Isoindole Derivatives from 2-Isonicotinoyl-acetophenone with Ammonia and its Derivatives

Seiko Nan'ya*, Takeo Kitahara, Taro Kuroda and Yasuo Butsugan

Department of Applied Chemistry, Nagoya Institute of Technology,
Gokiso, Showa-ku, Nagoya 466, Japan

Received May 27, 1992

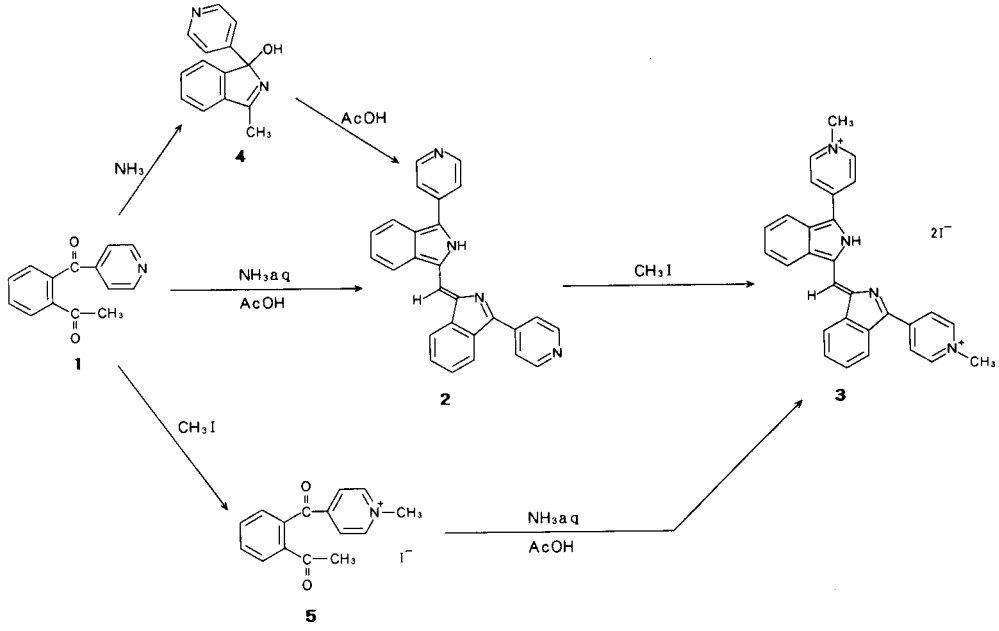
2-Isonicotinoylacetophenone (**1**) reacts with aqueous ammonia in the presence of acid to produce the deep blue 3-(4-pyridyl)-1-[3-(4-pyridyl)-1*H*-1-isoindolylidenemethyl]-2*H*-isoindole which changed to the deep bluish green adduct showing the wavelength maximum at 744 nm by treating with methyl iodide. From the reaction of **1** and glycine or its methyl ester the red 3,3'-di-(4-pyridyl)-1,1'-vinylenebis(2*H*-2-isoindoleacetic acid) or its derivative were obtained respectively.

J. Heterocyclic Chem., **29**, 1301 (1992).

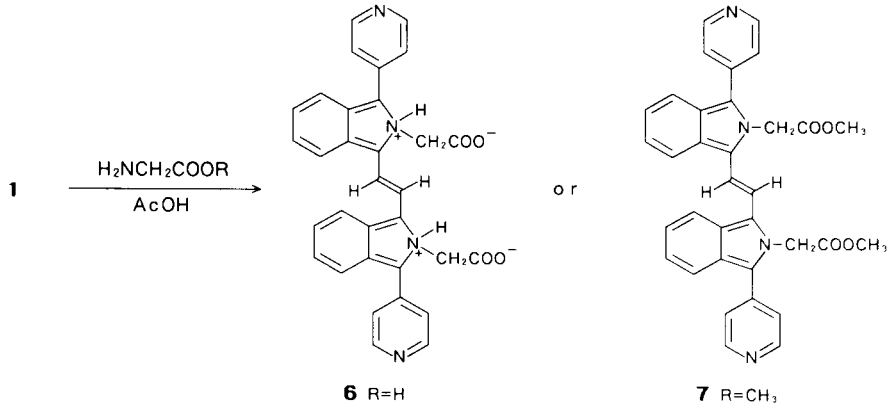
o-Diacylbenzenes show a deep blue or violet color upon reaction with human skin and primary amines in the presence of acetic acid [1]. Treating *o*-acetylbenzophenone with several primary amines in the presence of acid one type of red and three types of deep blue pigments including isoindole moieties were obtained [2]. The reaction of 2-isonicotinoylacetophenone (**1**) with aqueous ammonia in the presence of acetic acid at room temperature afforded a deep blue compound, 3-(4-pyridyl)-1-[3-(4-pyridyl)-1*H*-1-isoindolylidenemethyl]-2*H*-isoindole (**2**). The structure of **2** is presumed to be the *Z*-conformation shown in Scheme 1. In this form **2** may be stabilized by hydrogen bonding between nitrogens of the two isoindole rings. The chloroform solution of **2** was treated with methyl iodide at room temperature to produce the deep bluish green adduct **3** in good yield with the wavelength of the absorption peaks at 742 and 673 nm in methanol. From the ^{1}H nmr spectra and elemental analysis this adduct **3** consists of 1 mole of **2** and 2 moles of methyl iodide and is appreciably soluble in water. By adding hydrochloric acid to the methanol solution of **2** the wavelength of the absorption maximum of 589 nm shifted to 650 nm, however, the adduct of **2** with hydrochloric acid was not isolated.

