HETEROCYCLES, Vol. 78, No. 5, 2009, pp. 1271 - 1279. © The Japan Institute of Heterocyclic Chemistry
Received, 2nd December, 2008, Accepted, 26th January, 2009, Published online, 29th January, 2009
DOI: 10.3987/COM-08-11614

SYNTHESIS OF QUINOLIZINO[3,2-*a*]QUINOLIZINE DERIVATIVES AND THEIR FLUORESCENCE

Kenichirou Yokota,[a] Masayori Hagimori,[b] Yasuhiro Shigemitsu,[c] Naoko Mizuyama,[d] Bo-Cheng Wang,[e] and Yoshinori Tominaga[a]*

[a]Faculty of Environmental Studies, Nagasaki University, 1-14, Bunkyo-machi, Nagasaki 852-8521; [b]Faculty of Pharmaceutical Sciences, Nagasaki International University, 2825-7, Huis Ten Bosch Sasebo 859-3298; [c]Technology Center of Nagasaki 2-1308-8, Ikeda, Omura Nagasaki 856-0026, Japan. [d]Department of Pharmacy, Saga University Hospital, 5-1-1, Nabeshima, Saga 849-8521, [e]Department of Chemistry, Tamkang University, Tamsui 251, Taiwan. E-mail: ytomi@nagasaki-u.ac.jp

Abstract – Polycyclic quinolizine derivatives, quinolizino[3,2-*a*]quinolizines (**4a**–**c**), were synthesized in moderate yields by a one-pot method using ketene dithioacetal, methyl bis(methylsulfanyl)methylene-cyanoacetate (**2**), alkyl 2-pyridylacetates (**1a, b**), and 2-pyridylacetonitrile (**1c**). Compounds **4a, b** exhibited red fluorescence (Em max: 576 nm) in solid state.

Recently, organic electroluminescent (OEL) materials that exhibit fluorescence in solid state have gained considerable attention. OELs are now fast replacing liquid crystal displays (LCDs). Fluorescent dyes can be used as emitters in electroluminescence devices and as solar energy accumulators; they are also used to prepare fluorescent greenhouse films, copy-preventing inks, and fluorescent colorants.[1] Heteroaromatic compounds have attracted particular interest because most heterocyclic compounds contain a variety of fluorescent pigment molecules. We have synthesized many heterocyclic compounds from ketene dithioacetals, some of which exhibit fluorescence.[2] In general, chemical compounds that display fluorescence are mostly polycyclic aromatic and polyaryl-substituted compounds, such as rubulene derivatives. Recently, we found that 2-pyrone derivatives are potential electroluminescent materials.[3] The fused 2-pyrone derivative, the pyranoquinolizine derivative **A**[4] exhibits red fluorescence in solid state, which is an important and desired feature in the field of OEL research. Certain types of quinolizines have

attracted significant attention owing to their possible applications as photographic materials and dyes.[5–7] In particular, the fluorescence properties of fused quinolizine derivatives such as pyrroloquinolizine derivative **B** and quinolizino[3,2-*a*]quinolizine **C** are of interest to us.[2a-d,8] In this paper, we report the synthesis of fused quinolizine derivatives, quinolizino[3,2-*a*]quinolizines, by a one-pot synthesis method using a ketene dithioacetal.

