15 mL of methylene chloride was stirred at room temperature for 12 h. The solution was washed with 10 mL of 20% aqueous acetic acid and then twice with saturated aqueous sodium bicarbonate. Evaporation of the solvent followed by medium-pressure chromatography (30% ethyl acetate/hexanes) yielded 0.92 g (57%) of pure **4**: IR (film) 2860–2950, 1710, 1545, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.49 (sept, 1 H), 3.92 (s, 4 H), 2.45 (t, J = 7 Hz, 2 H), 2.41 (t, J = 7 Hz, 2 H), 1.26–2.18 (m, 16 H), 0.95 (t, J = 7 Hz, 3 H), 0.93 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.6 111.4, 88.0, 64.9 (2 C), 42.8, 39.3, 38.0, 36.1, 33.6, 27.8, 27.4, 22.0, 18.1, 17.1, 14.3, 13.6; HRMS, m/z 286.1647 (calcd for $C_{14}H_{24}NO_5$ ($M^+ - C_3H_7$), m/z 286.1655).

(*Z*)-2-Butyl-5-[3-(2-propyl-1,3-dioxolanyl)propyl]-pyrrolidine (5). A mixture of nitro ketone **4** (0.91 g, 2.77 mmol), 10% Pd on charcoal (0.39 g), and 0.72 g of anhydrous sodium sulfate in 20 mL of anhydrous methanol was hydrogenated at 45 psi for 72 h by using a Parr apparatus. The solution was filtered through Celite and concentrated to give 0.68 g of a yellow oil (86%), which upon addition of ethyl ether yielded 0.13 g (17%) of pyrrolidine **5** as a powdery white solid (mp 114–116 °C). The remaining oil was treated with anhydrous oxalic acid (0.21 g, 2.33 mmol) in 2 mL of ethyl ether to give 0.43 g (42%) of the corresponding oxalate salt (mp 156–158 °C): IR (KBr) 2850, 2780, 2740, 1462, 1197, 1140, 1088, 1058 cm^{-1}; ^1H NMR (acetone-d_6) δ 3.86 (s, 4 H), 3.35–3.39 (m, 2 H), 2.10 (sext, 2 H), 1.44–1.60 (m, 11 H), 1.12–1.34 (m, 9 H), 0.74 (t, J = 7 Hz, 3 H), 0.73 (t, J = 7 Hz, 3 H); ^{13}C NMR (D_2O) δ 112.1, 64.6 (2 C), 60.8, 60.4, 38.4, 35.5, 32.0, 31.6, 28.5, 28.3, 28.1, 21.7, 20.5, 16.7, 13.6, 13.1; HRMS, m/z 240.1945 (calcd for $C_{14}H_{26}NO_2$ ($M^+ - C_3H_7$), m/z 240.1964).

(5*Z*,9*Z*)-3-Butyl-5-propylindolizidine (1c), Isomer of Gephyrotoxin 223AB. A solution of **5** (0.432 g, 1.16 mmol) in 3.0 mL of water, 0.7 mL of 2 N hydrochloric acid, and 0.7 mL of THF were stirred at room temperature for 12 h. The mixture was then basified by the dropwise addition of a 10% aqueous potassium hydroxide solution and extracted three times with methylene chloride. The organic extracts were dried over sodium sulfate and concentrated to give 0.25 g of the unstable enamine **7** as a yellow oil (IR absorption at 1635 cm^{-1}).