Dry ammonia was bubbled through an ether solution of **1** to produce 1-hydroxy-3-methyl-1-(4-pyridyl)-1*H*-isoindole (**4**) in good yield. This colorless compound **4** changed by addition of acetic acid in methanol into the deep blue compound **2** suggesting **4** to be the intermediate of **2**. While the methanol solution of **1** reacts with aqueous ammonia at room temperature to form also **4** on a thin layer chromatogram of aluminium oxide showing only one spot, the column or preparative layer chromatography of the reaction mixture brought about decomposition of the product. The formation of **4** in the reaction mixture was determined by ms and ^{1}H nmr spectra in deuteriomethanol in comparison with the authentic product **4** described above. The chloroform solution of **1** was treated with methyl iodide to afford a yellow adduct **5** in quantitative yield be-

Scheme 1



Scheme 2



ing fairly soluble in water. The reaction of the resulting **5** with aqueous ammonia produced **3** and a complicated mixture.

The reaction of **1** with glycine and its methyl ester in methanol in the presence of acetic acid at room temperature formed the red products, 3,3'-di-(4-pyridyl)-1,1'-vinylenebis(2*H*-2-isoindoleacetic acid) (**6**) and the dimethyl ester of **6** (**7**) respectively. The structure of these red products were assigned from the ms and ir spectra as well as elemental analysis. The methanol solution of **6** is fairly stable compared with **7** as well as the red compounds formed from *o*-acetylbenzophenone and primary amines [3], presumably because of the zwitterionic structure of **6**. The existence of the tertiary ammonium hydrogen of carboxylate was not identified by ^{1}H nmr because we found no satisfactory solvent.

EXPERIMENTAL

Melting points were determined on a Yanaco micro-melting point apparatus and are uncorrected. The ir spectra were taken on a JASCO A-102 spectrometer using potassium bromide pellets and the uv spectra were recorded with a JASCO UVIDEC-505. The ^{1}H nmr spectra were measured on Varian Gemini 200 or Hitachi R-90 spectrometer using tetramethylsilane as the internal standard. Mass spectra were obtained with Hitachi M-2000 spectrometer. For column chromatography, silica gel (Kieselgel 60, Merck, 70-230 mesh ASTM and Cosmosil 75C_{18}-OPN for reversed phase, Nacalai Tesque) and aluminium oxide (Alumina Activated 300, Nacalai Tesque, 300 mesh) as well as for preparative layer chromatography, silica gel pre-coated plates (Kieselgel 60, Merck) were used. Elemental analyses were performed at Elemental Analysis Center in Kyoto University.

3-(4-Pyridyl)-1-[3-(4-pyridyl)-1*H*-1-isoindolylidenemethyl]-2*H*-isoindole (**2**).

To a methanol solution (10 ml) of **1** [4] (225 mg, 1 mmole) 3 ml of aqueous ammonia and acetic acid (5 ml) were added with stirring and then the mixture was allowed to stand at room temperature for 70 hours. After concentrating the mixture the product was extracted with chloroform. The resulting residue was chromatographed on silica gel column using chloroform-methanol (9:1) and then acetone as the eluent to give 56 mg of pure **2** as deep blue needles. Compound **2** had mp 361-362.5°; ms: (EI) m/z 398 (M^+); ^{1}H nmr (deuteriochloroform): δ 8.80 (m, 4H), 8.05-7.80 (m, 8H), 7.62 (s, 1H, =CH), 7.47-7.31 (m, 4H) and 3.10 (br, 1H, NH); ir (potassium bromide): 1610 cm^{-1} (ν conjugated C=N); uv (methanol): 589 (log ϵ 4.39), 348 (sh, 4.04), 319 (4.11), 256 nm (4.15); (methanol + hydrogen chloride): 650 (4.44), 455 (sh, 3.94), 358 nm (4.11).