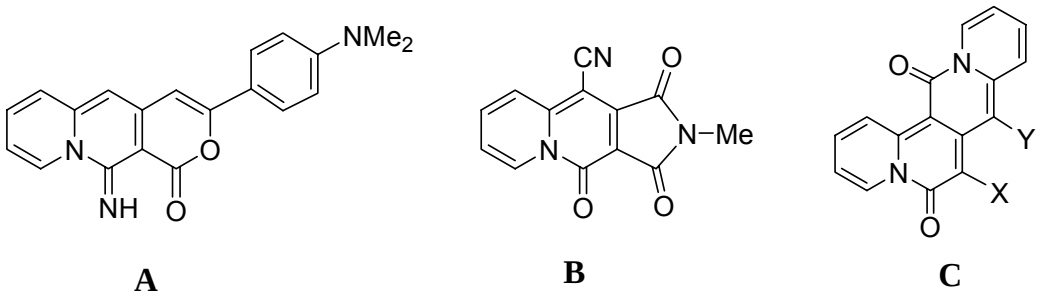
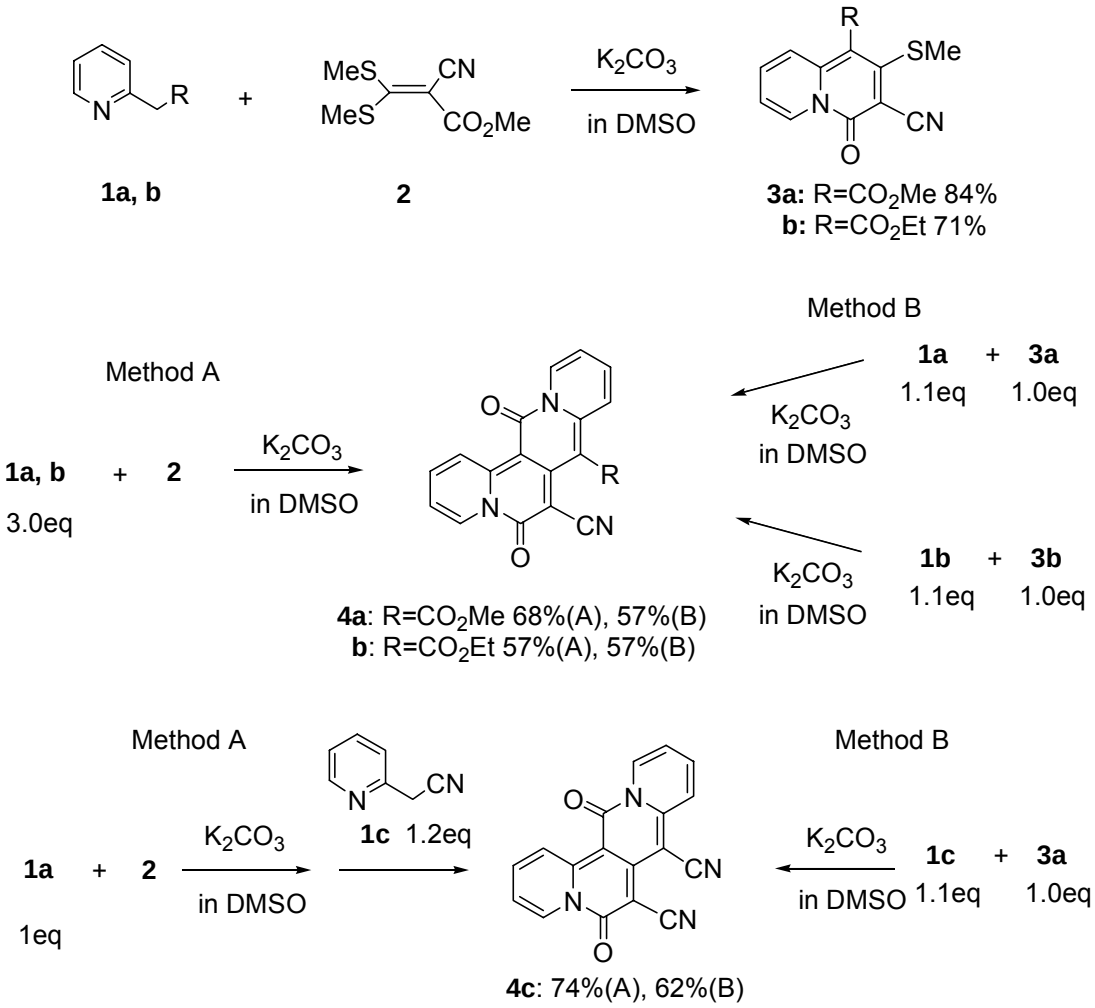
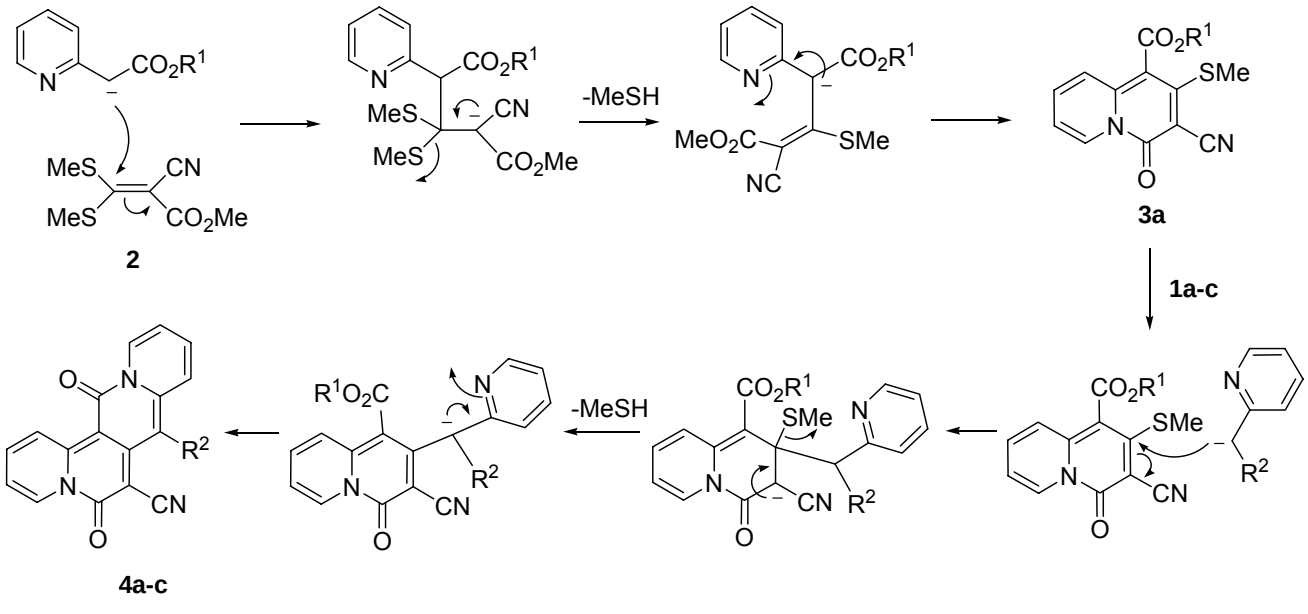


