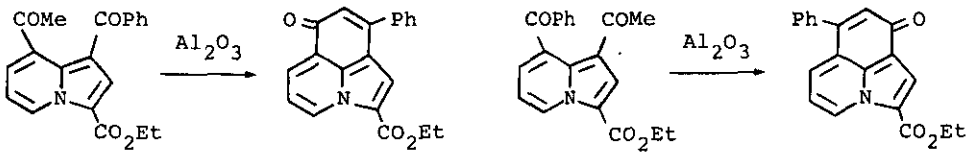
A NOVEL SYNTHESIS OF PYRROLO[2,1,5-de]QUINOLIZINONES (CYCL[3.3.2]AZINONES)

Yasuyoshi Miki,* Hisashi Kinoshita, Toshihiko Yoshimaru, and Shoji Takemura
Faculty of Pharmaceutical Sciences, Kinki University, 3-4-1 Kowakae, Higashi-Osaka 577, Japan
Masazumi Ikeda
Kyoto Pharmaceutical University, Misasagi, Yamashina, Kyoto 607, Japan

Abstract ——3H-Pyrrolo[2,1,5-de]quinolizin-3-ones and a 5H-pyrrolo-[2,1,5-de]quinolizin-5-one were synthesized by the intramolecular aldol condensation of the appropriate 3,5-diacylindolizines.

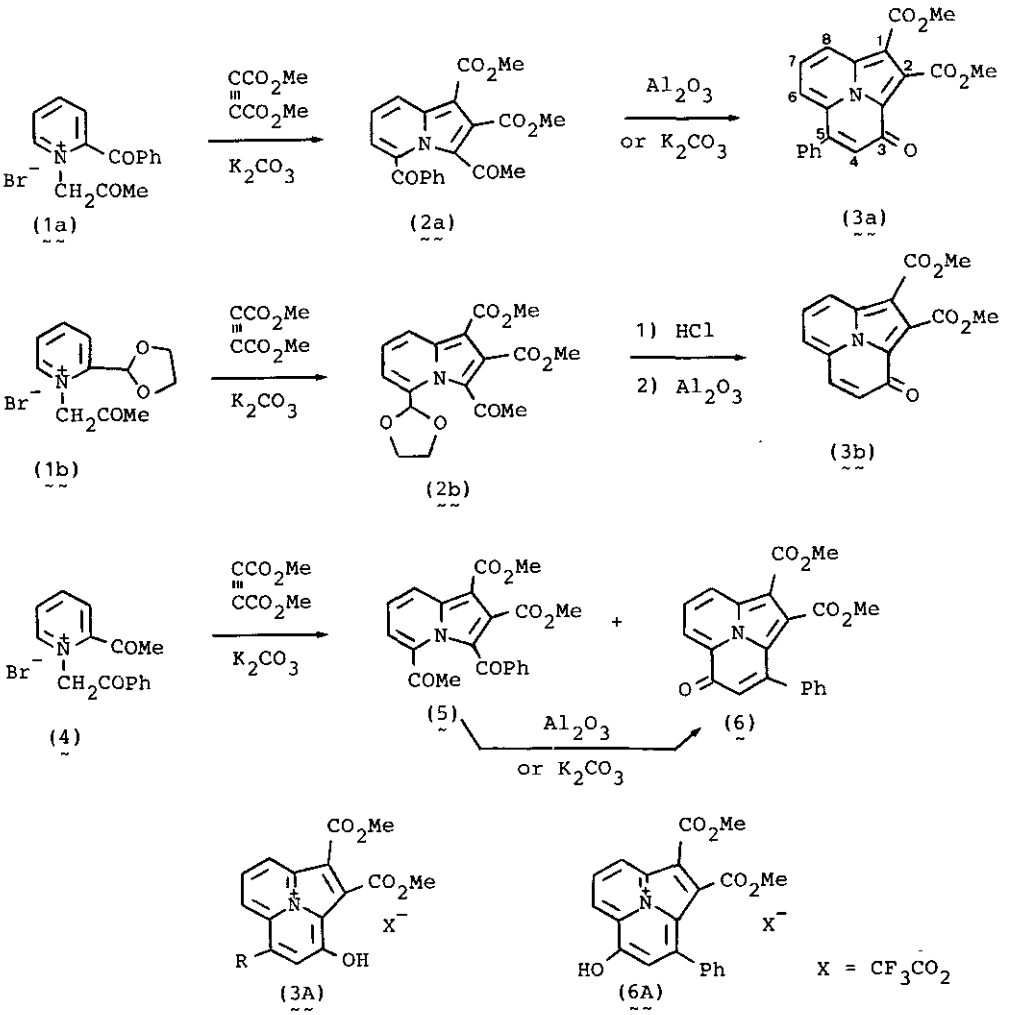
We recently reported a simple synthesis of pyrrolo[3,2,1-ij]quinolinones by the intramolecular aldol condensation of the 1,8-diacylindolizines (Scheme 1).[1] We have now extended this synthetic methodology to the preparation of pyrrolo-[2,1,5-de]quinolizinones (cycl[3.3.2]azinones) (3) and (6), which have been shown to have some interesting spectroscopic and chemical properties.[2]



