; Y. Kanaoka, C. Nagasawa, H. Nakai, Y. Sato, H. Ogiwara, and T. Mizoguchi, *Heterocycles*, **3**, 553 (1975); M. Terashima, K. Koyama, and Y. Kanaoka, *Chem. Pharm. Bull.*, **26**, 630 (1978).
5) P. G. Gassman, P. K. G. Hodgson, and R. J. Balchunis, *J. Am. Chem. Soc.*, **98**, 1275 (1976).