Figure 1. Structure of fluorescent quinolizine derivatives

4*H*-Quinolizine derivatives are usually synthesized by the condensation of alkyl 2-pyridylacetates (**1a, b**) or 2-pyridylacetonitrile (**1c**) with ethoxymethylene compounds and ketene dithioacetals.[7] During their study on [3.3.3]cyclazine derivatives, Schwarz et al. synthesized 4*H*-quinolizines and analyzed their ultraviolet-visible (UV-Vis) spectra[7b] in detail;[8] however, they did not investigate the fluorescence properties of these compounds. In our previous research, we synthesized 2-methylsulfanyl-4-oxo-4*H*-quinolizine-3-carbonitriles (**3a, b**) in 48–50% yield by direct heating of a mixture of ketene dithioacetal (**2**) and **1a** or **1b** without any solvent or catalyst (base or acid).[6] Since the yield of the products formed under these reaction conditions was unexpectedly low (48–50%), we carried out the above-mentioned reaction under basic conditions. We carried out the condensation of methyl 2-pyridylacetate (**1a**) with methyl bis(methylsulfanyl)methylene-cyanoacetate (**2**) in the presence of potassium carbonate at room temperature for 4–5 h and obtained methyl 3-cyano-4-oxo -4*H*-quinolizine-1-carboxylate (**3a**) in 84% yield. With 3 equiv of **1a**, we could isolate methyl 7-cyano-6,14-dioxo-6*H*,14*H*-quinolizino[3,2-*a*]quinolizine-8-carboxylate (**4a**) in 68% yield. In this case, we carried out the reaction at room temperature for 1 h, after which we heated the reaction mixture at 50–60 °C for 20 min (short reaction time) and then stirred it at room temperature for 3 h. We synthesized **4b** (57% yield) in a similar manner from **2** and **1b**. We also obtained **4c** from **1a**, **2**, and **1c** by a one-pot reaction (Scheme 1). These quinolizino[3,2-*a*]quinolizine derivatives were presumably formed *via* the addition-elimination and cyclization mechanism shown in Scheme 2.

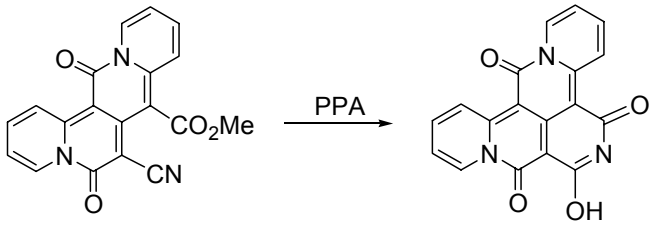


Scheme 1. Synthesis of **3a, b** and **4a-c**



Scheme 2. Presumed reaction pathway for synthesis of **4a-c**

Treatment of **4a** with polyphosphoric acid (PPA) at 100°C for 30 min afforded a five-ring system, 7-Hydroxy-6,9,15-trioxo-6*H*,9*H*,15*H*-pyrido[3,4,5-*g*.*h*]quinolizino[3,2-*a*]quinolizine (**5**), in 54% yield (mp > 300°C) (Scheme 3). The structure of **5** was established on the basis of its spectroscopic data.