Scheme 1

The starting indolizine (2a) was obtained in 64% yield by the 1,3-dipolar cycloaddition of N-acetonyl-2-benzoylpyridinium bromide (1a), prepared from 2-benzoylpyridine and bromoacetone, with dimethyl acetylenedicarboxylate (DMAD) in tetrahydrofuran in the presence of potassium carbonate. The indolizine (2a) underwent the intramolecular aldol condensation, upon treatment either with alumina or with potassium carbonate, to afford yellow crystals of dimethyl 3-oxo-5-phenyl-3H-pyrrolo[2,1,5-de]quinolizine-1,2-dicarboxylate (3a) in 62 and 38% yields, respectively. Similarly, the reaction of N-acetonyl-2-[2-(1,3-di-

oxolanyl)]pyridinium bromide (1b)[3] with DMAD gave the corresponding indolizine (2b)(75%), which was hydrolyzed with 10% hydrochloric acid followed by treatment of the resulting aldehyde with alumina to give yellow crystals of the 3H-pyrrolo[2,1,5-de]quinolizin-3-one (3b)[2] in 48% overall yield [from (2b)]. The 5H-pyrrolo[2,1,5-de]quinolizin-5-one derivative (6) was obtained as orange crystals directly in 64% yield, along with the indolizine (5)(6% yield), by the reaction of 2-acetyl-N-phenacylpyridinium bromide (4)[4] with DMAD in the presence of potassium carbonate. The indolizine (5) was also converted into (6) by treatment either with alumina or with potassium carbonate.



Scheme 2

Thus, the present method provides a simple and general route to both the 3H-

pyrrolo[2,1,5-de]quinolizin-3-ones and the 5H-pyrrolo[2,1,5-de]quinolizin-5-ones. The spectroscopic properties of the pyrrolo[2,1,5-de]quinolizinones have already been discussed by referring to acenaphthylene and naphthalene.[2] Here we wish to record our own results on the behavior of the ring protons of (3a,b) and (6) in the ^{1}H-nmr spectra. Addition of a few drops of CF_3CO_2D to the solution of (3a,b) and (6) in $CDCl_3$ (0.4 ml) caused the chemical shifts to more significantly downfield (0.30∿1.18 ppm)(Table 1). This behavior is compatible with the formation of the corresponding cyclazinylium ions (3A) and (6A) in the acidic media.

Table 1. The ^{1}H-nmr spectra for (3a,b) and (6) (200 MHz)

