Synthesis of 2-Arylquinoline and 2-Aryl-4-quinolone Alkaloids via Diels–Alder Reaction of 1,2,3-Benzotriazine with Enamines

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Received February 22, 1999; accepted April 7, 1999

Synthesis of the 2-arylquinoline alkaloids, 2-phenylquinoline and dubamine, and the 2-arylquinolone alkaloids, 1-methyl-2-phenyl-4-quinolone, graveoline, reevesianine-A, and eduline, was accomplished by the Diels–Alder reaction of 1,2,3-benzotriazine with enamines as a key step.

Key words Diels–Alder reaction; 1,2,3-benzotriazine; quinoline alkaloid; quinolone alkaloid

Many 2-arylquinoline and 2-arylquinolone alkaloids belong to the family Rutaceae. The 2-arylquinoline alkaloids, 2-phenylquinoline (**1**)¹⁾ and dubamine (**2**)²⁾ were isolated from *Galipea longiflora* KRAUSE and *Haplophyllum dubium*, and the 2-arylquinolone alkaloids, 1-methyl-2-phenyl-4-quinolone (**3**)³⁾ graveoline (**4**)⁴⁾ reevesianine-A (**5**)⁵⁾ and eduline (**6**)⁶⁾ were isolated from *Balfourodendron riedelianum*, *Ruta graveolens*, *Skimmia reevesiana*, and *Casimiroa dulis* and *Skimmia japonica* THUNB, respectively. These alkaloids have similar antibacterial and other biological activities due to the close structural relationship with 2-[(*E*)-2-heptenyl]-3-methyl-4-quinolone (**7**)⁷⁾ and 2-*n*-pentylquinoline (**8**)⁸⁾. To investigate the pharmacological activity of these alkaloids and identify the modifications needed to optimize their activity, it was necessary to develop a general synthetic route for these compounds. Synthesis of these alkaloids has been achieved by several groups⁹⁾ as well as ourselves.¹⁰⁾ We have already reported that 1,2,3-benzotriazine undergoes an inverse-electron-demand Diels–Alder reaction with ketone pyrrolidine enamines to afford 2-substituted quinolines.¹¹⁾ In this paper, we describe the synthesis of these alkaloids (**1**–**6**) by the Diels–Alder reaction of 1,2,3-benzo-

triazine with enamines as a key reaction.

A mixture of 1,2,3-benzotriazine (**10a**),¹²⁾ prepared by oxidation of 1-amino-1*H*-indazole (**9a**) with lead tetraacetate, and the pyrrolidine enamine of acetophenone (**11a**) in dry chloroform, in the presence of zinc bromide, was heated in a sealed glass tube at about 100 °C for 2 h to give 2-

Chart 1

Chart 2

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phenylquinoline (**1**) in 45% yield from **9a**. 1,2,3-Benzotriazine is difficult to isolate in good yield, and so it was used without purification. Methylation of **1** with methyl trifluoromethanesulfonate followed by oxidation with potassium ferricyanide gave 1-methyl-2-phenyl-4-quinolone (**3**) in 42% yield.¹⁰ Melting points and the spectroscopic properties of **1** and **3** agreed with those described in references 1 and 3, respectively.

The Diels–Alder reaction of 3,4-methylenedioxyacetophenone enamine (**11b**) with **10a** gave 2-(3,4-methylenedioxyphenyl)quinoline (dubamine) (**2**) in 42% yield from **9a**. Methylation of **2**, followed by oxidation, gave graveoline (**4**) in 40% yield. The Diels–Alder reaction of 4-methoxyacetophenone enamine (**11c**) and **10a** gave 2-(4-methoxyphenyl)quinoline (**12**) in 50% yield from **9a**, and methylation of **12** followed by oxidation and *O*-demethylation gave reevesianine-A (**5**) in 15% yield from **12**. In the same manner, eduline (**6**) was produced from **13** (prepared from **11a** and **10b** in 69% yield from 1-amino-5-methoxy-1*H*-indazole (**9b**)). Melting points and the spectroscopic properties of **2**, **4**, **5**, and **6** agreed with those described in references 2, 4, 5, and 6, respectively.