4a **5** 54%

Scheme 3. Reaction of **4a** with PPA

FLUORESCENCE

Research on 2-pyrone derivatives revealed that pyrano[3,4-*d*]quinolizine derivatives emit red fluorescence in solid state.[4] Further research on the fluorescence of chemical compounds with a fused quinolizine skeleton is expected to be carried out in the future. We focused our research on the fluorescence properties of 6*H*,14*H*-quinolizino[3,2-*a*]quinolizine-6,14-dione derivatives synthesized. We analyzed the room-temperature fluorescence emission spectra of **3a**, **3b**, **4a**–**c**, and **5** in their solid states. The fluorescence maxima (Em max) and relative fluorescent intensities (RI) of these compounds are listed in Table 1. The Em max and RIs of **3a**, **b**, **4a**–**c**, and **5** ranged from 541 to 576 nm and 0.01 to 0.44, respectively. Among these compounds, **4a** and **4b** showed red fluorescence similar to DCM: [4-(dicyanomethylene)-2-methyl-6-(*p*-dimethylaminostyryl)-4*H*-pyran], which is a red laser dye (Em max: 577 nm)[1b,9]. The implications of the present results are discussed on the fluorescence of 4*H*-quinolizine derivatives as a basic structure in the field of organic electroluminescent materials. Currently, we are in the process of evaluating the relationship between structure and fluorescence properties of these compounds.

Table 1. Fluorescence data of quinolizino[3,2-*a*]quinolizine derivatives in solid state.

No.	Ex max (nm) Solid	Em max (nm) Solid	SS[a]	RI[b]
3a	337	568	231	0.43
3b	341	541	200	0.44
4a	336	576	240	0.12
4b	328	576	248	0.13
4c	329	563	234	0.01
5	343	569	226	0.04
DMPC	301	608	307	-

[a]Stokes' shift; Em, Ex in solid states.
[b]Relative fluorescence intensities in solid state calculated using DMPC as the standard.

In conclusion, polycyclic quinolizine derivatives, 6*H*,14*H*-quinolizino[3,2-*a*]quinolizines (**4a**–**c**), were synthesized in moderate yields by a one-pot method using a ketene dithioacetal, methyl bis(methylsulfanyl)methylene-cyanoacetate (**2**), alkyl 2-pyridylacetates (**1a, b**), and 2-pyridylacetonitrile (**1c**). These compounds exhibited red fluorescence (**4a**, Em max: 576 nm; **4b**, Em max: 576 nm) similar to DCM.

EXPERIMENTAL

Identifications of compounds and measurements of properties were carried out by general procedures using the following equipment. All melting points were determined in a capillary tube and uncorrected. Infrared (IR) spectra were recorded in potassium bromide pellets on JASCO 810 or Shimazu IR-460 spectrometer and ultraviolets (UV) absorption spectra were determined in 95% ethanol on a Hitachi 323 spectrometer. Fluorescence spectra were determined on Shimazu RF-5300pc. Nuclear magnetic resonance (NMR) spectra were obtained on Gemini 300NMR (300MHz), JEOL-GX-400 (400MHz), and Varian UNITYplus 500NMR (500MHz) spectrometers with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on JEOL-DX-303 mass spectrometers. Microanalyses were performed by K.Yoshida on a Perkin Elmer at Nagasaki University. All compounds were reagent grade and used without further purification unless otherwise specified.

Method of Measurement of Fluorescence.

A powder sample of subject compound is heaped in a tray. After covering the sample with a quartz plate, this part was fixed in fluorescence spectrometer. After fixing the fluorescent wavelength, the excitation spectrum was determined by the scanning with the fluorescent wavelength. Similarly, Fluorescent spectrum was obtained after scanning with the excitation wavelength. After obtaining these results, the excitation wavelength was decided and the fluorescence spectrum was measured. The fluorescent relative intensity was determined by using DMPC: [6-(4-*N*,*N*-dimethylaminophenyl)-4-methylsulfanyl-2-oxo-2*H*-pyran-3-carbonitrile][3g] as standard sample. Fluorescence of standard sample and all subject compounds were measured on 345 nm excitation.