Compd.	Solvent	Chemical shifts (δ) H-4	H-5	H-6	H-7	H-8	Coupling constants (Hz) $J_{6,7}$	$J_{6,8}$	$J_{7,8}$
(3a)	$CDCl_3$	7.30 (s)	——	7.8∿7.85 (m)	7.8∿7.85 (m)	8.8∿8.9 (m)	—	—	—
	+CF_3CO_2D[a]	8.12 (s)	——	8.54 (d)	8.40 (t)	9.20 (d)	8	∿0	8
the difference		-0.82	——	-0.74∿-0.69	-0.60∿-0.55	-0.40∿-0.30			
(3b)	$CDCl_3$	7.34[b] (d)	7.96[b] (d)	7.8∿7.85 (m)	7.8∿7.85 (m)	8.75∿8.8 (m)	—	—	—
	+CF_3CO_2D[a]	8.40[b] (d)	9.00[b] (d)	8.98 (d)	8.72 (t)	9.18 (d)	8	∿0	8
the difference		-1.06	-1.04	-1.18∿-1.13	-0.92∿-0.87	-0.43∿-0.38			
(6)	$CDCl_3$	6.93 (s)	——	8.54 (dd)	7.91 (dd)	8.83 (dd)	8	1	9
	+CF_3CO_2D[a]	7.97 (s)	——	9.14 (d)	8.55 (t)	9.34 (d)	8	∿0	8
the difference		-1.04	——	-0.60	-0.64	-0.51			

[a] A few drops of CF_3CO_2D were added to the $CDCl_3$ solution (0.4 ml).

[b] $J_{4,5}$ = 10 Hz.

EXPERIMENTAL

^{1}H-Nmr spectra were determined with a JEOL FX200 spectrometer (200 MHz; $SiMe_4$ as internal standard). Ir spectra were recorded with a Hitachi EPI-G2 spectro-

photometer. Uv spectra were recorded with a Hitachi spectrophotometer 323-S. All melting points were uncorrected.

N-Acetonyl-2-benzoylpyridinium Bromide (1a).

A mixture of 2-benzoylpyridine (1.50 g, 8.2 mmol) and bromoacetone (5.55 g, 40.5 mmol) was heated at 75°C for 3 h and left at room temperature overnight. Ether was added to the reaction mixture, and the precipitated solid was collected and washed with ether to give (1a)(1.90 g, 73%), mp 165-166°C (from 2-propanol); ir (Nujol): 1725, 1660 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 2.44 (3H, s, $COCH_3$), 6.65 (2H, s, NCH_2COCH_3), 7.6-7.7, 7.7-7.9, and 7.95-8.1 (2H, 1H, and 2H, respectively, m, C_6H_5), 8.08 (1H, dd, J=8, 2 Hz, H-3), 8.50 (1H, ddd, J=8, 6, 2 Hz, H-5), 8.88 (1H, br t, J=8 Hz, H-4), and 10.34 (1H, br d, J=6 Hz, H-6). Anal. Calcd for $C_{15}H_{14}BrNO_2$: C, 56.27; H, 4.41; N, 4.37. Found: C, 55.99; H, 4.53; N, 4.27.

Dimethyl 3-Acetyl-5-benzoylindolizine-1,2-dicarboxylate (2a).

A suspension of the pyridinium salt (1a)(320 mg, 1.0 mmol), dimethyl acetylenedicarboxylate (284 mg, 2.0 mmol), and K_2CO_3 (414 mg) in tetrahydrofuran (10 ml) was stirred at room temperature for 20 h. The inorganic salts were then filtered off and the filtrate was concentrated in vacuo. The residue was chromatographed [silica gel: benzene-ethyl acetate (5:1)] to give (2a)(244 mg, 64%), mp 170-171°C (from methanol); ir ($CHCl_3$): 1735, 1700, and 1660 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 2.36 (3H, s, $COCH_3$), 3.95 and 4.04 (2x3H, 2xs, 2x$COOCH_3$), 7.10 (1H, dd, J=7, 1.5 Hz, H-6), 7.43 (1H, dd, J=9, 7 Hz, H-7), 7.5-7.7 and 8.0-8.1 (3H and 2H, respectively, m, C_6H_5), and 8.54 (1H, dd, J=9, 1.5 Hz, H-8). Anal. Calcd for $C_{21}H_{17}NO_6$: C, 66.48; H, 4.52; N, 3.69. Found: C, 66.25; H, 4.30; N, 3.60.

Dimethyl 3-Oxo-5-phenyl-3H-pyrrolo[2,1,5-de]quinolizine-1,2-dicarboxylate (3a).