The crude enamine was dissolved in 1.5 mL of THF and 0.4 mL of dry methanol, then treated with sodium cyanoborohydride (0.07 g, 1.11 mmol) and a trace of bromocresol green indicator. Methanolic hydrochloric acid was added dropwise until a pale yellow color persisted for 15 min. After the mixture was stirred at room temperature for an additional 2.5 h, 3 mL of 1 N sodium hydroxide was added, and the mixture was extracted three times with ether. The combined organic extracts were dried over sodium sulfate and concentrated. Chromatography on neutral aluminum oxide using ethyl acetate as eluant yielded 0.16 g (62% from the oxalate salt of **5**) of pure gephyrotoxin 223AB (**1c**) as a colorless oil: IR (film) 2945, 2915, 2855, 1785, 2715, 2580, 1465, 1457, 1377, 1120 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (t, J = 9 Hz, 1 H), 2.13–2.36 (m, 2 H), 1.14–1.85 (m, 20 H), 0.99 (t, J = 7 Hz, 3 H), 0.98 (t, J = 7 Hz, 3 H); ^{13}C NMR (C_6D_6) δ 67.8, 65.1, 61.9, 39.7, 38.3, 32.3, 31.5, 31.0, 29.9, 29.1, 25.5, 23.4, 19.5, 14.7, 14.4; HRMS, m/z 223.2301 (calcd for $C_{15}H_{29}N$, m/z 223.2301).

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Supplementary Material Available: Experimental details and characterization of compound **1b**, (5*E*,9*Z*)-GTX223AB (5 pages). Ordering information is given on any current masthead page.

Total Syntheses of Vasicoline and Vasicolinone

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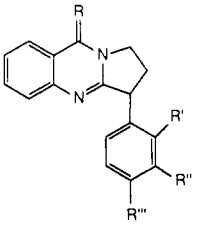
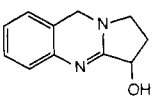
Bis-ortho-nitration of α-phenyl-*N*-(phenylmethyl)-γ-butanelactam (**6**) using acetyl nitrate followed by reduction and regiospecific dehydrative cyclization afforded quinazoline **12**. The aniline moiety in **12** could be dimethylated by using aqueous formaldehyde and $KHFe(CO)_4$, affording vasicoline (**1**) in high yield. Compound **1** could be oxidized to vasicolinone (**2**) upon exposure to air.

In 1971 three new quinazoline alkaloids, vasicoline (**1**), vasicolinone (**2**), and adhatodine (**3**), were isolated from the leaves of the Indian plants of *Adhatoda vasica* Nees (Acanthaceae).[1] The plant extracts were also found to contain the closely related compounds anisotine (**4**) and vasicine (**5**). Syntheses of various pyrrolidinoquinazolines have been developed due to the interest in the bronchodilatory activity of vasicine.[2,3] We now report a synthesis of vasicolinone[4] and the first total synthesis of vasicoline.

The key dihydroquinazoline **12** was envisaged as arising from the selective cyclization of the bis(*o*-aminophenyl) lactam **11**, which in turn would result from reduction of the bis(*o*-nitrophenyl) lactam **7**. We therefore sought conditions which would lead to selective ortho-nitration of a substrate such as **6**.



1 R = H_2 R' = $N(CH_3)_2$ R'' = H R''' = H
2 R = O R' = $N(CH_3)_2$ R'' = H R''' = H
3 R = H_2 R' = H R'' = $COOCH_3$ R''' = $NHCH_3$
4 R = O R' = H R'' = $COOCH_3$ R''' = $NHCH_3$



5

N-benzylpyrrolidone **6** was synthesized in large quantities following the procedure of Gittos and Wilson.[5]

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† Deceased March 9, 1984.

(1) Johne, S.; Groger, D.; Hesse, M. *Helv. Chim. Acta* **1971**, *54*, 826.
(2) Cambridge, J. W.; Hensen, A. B. A.; Jarman, D. A. *Nature (London)* **1962**, *196*, 1217.