Methyl 3-Cyano-2-methylsulfanyl-4-oxo-4*H*-quinolizine-1-carboxylate (3a)

A mixture of 0.76 g (5.00 mmol) of methyl 2-pyridylacetate (**1a**), 1.0 g (5.0 mmol) of **2**, and 1.38 g (10.0 mmol) of potassium carbonate in 15 mL of DMSO was stirred for 2 h at rt. This mixture was stirred and heated for 20 min at 50-60°C and for additional 2 h at rt. The reaction mixture was poured into 300 mL of ice water and then neutralized with 10% hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried by air to give yellow products. The products was collected by filtration to

give 1.15 g (4.19 mmol, 84% yield). Analytical sample was recrystallized from MeOH to give dark red crystals, mp 131-132°C (Lit.,[6c] 133-134°C). IR (KBr, cm^{-1}): 2217 (CN), 1734 (CO), 1671 (CO), 1625, 1509, 1467. ^{1}H NMR ($CDCl_3$) δ: 2.75 (3H, s, SMe), 4.00 (3H, s, OMe), 7.31 (1H, m, 7-H), 7.78 (1H, dd, *J*=1.4, 5.5 Hz, 9-H), 7.78 (1H, m, 8-H), 9.26 (1H, ddd, *J*=1.2, 1.2, 9.3 Hz, 6-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 19.11, 53.01, 93.71, 112.01, 115.77, 117.60, 123.13, 129.22, 136.53, 141.70, 153.57, 156.22, 165.70. Fluoresence (solid): Ex max, 337 nm; Em max, 568 nm; RI=0.43.

Ethyl 3-Cyano-2-methylsulfanyl-4-oxo-4*H*-quinolizine-1-carboxylate (3b)

This compound was prepared in 71% yield from, 1.65 g (10.0 mmol) of ethyl 2-pyridylacetate (**1b**), 2.44 g (12.0 mmol) of **2** and 2.76 g (20.0 mmol) of potassium carbonate in a manner similar to that described for synthesis of **3a**. In this case, an insoluble side product in EtOH was obtained 0.042 g (1.2%) as orange needles, mp 311-312°C. This product was compound **4a**. An analytical sample was recrystallized from EtOH to give yellow needles, mp 126-128°C (Lit.,[6c] mp 128-129°C). IR (KBr, cm^{-1}): 2202 (CN) 1666 (CO), 1623, 1459 1223. ^{1}H NMR ($CDCl_3$) δ: 1.44 (3H, t, *J*=7.3 Hz, O-CH_2-$\underline{CH_3}$), 2.75 (3H, s, SMe), 4.48 (2H, q, *J*=7.3 Hz, O-CH_2-), 7.30 (1H, m, 7-H), 7.74-7.84 (2H, m, 8, 9-H), 9.26 (1H, *J*=7.2 Hz, 6-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.08, 19.15, 62.59, 93.84, 112.52, 115.80, 117.53, 123.11, 129.22, 136.39, 141.63, 153.35, 156.27, 165.26. Fluoresence (solid): Ex max, 341 nm; Em max, 541 nm; RI=0.44.

Methyl 7-Cyano-6,14dioxo-6*H*,14*H*-quinolizino[3,2-*a*]quinolizine-8-carboxylate (4a)

Method A: A mixture of, 2.27 g (15.0 mmol) of methyl 2-pyridylacetate (**1a**), 1.0 g (5.0 mmol) of **2**, and 2.76 g (20.0 mmol) of potassium carbonate in 15 mL of DMSO was stirred for 2 h at rt. This mixture was stirred and heated for 30 min at 50-60°C and stirred for additional 2 h at rt. The reaction mixture was poured into 300 mL of ice water and then neutralized with 10% hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried by air to give dark red products. A mixture of this compounds and 50 mL of MeOH was refluxed for 1 h. After cooling, the product was collected by filtration to give 1.17 g (3.39 mmol, 68% yield). Analytical sample was recrystallized from DMF to give orange red crystals, mp 311-313°C. **Method B:** A mixture of, 0.302 g (2.0 mmol) of methyl 2-pyridylacetate (**1a**), 0.332 g (2.2 mmol) of **3a**, and 0.552 g (4.0 mmol) of potassium carbonate in 10 mL of DMSO was stirred for 2 h at rt. This mixture was stirred and heated for 30 min at 50-60°C and stirred for additional 2 h at rt. The reaction mixture was poured into 300 mL of ice water. The precipitate was collected by filtration, washed with water, and dried by air to give dark red products. A mixture of this compounds and 50 mL of MeOH was refluxed for 1 h. After cooling, the product was collected by filtration to give 0.409 g (1.14 mmol, 57% yield). IR (KBr, cm^{-1}): 3094, 2206 (CN), 1720 (CO), 1683, 1653, 1551, 1517, 1498. UV (EtOH) λ nm (log ε): 270 (4.10), 377 (4.23), 429 (3.93). ^{1}H NMR (DMSO-D6) δ: 3.94 (3H, s, OMe), 7.19 (1H, ddd, *J*=1.4, 6.6, 7.1 Hz, 11-H), 7.67 (1H, dd, *J*=1.4, 8.9 Hz, 9-H), 7.74 (1H, ddd, *J*=1.4, 6.6, 8.9 Hz, 10-H), 7.90 (1H, ddd, *J*=1.4, 6.0, 7.1 Hz, 3-H), 8.53 (1H, ddd,