(a) With Alumina. Compound (2a)(203 mg, 0.54 mmol) was dissolved in benzene (5 ml) and the solution was transferred to the column packed with alumina (15 g, Merck aluminium oxide 1077, 70-230 mesh) which was premoistened with benzene. Elution with ethyl acetate-methanol (10:1) gave (3a)(119 mg, 62%), 252-257°C (from benzene); ir ($CHCl_3$): 1740, 1710, and 1615 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 4.00 and 4.12 (2x3H, 2xs, 2x$COOCH_3$), 7.30 (1H, s, H-4), 7.5-7.65 (5H, m, C_6H_5), 7.8-7.85 (2H, m, H-6 and H-7), and 8.8-8.9 (1H, m, H-8); uv λ_{max}^{EtOH}: 255 nm (log ε 4.27), 273 (4.33), 283 (4.32), 307sh (3.71), 318 (3.67), 331 (3.43), 396 (3.71), 417 (3.92), and 440 (3.94). Anal. Calcd for $C_{21}H_{15}NO_5$: C, 69.80; H, 4.18; N,

3.88. Found: C, 69.50; H, 4.03; N, 3.79.

(b) With Potassium Carbonate. A suspension of (2a)(25 mg, 0.07 mmol) and K_2CO_3 (27 mg, 0.20 mmol) in tetrahydrofuran (1 ml) was stirred for 77 h at room temperature, and then refluxed for 10 h. Inorganic salts were filtered off and the filtrate was concentrated. The residue was chromatographed [silica gel: benzene-ethyl acetate (5:1)] to give (3a)(9 mg, 38%) and the unreacted (2a)(4 mg, 16%).

Dimethyl 3-Acetyl-5-[2-(1,3-dioxolanyl)]indolizine-1,2-dicarboxylate(2b).

Using a similar procedure to that described above for the preparation of (2a), (2b)(260 mg, 75%) was obtained from (1b)(288 mg, 1.0 mmol); mp 109-110°C (from cyclohexane); ir ($CHCl_3$): 1735, 1695, and 1665 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 2.51 (3H, s, $COCH_3$), 3.6-3.7 and 3.8-4.0 (2x2H, m, OCH_2CH_2O), 3.88 and 3.99 (2x3H, 2xs, 2x$COOCH_3$), 6.32 (1H, s, OCHO), 7.3-7.35 (2H, m, H-6 and H-7), and 8.3-8.35 (1H, m, H-8). Anal. Calcd for $C_{17}H_{17}NO_7$: C, 58.79; H, 4.93; N, 4.03. Found: C, 58.59; H, 4.80; N, 4.06.

Dimethyl 3-Oxo-3H-pyrrolo[2,1,5-de]quinolizine-1,2-dicarboxylate (3b).

A solution of (2b)(58 mg, 0.17 mmol) in 10% HCl (0.2 ml) and tetrahydrofuran (2 ml) was refluxed for 2 min. The reaction mixture was neutralized with a saturated $NaHCO_3$ aqueous solution, and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and concentrated. The residue was chromatographed [silica gel: benzene-ethyl acetate (3:1)] to give unstable dimethyl 3-acetyl-5-formylindolizine-1,2-dicarboxylate (30 mg), which was used for the next reaction without further purification. Ir ($CHCl_3$): 1735, 1700, and 1640 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 2.55 (3H, s, $COCH_3$), 3.97 and 4.07 (2x3H, 2xs, 2x$COOCH_3$), 7.5-7.65 (2H, m, H-6 and H-7), 8.55-8.65 (1H, m, H-8), and 9.72 (1H, s, CHO).

The aldehyde (30 mg) was treated with alumina (5 g) as described for the preparation of (3a) to give (3b)[23 mg, 48% from (2b)], mp 229-230°C (from ethyl acetate) (lit.[2] mp 225°C); ir ($CHCl_3$): 1735, 1705, and 1620 cm^{-1}; nmr ($CDCl_3$) δ: 4.00 and 4.12 (2x3H, 2xs, 2x$COOCH_3$), 7.34 (1H, d, J=10 Hz, H-4), 7.8-7.85 (2H, m, H-6 and H-7), 7.96 (1H, d, J=10 Hz, H-5), and 8.75-8.8 (1H, m, H-8); uv λ_{max}^{EtOH} : 251 (log ε 4.43), 269 (4.51), 299 (3.50), 303 (3.49), 313 (3.60), 316 (3.60), 328 (3.58), 392sh (3.77), 412 (4.04), and 434 (4.08).