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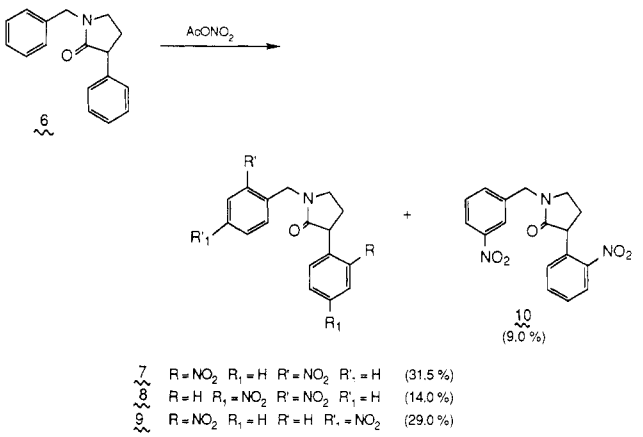
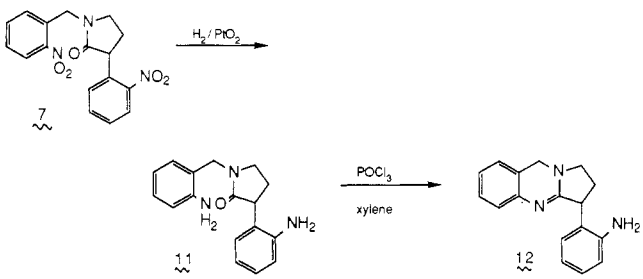
Nitration of the pyrrolidine was performed by using a modification of Nozoye's nitration of α-phenyl-γ-butyrolactone[6] which involved mixing 70% nitric acid in acetic anhydride at −5 °C. However, these conditions do not generate a high concentration of the desired reagent (acetyl nitrate).[7] Thus, acetyl nitrate was generated at room temperature, and 20 equiv was added to a solution of **6** in dichloromethane at −23 °C. The optimized yield of the desired bis-ortho-nitrated lactam **7** was 31.5% and products of nitration at other positions were also observed.



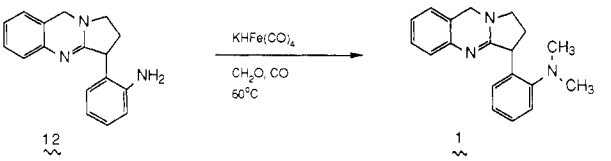
7 R = NO_2, R_1 = H, R' = NO_2, R'$_1$ = H (31.5 %)
8 R = H, R_1 = NO_2, R' = NO_2, R'$_1$ = H (14.0 %)
9 R = NO_2, R_1 = H, R' = H, R'$_1$ = NO_2 (29.0 %)

Reduction of both nitro groups to give the bis(*o*-aminophenyl) compound **11** was achieved in high yield by hydrogenation using platinum oxide as catalyst. A variety of conditions were examined for the cyclization of **11** to the pyrrolidinoquinazoline **12**.[8] Use of phosphorus pentachloride in a number of solvents ($CHCl_3$, benzene, toluene)[9] resulted in recovery of starting material, as did attempts to induce cyclization by azeotropic removal of water. Compound **11** was heated in aqueous as well as glacial acetic acid following a procedure described by Southwick and Cassanova,[10] but these methods were also unsuccessful. Finally it was discovered that amidine formation did occur by refluxing purified **11** in a solution of xylene and phosphorus oxychloride for 3 h.



Following basic workup, the aqueous portion was acidified with concentrated hydrochloric acid, refluxed overnight, and extracted with ethyl acetate to afford the cyclized product **12**. It is believed that phosphoramidate formation (from reaction of the free amino group with phosphorus oxychloride followed by hydrolysis) prevents the cyclized material from being soluble in the organic phase under basic conditions; therefore hydrolysis with acid is necessary to isolate the desired compound.[11]

In principle, either amino group could have cyclized onto the lactam carbonyl. It was apparent from the ^1H and ^{13}C NMR spectra that only one isomer had been formed, and the compound obtained exhibited amidine IR absorptions very similar to those reported for vasicoline (1623, 1596, and 1575 cm^{-1}).[1] Eventual conversion of the cyclization product into **1** demonstrated that the desired mode of cyclization to **12** had occurred.