J=1.4, 7.1, 8.5 Hz, 2-H), 9.08 (1H, d, *J*=7.1 Hz, 12-H), 9.62 (1H, d, *J*=6.0 Hz, 4-H), 10.18 (1H, d, *J*=8.5 Hz, 1-H). ^{13}C NMR (100 MHz, DMSO-D6) δ: 51.95, 75.52, 95.29, 95.65, 114.66, 117.30, 120.73, 121.07, 124.59, 128.25, 131.83, 135.80, 139.94, 141.27, 142.38, 146.38, 155.64, 156.45, 166.62. Fluoresence (solid): Ex max, 336 nm; Em max, 576 nm; RI=0.12. Ms: m/z 346 (M^++1, 36), 345 (M^+, 100), 319 (15), 317 (57), 314 (40), 302 (13), 287 (24), 286 (69), 259 (48), 230 (49), 78 (26). *Anal.* Calcd for $C_{19}H_{11}N_3O_4$=345.3085: C, 66.09; H, 3.21; N, 12.17. Found: C, 65.81; H, 3.21; N, 12.09.

Ethyl 7-Cyano-6,14-dioxo-6*H*,14*H*-quinolizino[3,2-*a*]quinolizine-8-carboxylate (4b)

This compound (0.51 g, 1.43 mmol) was prepared in 57% yield from 1.24 g (7.5 mmol) of ethyl 2-pyridylacetate (**1b**), 0.51 g (2.5 mmol) of **2**, and 1.38 g (10.0 mmol) of potassium carbonate in a manner similar to that described for synthesis of **4a**. This compound (**4b**) was also prepared from **3b** and **1b** under the same reaction condition in 57% yield (**Method B**). An analytical sample was recrystallized from DMF to give dark red needles, mp 305-306°C. IR (KBr, cm^{-1}): 3092, 2203 (CN), 1723 (CO), 1681 (CO), 1645, 1556, 1520, 1498. UV (EtOH) λ nm (log ε): 270 (4.24), 273 (4.10), 346 (4.25), 364 (4.32), 378 (4.34), 430 (4.03). ^{1}H NMR ($CDCl_3$) δ: 1.42 (3H, t, OCH_2-$\underline{CH_3}$), 4.61 (2H, q, O-$\underline{CH_2}$-Me), 6.96 (1H, m, 11-H), 7.52 (1H, m, 10-H), 7.67 (1H, m, 3-H), 7.81 (1H, d, *J*=9.2 Hz, 9-H), 8. 27 (1H, m, 2-H), 9.10 (1H, d, *J*=7.8 Hz, 12-H), 9.78 (1H, d, *J*=7.7 Hz, 4-H), 10.37 (1H, d, *J*=9.7 Hz, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.53, 64.81, 92.72, 110.02, 112.85, 115.69, 118.52, 120.13, 122.03, 124.21, 125.90, 131.91, 133.20, 141.91, 143.06, 145.74, 146.99, 147.94, 154.85, 156.19, 166.59. Fluoresence (solid): Ex max, 328 nm; Em max, 576 nm; RI= 0.13. Ms: m/z 360 (M^++1, 23), 359 (M^+, 100), 331 (29), 314 (29), 303 (18), 287 (30), 286 (20), 260 (11), 259 (54), 230 (63). *Anal.* Calcd for $C_{20}H_{13}N_4O_4$=359.355: C, 66.85; H, 3.65; N, 11.69. Found: C, 66.73; H, 3.41; N, 11.61.