Experimental

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. ¹H-NMR spectra were determined in CDCl₃ with Me₄Si as an internal reference on a NEVA NV-21 instrument. Mass spectra were recorded on a JEOL JMS-OISG spectrometer. Infrared (IR) spectra were measured on a Perkin Elmer 1650 FT-IR spectrophotometer. Preparative thin-layer chromatography (PTLC) was carried out on Kieselgel 60F₂₅₄ plates (Merck) with appropriate solvents.

1-Amino-5-methoxy-1*H*-indazole (9b**)** Hydroxylamine-*O*-sulfonic acid (0.5 g) was added in portions to a suspension of 5-methoxy-1*H*-indazole¹³ (300 mg) in 15% NaOH (10 ml). After stirring the mixture for 1 h at 55 °C, it was extracted with CHCl₃. The extract was washed with water and dried over MgSO₄. After removal of CHCl₃, the residue was purified by PTLC on silica gel (CHCl₃:MeOH=50:1) to give aminoindazole as crystals. Yield: 42%. mp 136–138 °C (MeOH). IR (CHCl₃) cm⁻¹: 3367, 1616, 1509. ¹H-NMR (CDCl₃) δ: 3.83 (3H, s, OCH₃), 5.28 (2H, s, NH₂), 6.97 (1H, d, *J*=2 Hz, 4-H), 7.06 (1H, dd, *J*=9, 2 Hz, 6-H), 7.46 (1H, d, *J*=9 Hz, 7-H), 7.73 (1H, s, 3-H). HR-MS *m/z*: 163.0736 (M⁺, Calcd for C₈H₉N₃O: 163.0745).

General Method for the Diels–Alder Reaction of 1,2,3-Benzotriazine (10a**, **b**) with Enamines** A mixture of freshly prepared enamine **11a** (or **11b**, **c**) (1.3 eq) and 1,2,3-benzotriazine (**10a**) (or **10b**) (without purification) (prepared from **9a** (or **9b**) (100 mg)) in dry CHCl₃ (2 ml) was heated in a sealed glass tube at 90–100 °C for 2 h in the presence of zinc bromide (1.2 eq).¹¹ The solvent was evaporated *in vacuo*, and the residue was chromatographed on silica gel using C₆H₆ and CHCl₃ (1:1) as the eluent. The crude product was purified by PTLC on silica gel (CHCl₃:MeOH=50:1) to give the corresponding quinoline derivatives as an oil or crystals.

2-Phenylquinoline (1**):** Yield: 45% (from **9a**). mp 84–85 °C (MeOH) (Ref. 1), 84 °C. IR (CHCl₃) cm⁻¹: 1600. ¹H-NMR (CDCl₃) δ: 7.42–7.64 (4H, m, 6, 3', 4', 5'-H), 7.71 (1H, dd, *J*=7, 2 Hz, 7-H), 7.80 (1H, d, *J*=8 Hz, 5-H), 7.85 (1H, d, *J*=8.5 Hz, 3-H), 8.16–8.32 (4H, m, 4, 8, 2', 6'-H). HR-MS *m/z*: 205.0885 (M⁺, Calcd for C₁₅H₁₁N: 205.0890).

Dubamine (2**):** Yield: 42% (from **9a**). mp 93 °C (MeOH) (Ref. 2), 95–96 °C. IR (CHCl₃) cm⁻¹: 1600. ¹H-NMR (CDCl₃) δ: 6.06 (2H, s, CH₂), 6.98 (1H, d, *J*=8 Hz, 3 or 5'-H), 7.48–7.88 (6H, m, aromatic-H), 8.19 (2H, t-like, *J*=8.7 Hz, 4, 8-H). HR-MS *m/z*: 249.0781 (M⁺, Calcd for C₁₆H₁₁NO₂: 249.0788).

2-(4-Methoxyphenyl)quinoline (12**):** Oil. Yield: 50% (from **9a**). IR (CHCl₃) cm⁻¹: 1600, 1500. ¹H-NMR (CDCl₃) δ: 3.91 (3H, s, CH₃), 7.09 (2H, d, *J*=9 Hz, 3', 5'-H), 7.54 (1H, d, *J*=8 Hz, 3-H), 7.80 (3H, m, 5, 6, 7-H), 8.18 (4H, m, 4, 8, 2', 6'-H). HR-MS *m/z*: 235.1003 (M⁺, Calcd for C₁₆H₁₃NO: 235.0997).