Anal. Calcd. for $C_{27}H_{18}N_4$: C, 81.39; H, 4.55; N, 14.06. Found: C, 81.24; H, 4.72; N, 13.84.

3-(1-Methyl-4-pyridinio)-1-[3-(1-methyl-4-pyridinio)-1*H*-1-isoindolylidenemethyl]-2*H*-isoindole Diiodide (**3**).

A mixture of **2** (30 mg) and methyl iodide (2.5 ml) in chloroform (6 ml) was permitted to stand at room temperature in the dark for 3 days. After evaporating the mixture, the residue was chromatographed on silica gel column for reversed phase using acetic acid-water (1:499) and then acetic acid-acetonitrile-water (1:50:499) as the eluent to give 43 mg (87%) of **3** as deep bluish green needles. Compound **3** had mp 225° dec; ms: (CI) m/z 428 ($M+H-2I-1)^+$, 399 ($M+H-2CH_3I)^+$, 398 ($M+H-2CH_3I-1)^+$; ^{1}H nmr (DMSO-d_6): δ 9.02 (m, 4H), 8.76 (m, 4H), 8.55-8.50 (m, 3H, arom and =CH), 8.34 (m, 2H), 7.62 (m, 4H), 4.39 (s, 6H, 2NCH_3) and 3.33 (br, NH with water); ir (potassium bromide): 1638 (ν C=N$^+$), 1610 (ν conjugated C=N) and 1378 cm^{-1} (ν CH_3); uv (methanol): 742 (log ϵ 4.68), 673 (4.63), 460 (4.11), 396 nm (4.35).

Anal. Calcd. for $C_{29}H_{24}N_4I_2\cdot 2H_2O$: C, 48.49; H, 3.93; N, 7.80; O. 4.45. Found: C, 48.38; H, 3.67; N, 7.69; O, 4.76.

1-Hydroxy-3-methyl-1-(4-pyridyl)-1*H*-isoindole (**4**).

In Dry Ammonia.

Anhydrous ammonia was bubbled into an ether solution (50 ml) of **1** (450 mg) at room temperature for 5 hours. After evaporating the solvent under reduced pressure, the residue was recrystallized from benzene to give 367 mg (82%) of **4** as colorless crystals. Compound **4** had mp 161° dec; ms: (EI) m/z (relative intensity) 224 (M^+, 50), 206 ($M-H_2O^+$, 31), 146 ($M-C_5H_4N^+$, 100); ^{1}H nmr (DMSO-d_6): δ 8.46 (m, 2H), 7.60-7.24 (m, 6H), 6.88 (s, 1H, OH) and 2.46 (s, 3H); ir (potassium bromide): 3100 (br, ν OH), 1600

cm^{-1} (ν C=N); uv (methanol): 259 (log ϵ 3.88) 215 nm (4.42).

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found: C, 75.16; H, 5.28; N, 12.28.

In Aqueous Ammonia.

To a stirring solution of **1** (45 mg) in deuteriomethanol (0.5 ml), 0.1 ml of aqueous ammonia in deuteriomethanol (0.5 ml) was added dropwise at room temperature. After 2 hours the mixture showed one spot on the thin-layer chromatogram of aluminium oxide and ms as well as ^1H nmr spectra of the mixture were recorded immediately. This mixture had ms: (EI) m/z (relative intensity) 225 (M^+, 61), 206 (M-HDO$^+$, 98) 147 (M-$C_5H_4N^+$, 100); ^1H nmr (mixture in methanol-d_6): δ 8.46 (m, 2H), 7.67-7.36 (m, 6H) 2.56 (s, 3H).

Formation of **2** by the reaction of **4** and acetic acid. A mixture of **4** (0.5 mmole) and acetic acid (0.5 ml) in methanol allowed to stand at room temperature for 3 days. By treating the mixture in a similar manner to that of **2**, a deep blue solid of **2** was obtained in the yield of 13% (pure).

4-(*o*-Acetylbenzoyl)-1-methylpyridinium Iodide (**5**).

