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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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 *Haplophylum dubuim*, 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 *Casimiroae dulis* and *Skimmia japonica* THUNB, respectively. These alkaloids have similar antibacterial and other biological activities due to the close structual 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 groups[9] 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-benzotriazine 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-

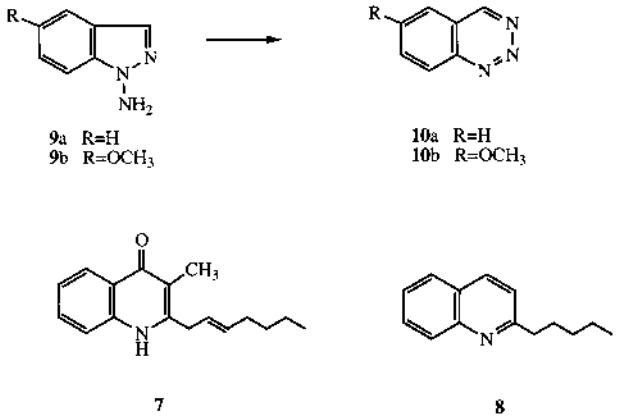

Chart 1

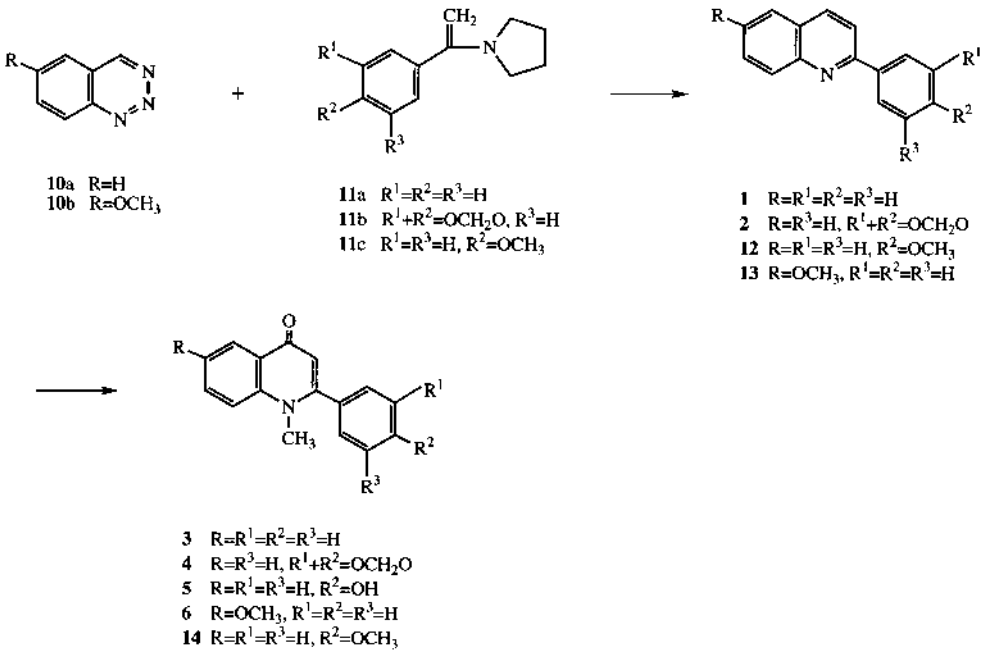

Chart 2

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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. ^{1}H-NMR spectra were determined in $CDCl_3$ with Me_4Si as an internal reference on a NEVA NV-21 instrument. Mass spectra were recorded on a JEOL JMS-O1SG spectrometer. Infrared (IR) spectra were measured on a Perkin Elmer 1650 FT-IR spectrophotometer. Preparative thin-layer chromatography (PTLC) was carried out on Kieselgel $60F_{254}$ 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*-indazole[13] (300 mg) in 15% NaOH (10 ml). After stirring the mixture for 1 h at 55 °C, it was extracted with $CHCl_3$. The extract was washed with water and dried over $MgSO_4$. After removal of $CHCl_3$, the residue was purified by PTLC on silica gel ($CHCl_3$: MeOH=50 : 1) to give aminoindazole as crystals. Yield: 42%. mp 136—138 °C (MeOH). IR ($CHCl_3$) cm^{-1}: 3367, 1616, 1509. ^{1}H-NMR ($CDCl_3$) δ: 3.83 (3H, s, OCH_3), 5.28 (2H, s, NH_2), 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 $C_8H_9N_3O$: 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 $CHCl_3$ (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 C_6H_6 and $CHCl_3$ (1 : 1) as the eluent. The crude product was purified by PTLC on silica gel ($CHCl_3$: 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 ($CHCl_3$) cm^{-1}: 1600. ^{1}H-NMR ($CDCl_3$) 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 $C_{15}H_{11}N$: 205.0890).

Dubamine (**2**): Yield: 42% (from **9a**). mp 93 °C (MeOH) (Ref. 2), 95—96 °C). IR ($CHCl_3$) cm^{-1}: 1600. ^{1}H-NMR ($CDCl_3$) δ: 6.06 (2H, s, CH_2), 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 $C_{16}H_{11}NO_2$: 249.0788).