2-Methoxy-6-phenylquinoline (13**):** Oil. Yield: 69% (from **9b**). IR (CHCl₃) cm⁻¹: 1596. ¹H-NMR (CDCl₃) δ: 3.96 (3H, s, OCH₃), 7.15 (1H, d, *J*=2 Hz, 5-H), 7.41–7.62 (5H, m, aromatic-H), 7.89 (1H, d, *J*=8.5 Hz, 4-H),

8.08–8.21 (3H, m, 8, 2', 6'-H). HR-MS *m/z*: 235.1016 (M⁺, Calcd for C₁₆H₁₃NO: 235.0997).

General Method for the Synthesis of *N*-Methyl-4-quinolone A mixture of quinoline (100 mg) and methyl trifluoromethane sulfonate (150 mg) was warmed at 50 °C for 1 h. After removal of the methyl trifluoromethane sulfonate, the residue was added to a suspension of K₃Fe(CN)₆ (260 mg) in 20% NaOH (10 ml) and stirred at room temperature for 2 h. The mixture was extracted with AcOEt, and the extract was washed with brine and dried over MgSO₄. After removal of AcOEt, the residue was purified by PTLC on silica gel (CHCl₃:MeOH=50:1) to give quinolone as crystals.

1-Methyl-2-phenyl-4-quinolone (3**):** Yield: 32%. mp 143–145 °C (MeOH) (Ref. 3), 143.5–144.5 °C. IR (CHCl₃) cm⁻¹: 1620, 1600. ¹H-NMR (CDCl₃) δ: 3.63 (3H, s, CH₃), 6.34 (1H, s, 3-H), 7.44–7.54 (7H, m, aromatic-H), 7.73 (1H, d, *J*=8 Hz, 8-H), 8.54 (1H, d, *J*=8 Hz, 5-H). HR-MS *m/z*: 235.0996 (M⁺, Calcd for C₁₆H₁₃NO: 235.0997).

Graveoline (4**):** Yield: 40%. mp 203–205 °C (MeOH) (Ref. 4), 204–205 °C. IR (CHCl₃) cm⁻¹: 1620, 1600. ¹H-NMR (CDCl₃) δ: 3.64 (3H, s, CH₃), 6.07 (2H, s, CH₂), 6.30 (1H, s, 3-H), 6.88 (2H, d-like, *J*=7 Hz, 5', 6'-H), 6.91 (1H, d, *J*=1 Hz, 2'-H), 7.43 (1H, t-like, *J*=7 Hz, 6-H), 7.55 (1H, d, *J*=8.4 Hz, 8-H), 7.72 (1H, t-like, *J*=7 Hz, 7-H), 8.50 (1H, d, *J*=8 Hz, 5-H). HR-MS *m/z*: 279.0926 (M⁺, Calcd for C₁₇H₁₃NO₂: 279.0895).

2-(4-Methoxyphenyl)-1-methyl-4-quinolone (14**):** Oil. Yield: 25%. IR (CHCl₃) cm⁻¹: 1630, 1610, 1580. ¹H-NMR (CDCl₃) δ: 3.60 (3H, s, NCH₃), 3.85 (3H, s, OCH₃), 6.29 (1H, s, 3-H), 6.99 (2H, d, *J*=8.5 Hz, 3', 5'-H), 7.33 (2H, d, *J*=8.5 Hz, 2', 6'-H), 7.42 (1H, td, *J*=8, 2 Hz, 6 or 7-H), 7.54 (1H, dd, *J*=8, 2 Hz, 8-H), 7.70 (1H, td, *J*=8, 2 Hz, 7 or 6-H), 8.50 (1H, dd, *J*=8, 2 Hz, 5-H). HR-MS *m/z*: 265.1102 (M⁺, Calcd for C₁₇H₁₅NO₂: 265.1101).