6,14-Dioxo-6*H*,14*H*-quinolizino[3,2-*a*]quinolizine-7, 8-dicarbonitrile (4c)

A mixture of 0.76 g (5.0 mmol) of methyl 2-pyridylacetate (**1a**), 1.0 g (5.0 mmol) of **2** and 1.38 g (10.0 mmol) of potassium carbonate in 15 mL of DMSO was stirred for 2 h at rt. This mixture was stirred and heated for 10 min at 50-60°C and stirred for additional 2 h at rt. 0.71 g (6.0 mmol) of 2-pyrdylacetonitrile (**1c**) and 1.38 g (10.0 mmol) of potassium carbonate were added to the reaction mixture. After stirring for 4 h at rt, the reaction mixture was poured into 300 mL of ice water and then neutralized with 10% hydrochloric acid. The precipitate was collected by filtration, washed with water, and dried by air to give dark red product. A mixture of this compounds and 50 mL of MeOH was refluxed for 1 h. After cooling, the products were collected by filtration to give 1.15 g (3.69 mmol, 74% yield). This compound (**4c**) was also synthesized from **3a** and **1c** in 62% yield (**Method B**). Analytical sample was recrystallized from DMF to give brown yellow crystals, mp > 300°C. IR (KBr, cm^{-1}): 3100, 2210 (CN), 1691 (CO), 1655 (CO), 1617, 1561, 1515. UV (EtOH) λ nm (log ε): 269 (4.35), 309 (4.30), 341 (4.37), 358 (4.35), 373 (4.32), 426 (4.18). ^{1}H NMR ($CDCl_3$) δ: 7.42 (1H, m, 11-H), 7.88 (2H, m, 10-H), 8.03 (1H, m, 3-H), 8.14

(1H, d, *J*=8.8 Hz, 9-H), 8.48 (1H, m, 2-H), 9.37 (1H, d, *J*=6.8 Hz, 12-H), 9.79 (1H, d, *J*=6.8 Hz, 4-H), 10.31 (1H, d, *J*=8.8 Hz, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 96.35, 110.01, 112.84, 115.67, 117.41, 118.50, 121.63, 122.71, 125.75, 130.00, 132.46, 139.71, 142.10, 143.30, 146.61, 147.92, 155.63, 158.75. Fluoresence (solid): Ex max, 329 nm; Em max, 563 nm; RI=0.01. Ms: m/z 313 (M^++1, 5), 312 (M^+, 21), 284 (27), 255 (12), 44 (00). HRMS (EI): 312.0629 (Calcd. 312.0647 for $C_{18}H_8N_4O_2$).

7-Hydroxy-6,9,15-trioxo-6*H*,9*H*,15*H*-pyrido[3,4,5-*g*.*h*]quinolizino[3,2-*a*]quinolizine (5)

A mixture of **4a** (0.39 g, 1.1 mmol) was heated at 100°C for 1 h. After cooling, the mixture was poured into 100 mL of water and stand over for 2 h. The precipitate was collected by the filtration to give 0.20 g (0.59 mmol, 54% yield) of yellow brown crystals which was recrystalized from DMF to give yellow crystals, mp > 300°C. IR (KBr, cm^{-1}): 2537 (br), 3128, 3002, 1731 (CO), 1667 (CO), 1623, 1560, 1519. UV (EtOH) λ nm (log ε): 285 (4.09), 305 (4.06), 332 (4.08), 431 (3.98). ^{1}H NMR ($CDCl_3$ + CF_3COOH 0.04 ml) δ: 7.85 (1H, m, 12-H), 7.94 (1H, m, 11-H), 8.46 (1H, m, 3-H), 8.62 (1H m, 2-H), 9.70 (1H, d, *J*=7.3 Hz, 10-H), 9.81 (1H, d, *J*=8.3 Hz, 13-H), 10.02 (1H, d, *J*=8.9 Hz, 4-H), 10.25 (1H, d, *J*=8.6 Hz, 1-H). ^{13}C NMR (100 MHz, $CDCl_3$ + CF_3COOH 0.04 mL) δ: 110.08, 112.91, 115.75, 118.58, 120.97, 121.86, 124.80, 126.04, 132.35, 139.99, 143.60, 145.77, 146.67, 148.19, 155.00, 159.83, 160.60, 167.10. Fluoresence (solid): Ex max, 343 nm; Em max, 569 nm; RI=0.04. Ms: m/z 332 (M^++1, 28), 331 (M^+, 100), 303 (38), 232 (15), 231 (12), 230 (17), 204 (15), 203 (18). HRMS (EI): 331.0578 (Calcd. 331.0593 for $C_{18}H_9N_3O_4$).