2-(4-Methoxyphenyl)quinoline (**12**): Oil. Yield: 50% (from **9a**). IR ($CHCl_3$) cm^{-1}: 1600, 1500. ^{1}H-NMR ($CDCl_3$) δ: 3.91 (3H, s, CH_3), 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 $C_{16}H_{13}NO$: 235.0997)

2-Methoxy-6-phenylquinoline (**13**): Oil. Yield: 69% (from **9b**). IR ($CHCl_3$) cm^{-1}: 1596. ^{1}H-NMR ($CDCl_3$) δ: 3.96 (3H, s, OCH_3), 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 $C_{16}H_{13}NO$: 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 $K_3Fe(CN)_6$ (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 $MgSO_4$. After removal of AcOEt, the residue was purified by PTLC on silica gel ($CHCl_3$: 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 ($CHCl_3$) cm^{-1}: 1620, 1600. ^{1}H-NMR ($CDCl_3$) δ: 3.63 (3H, s, CH_3), 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 $C_{16}H_{13}NO$: 235.0997).

Graveoline (**4**): Yield: 40%. mp 203—205 °C (MeOH) (Ref. 4), 204—205 °C). IR ($CHCl_3$) cm^{-1}: 1620, 1600. ^{1}H-NMR ($CDCl_3$) δ: 3.64 (3H, s, CH_3), 6.07 (2H, s, CH_2), 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 $C_{17}H_{13}NO_3$: 279.0895).

2-(4-Methoxyphenyl)-1-methyl-4-quinolone (**14**): Oil. Yield: 25%. IR ($CHCl_3$) cm^{-1}: 1630, 1610, 1580. ^{1}H-NMR ($CDCl_3$) δ: 3.60 (3H, s, NCH_3), 3.85 (3H, s, OCH_3), 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 $C_{17}H_{15}NO_2$: 265.1101).

Reevesianine-A (5) To a stirred solution of **14** (50 mg) in CH_2Cl_2 (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 $CHCl_3$, and the extract was washed and dried over $MgSO_4$. The solvent was evaporated *in vacuo*, and the residue was purified by PTLC on silica gel ($CHCl_3$: MeOH=100 : 3) to give **5** as crystals in 60% yield. mp 322—324 °C (MeOH) (Ref. 5), 322—326 °C). IR ($CHCl_3$) cm^{-1}: 3420, 1620, 1600, 1580, 1550. ^{1}H-NMR ($CDCl_3$) δ: 3.74 (3H, s, CH_3), 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 $C_{16}H_{13}NO_2$: 251.0945).

Eduline (**6**): Yield: 19%. mp 182—184 °C (MeOH) (Ref. 6), 183—186 °C). IR ($CHCl_3$) cm^{-1}: 1623. ^{1}H-NMR ($CDCl_3$) δ: 3.62 (3H, s, NCH_3), 3.96 (3H, s, OCH_3), 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 $C_{17}H_{15}NO_2$: 265.1101).

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