Reevesianine-A (5**)** To a stirred solution of **14** (50 mg) in CH₂Cl₂ (10 ml) borontribromide (0.1 ml) was slowly added at –10 °C. The mixture was allowed to stand at room temperature for 5 h, then diluted with water. It was then extracted with CHCl₃, and the extract was washed and dried over MgSO₄. The solvent was evaporated *in vacuo*, and the residue was purified by PTLC on silica gel (CHCl₃:MeOH=100:3) to give **5** as crystals in 60% yield. mp 322–324 °C (MeOH) (Ref. 5), 322–326 °C. IR (CHCl₃) cm⁻¹: 3420, 1620, 1600, 1580, 1550. ¹H-NMR (CDCl₃) δ: 3.74 (3H, s, CH₃), 6.38 (1H, s, 3-H), 6.99 (2H, d, *J*=9 Hz, 3', 5'-H), 7.26 (2H, d, *J*=9 Hz, 2', 6'-H), 7.50 (1H, td, *J*=8, 2 Hz, 6 or 7-H), 7.64 (1H, dd, *J*=8, 2 Hz, 8-H), 7.79 (1H, td, *J*=8, 2 Hz, 7 or 6-H), 8.51 (1H, dd, *J*=8, 2 Hz, 5-H). HR-MS *m/z*: 251.0947 (M⁺, Calcd for C₁₆H₁₃NO₂: 251.0945).

Edule (6**):** Yield: 19%. mp 182–184 °C (MeOH) (Ref. 6), 183–186 °C. IR (CHCl₃) cm⁻¹: 1623. ¹H-NMR (CDCl₃) δ: 3.62 (3H, s, NCH₃), 3.96 (3H, s, OCH₃), 6.29 (1H, s, 3-H), 7.35–7.54 (7H, m, aromatic-H), 7.91 (1H, d, *J*=2 Hz, 5-H). HR-MS *m/z*: 265.1124 (M⁺, Calcd for C₁₇H₁₅NO₂: 265.1101).

References

- 1) Fournet A., Vagneur B., Richomme P., Bruneton J., *Can. J. Chem.*, **67**, 2116–2118 (1989).
- 2) Sidiyakina G. P., Pastukhova V. I., Yunusov S. Yu., *Uzbeksk. Khim. Zh.*, **6**, 56–59 (1962) [*Chem. Abstr.*, **58**, 4608g (1963)].
- 3) Rapaport H., Holden V. I., *J. Am. Chem. Soc.*, **82**, 4395–4404 (1960).
- 4) Arthur H. R., Cheung H. T., *Aust. J. Chem.*, **13**, 510–513 (1960).
- 5) Wu T. S., *Phytochemistry*, **26**, 873–875 (1987).
- 6) Kinel F. A., Romo J., Rosenkranz G., Sondheimer F., *J. Chem. Soc.*, **1956**, 4163–4169; Boyd D. R., Grundon M. F., *ibid.*, **1970**, 556–558.
- 7) Moon S. S., Kang P. M., Park K. S., Kim C. H., *Phytochemistry*, **42**, 365–368 (1996).
- 8) Vieira P. C., Kubo I., *Phytochemistry*, **29**, 813–815 (1990).
- 9) Ishikura M., Oda I., Terashima M., *Heterocycles*, **23**, 2375–2386 (1985); Kametani T., Takeda H., Suzuki Y., Kasai H., Honda H., *ibid.*, **24**, 3385–3395 (1986); Echavarren A. M., Stille J. K., *J. Am. Chem. Soc.*, **109**, 5478–5486 (1987); Coppola G. M., *J. Heterocycl. Chem.*, **19**, 727–731 (1982); Arthur H. R., Loh L. Y. S., *J. Chem. Soc.*, **1961**, 4360–4361.
- 10) Koyama J., Ogura T., Tagahara K., Irie H., *Chem. Express*, **6**, 197–200 (1991); Koyama J., Ogura T., Okatani T., Tagahara K., *ibid.*, **7**, 321–324 (1992).
- 11) Koyama J., Toyokuni I., Tagahara K., *Chem. Pharm. Bull.*, **46**, 332–334 (1998).
- 12) Adger B. M., Bradbury S., Keating M., Rees C. W., Storr R. C., Williams M. T., *J. Chem. Soc., Perkin Trans. 1*, **1975**, 31–40.
- 13) Ruchardt C., Hassmann V., *Justus Liebig's Ann. Chem.*, **1980**, 908–927.