Methyl iodide (20 mmoles) was added to **1** (2 mmoles) in chloroform (3 ml) and the mixture was allowed to stand at room temperature for 3 days in the dark. The resulting adduct was collected by filtration to give yellow needles (99%). Compound **5** had mp 174-175.4°; ms: (EI) m/z 367 (M^+) and 225 (M-CH_3I)$^+$; ir (potassium bromide): 1688 and 1670 (ν C=O) as well as 1637 cm^{-1} (ν C=N$^+$); ^1H nmr (DMSO-d_6): δ 9.09 (m, 2H), 8.34-8.10 (m, 3H), 7.88 (m, 2H), 7.61 (m, 1H), 4.41 (s, 3H, N$^+CH_3$), 2.58 (s, 3H, $COCH_3$); uv (chloroform): 434 (log ϵ 3.05), 267 nm (3.96).

Anal. Calcd. for $C_{15}H_{14}NO_2I$: C, 49.07; H, 3.84; N, 3.81. Found: C, 48.91; H, 3.69; N, 3.77.

Formation of **3** by the Reaction of **5** in Aqueous Ammonia and Acetic Acid.

To a methanol solution (10 ml) of **5** (367 mg) a mixture of aqueous ammonia (6 ml) and acetic acid (10 ml) was added and was left at room temperature for 4 days. The mixture was treated in a manner similar to that for **3** to give deep green **3** (15%).

3,3'-Di-(4-pyridyl)-1,1'-vinylenebis(2*H*-2-isoindoleacetic) Acid (**6**).

To a solution (10 ml) of **1** (450 mg, 2 mmoles) and acetic acid (0.5 ml) and glycine (300 mg, 4 mmoles) in water (2 ml) was added dropwise with stirring. After standing at room temperature for 15 hours the precipitate was filtered and washed with water to give 470 mg (86%) of a deep red solid. Furthermore the solid was washed with methanol because there were no adequate solvents for recrystallization to afford 290 mg (53%) of **6**. When the reaction mixture was allowed to stand for 3 days 377 mg (69%) of pure **6** was obtained. Compound **6** had mp 202.5-205° hygroscopic; ms: (CI) m/z 441 (M+H -2CO_2)$^+$, 427 (M+H -CO_2-CH_2CO_2)$^+$; ir (potassium bromide): 1610, 1415 cm^{-1} (ν CO of COO^-); uv (methanol): 564 (log ϵ 4.18), 398 (3.89), 255 (sh), 219 (4.21).

Anal. Calcd. for $C_{32}H_{24}N_4O_4 \cdot H_2O$: C, 70.32; H, 4.79; N, 10.25. Found; C, 69.99; H, 4.48; N, 10.10.

Dimethyl 3,3'-Di-(4-pyridyl)-1,1'-vinylenebis(2*H*-2-isoindoleacetate) (**7**).

A mixture of **1** (2 mmoles) in methanol (10 ml) and acetic acid (0.2 ml) as well as glycine methyl ester hydrochloride (4 mmoles) and sodium carbonate (2 mmoles) in water (4 ml) was allowed to react at room temperature for 24 hours. After adding 100 ml of water to the mixture the resulting solid was collected by filtration and washed with water to give 330 mg (57%) of **7** as a deep red compound. Because the solution of **7** in methanol or acetone is unstable, the product was purified by washing with methanol to give 52 mg of product. Compound **7** had mp 220° dec; ms: (CI) m/z 556 (M+H -1)$^+$, 498 (M+H -CO_2CH_3)$^+$, 439 (M+H -2CO_2CH_3)$^+$; ir (potassium bromide): 1750 (ν C=O), 965 (*trans* CH=CH) cm^{-1}; uv (methanol): 532 (sh), 502, 376, 290 and 231 nm.

Anal. Calcd. for $C_{34}H_{28}N_4O_4 \cdot H_2O$: C, 71.06; H, 5.26; N, 9.75. Found: C, 71.39; H, 4.95; N, 9.73.

REFERENCES AND NOTES

[1] F. Weygand, H. Weber, E. Maekawa and G. Eberhardt, *Chem. Ber.*, **89**, 1994 (1956); E. Maekawa, Y. Suzuki and S. Sugiyama, *ibid.*, **101**, 847 (1968); S. Nan'ya and E. Maekawa, *Nippon Kagaku Kaishi*, 1750 (1977).

[2] S. Nan'ya and E. Maekawa, *Nippon Kagaku Kaishi*, 1953 (1974); 1535 (1975); 1747 (1977).

[3] S. Nan'ya and E. Maekawa, *ibid.*, 144 (1978).

[4] A. Kotali and P. G. Tsoungas, *Tetrahedron Letters*. **28**, 4321 (1987).