REFERENCES AND NOTES

1. *a*) C. W. Tang and S. A. Van Slyke, *Appl. Phys. Lett.,* 1987, **51**, 913; *b*) C. W. Tang, S. A. Van Slyke, and C. H. Chen, *J. Appl. Phy.*, 1989, **65**, 3610; *c*) M. Matsuoka, *J. Soc. Dyers and Colourists*, 1989, **105**, 167; *d*) K. Shirai, A. Yanagisawa, H. Takahashi, K. Fukunishi, and M. Matsuoka, *Dyes and Pigments*, 1998, **39**, 49; *e*) K. Shirai, M. Matsuoka, and K. Fukunishi, *Dyes and Pigments*, 2000, **47**, 107; *f*) J. H. Burroughes, D. D. C. Bradley, A. R. Brown, R. N. Marks, K. Mackay, R. H. Friend, P. L. Burns, and A. B. Holmes, *Nature*, 1990, **347**, 539; *g*) M. A. Baldo, M. E. Thompson, and S. R. Forrest, *Nature*, 2000, **403**, 750.
2. *a*) Y. Tominaga and Y. Matsuda, *J. Heterocycl. Chem.*, 1985, **22**, 937; *b*) Y. Tominaga and Y. Matsuda, *J. Synth. Org. Chem. Japan*, 1985, **43**, 669; *c*) Y. Tominaga, *J. Synth. Org. Chem. Japan*, 1989, **47**, 413; *d*) Y. Tominaga, 'Synthesis of Heterocyclic Compounds Using Ketene Dithioacetals' in '*Trends in Heterocyclic Chemistry*', ed. by J. Menon, Council of Scientific Research Integration, *Research Trends*, 1991, **2**, 43; *e*) Y. Tominaga, S. Kohra, H. Honkawa, and A. Hosomi, *Heterocycles*, 1989, **29**, 1409; *f*) Y. Tominaga, Y. Shigemitsu, and K. Sasaki, *J. Heterocycl. Chem*., 2002, **39**, 571; *g*) M. Hagimori, N. Mizuyama, Y. Hisadome, J. Nagaoka, K.

Ueda, and Y. Tominaga, *Tetrahedron*, 2007, **63**, 2511.

3. *a*) N. Mizuyama, Y. Murakami, J. Nagaoka, S. Kohra, K. Ueda, K. Hiraoka, Y. Shigemitsu, and Y. Tominaga, *Heterocycles*, 2006, **68**, 1105; *b*) Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Heterocycles*, 1976, **4**, 1493; *c*) Y. Tominaga, A. Ushirogochi, Y. Matsuda, and G. Kobayashi, *Heterocycles*, 1977, **8**, 193; *d*) Y. Tominaga, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull*., 1984, **32**, 1665; *e*) Y. Tominaga, A. Ushirogochi, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull*., 1984, **32**, 3384; *f*) Y. Tominaga, A. Ushirogochi, and Y. Matsuda, *J. Heterocycl. Chem*., 1987, **24**, 1557; *g*) N. Mizuyama, Y. Murakami, S. Kohra, K. Ueda, K. Hiraoka, J. Nagaoka, K. Takahashi, Y. Shigemitsu, and Y. Tominaga, *J. Heterocycl. Chem*., 2007, **44**, 115.
4. M. Hagimori, N. Mizuyama, and Y.Tominaga, *ARKIVOC*, 2008, **13**, 16.
5. *a*) H. Awaya, C. Maseda, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Chem. Pharm. Bull*.,1974, **22**. 1424; *b*) H. Awaya, C. Maseda, Y. Tominaga, R. Natsuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi*, 1975, **95**, 13; *c*) G. Kobayashi, S. Furukawa, Y. Matsuda, and S. Matsunaga, *Yakugaku Zasshi*, 1969, **89**, 203.
6. *a*) G. Buchmann and W. Duchna, *Pharmazie*, 1968, **23**, 301; *b*) A. Schwartz, Z. Pal, L. Szabo, K. Simon, I. Hermecz, and Z. Meszaros, *J. Heterocycl. Chem*., 1987, **24**, 645; *c*) A. Schwartz, L. Szabo, K. Pusztay-Szabo, I. Hermecz, and Z. Meszaros, *J. Heterocycl. Chem*., 1987, **24**, 655.
7. Y. Tominaga, "Product Class 7, Cyclazines", in "Science of Synthesis", Vol. 17, ed. by S. M. Weinreb, Georg Thieme Verlag, Stuttgart, New York, p. 1075, 2004.
8. R. K. Dieter, *Tetrahedron*, 1986, **42**, 3029.
9. This compound (DCM) could not use as a standard sample because of too week fluorescence in the solid state (Ex: 345 nm) by using Shimazu RF-5300pc.
10. Compound **2** is commercially available reagent.