Dimethyl 5-Acetyl-3-benzoylindolizine-1,2-dicarboxylate (5) and Dimethyl 5-Oxo-3-phenyl-5H-pyrrolo[2,1,5-de]quinolizine-1,2-dicarboxylate (6).

Treatment of (4)(320 mg, 1.0 mmol) with DMAD (284 mg, 2.0 mmol) in the presence of K_2CO_3 (414 mg), as described for the preparation of (2a), gave a mixture of two products, which were separated by column chromatography [silica gel: benzene-ethyl acetate (3:1)] to give (5)(134 mg, 35%) and (6)(40 mg, 11%).

Compound (5) had mp 190-195°C (from benzene); ir ($CHCl_3$): 1735, 1700, and 1660 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 2.64 (3H, s, $COCH_3$), 3.31 and 3.89 (2x3H, 2xs, 2x$COOCH_3$), 7.35-7.45 and 7.85-7.95 (5H and 2H, respectively, m, H-6, H-7, and C_6H_5), and 8.5-8.6 (1H, m, H-8). Anal. Calcd for $C_{21}H_{17}NO_6$: C, 66.49; H, 4.52; N, 3.69. Found: C, 66.26; H, 4.34; N, 3.73.

Compound (6) had mp 168-170°C (from acetone); ir ($CHCl_3$): 1735, 1705, 1640, and 1600 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ: 3.37 and 3.91 (2x3H, 2xs, 2x$COOCH_3$), 6.93 (1H, s, H-4), 7.41 (5H, s, C_6H_5), 7.91 (1H, dd, J=9, 8 Hz, H-7), 8.54 (1H, dd, J=8, 1 Hz, H-6), and 8.83 (1H, dd, J=9, 1 Hz, H-8); uv λ_{max}^{EtOH}: 227 nm (log ε 4.34), 273 (4.29), 289 (4.29), 301 (4.31), 351 (3.42), 440 (4.07), and 465 (4.39). Anal. Calcd for $C_{21}H_{15}NO_5$: C, 69.80; H, 4.18; N, 3.88. Found: C, 69.92; H, 4.15; N, 3.95.

When the same reaction mixture of (4)(213 mg, 0.67 mmol) and DMAD (189 mg, 1.33 mmol) was stirred at room temperature for 48 h, (5)(15 mg, 6%) and (6)(154 mg, 64%) were obtained.

Dimethyl 5-Oxo-3-phenyl-5H-pyrrolo[2,1,5-de]quinolizine-1,2-dicarboxylate (6).

a) With Alumina. Compound (5)(50 mg) was treated with alumina (10 g) as described for the preparation of (3a) to give (6)(46 mg, 97%).

b) With Potassium Carbonate. A solution of (5)(25 mg) in tetrahydrofuran (1 ml) was stirred in the presence of K_2CO_3 (27 mg) for 70 h at room temperature to give a mixture of (6)(18 mg, 75%) and the unreacted (5)(6 mg, 24%).

REFERENCES AND NOTES

1. Y. Miki, N. Nishikubo, Y. Nomura, H. Kinoshita, S. Takemura, and M. Ikeda, Heterocycles, 1984, 22, 2467.
2. D. Farquhar, T. T. Gough, D. Leaver, J. F. Miller, J. W. Dick, and M. A. Jessep, J. Chem. Soc. Perkin 1, 1984, 2553, and references cited in.
3. P. A. Duke, A. Fozard, and G. Jones, J. Org. Chem., 1965, 30, 526.
4. F. Krȍhnke, H. Schnegelberger, and W. Weis, Chem. Ber., 1964, 97, 3566.

Received, 29th September, 1986