Dimethylation of anilines cannot be effected by Leuckart-type methods because of activation of the aromatic ring by the amino moiety.[12] It is known that anilines can be smoothly methylated by using formaldehyde and sodium cyanoborohydride,[4,13,14] but use of these reagents with **12** led to a complex mixture of products, presumably due to reduction of the amidine functionality.[15] Watanabe and co-workers have reported potassium tetracarbonylhydridoferrate ($KHFeCO_4$) as a mild source of hydride for the reductive alkylation of aromatic amines.[16] This reagent is generated from iron pentacarbonyl in ethanolic potassium hydroxide under a carbon monoxide atmosphere and, in the presence of formaldehyde and the cyclization product **12**, cleanly affords the dimethylated product **1** in nearly quantitative yield. This result is significant since reductive alkylations of this type are highly sensitive to steric effects (i.e., ortho substitution).[17] The final product was found to be identical spectroscopically to vasicoline (^1H NMR, IR, mass spectrum).[1] Of particular interest was the fragmentation pattern in the mass spectrum as vasicoline is known to undergo two interesting modes of fragmentation. Peaks corresponding to both of these rearrangement products were present in the mass spectrum of the synthetic sample.

Vasicoline was oxidized by exposure to air to vasicolinone (**2**) over a period of 3 days. The original proton NMR spectrum of vasicolinone was kindly provided by Dr. S. Johne[18] and found to be identical with that of the syn-

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(13) Lane, C. F. *Aldrichimica Acta* **1975**, *8*, 3.

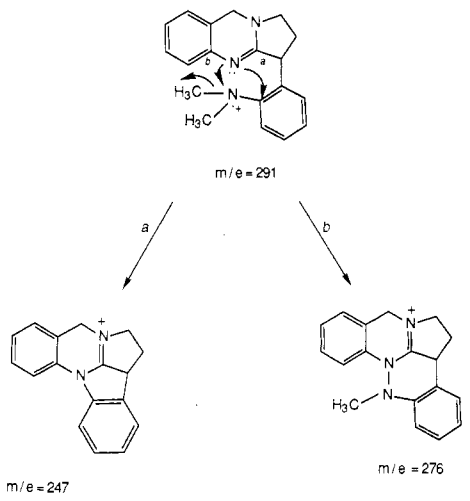
(14) Use of formaldehyde and sodium cyanoborohydride has been reported to lead to successful dimethylation of the aniline moiety in the oxidized quinazoline skeleton, yielding vasicolinone: see ref 4.

(15) Reduction of the amidine was apparent from the disappearance of the absorption at 1575–1630 cm^{-1} in the infrared spectrum.

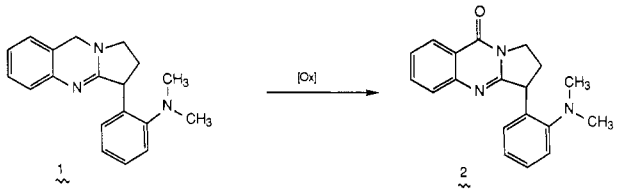
(16) (a) Takegami, Y.; Watanabe, Y.; Masada, H.; Kanaya, I. *Bull. Soc. Chem. Jpn.* **1967**, *40*, 1456. (b) Watanabe, Y.; Yamashita, M.; Mitsudo, T.; Tanaka, M.; Takegami, Y. *Tetrahedron Lett.* **1974**, 1879. (c) Watanabe, Y.; Shim, S.-C.; Mitsudo, T.; Yamashita, M.; Takegami, Y. *Bull. Soc. Chem. Jpn.* **1976**, *49*, 1378. (d) Krumholtz, P.; Stettiner, H. M. A. *J. Am. Chem. Soc.* **1949**, *71*, 3035.

(17) Benassi, R.; Folli, U.; Iarossi, D. *Synthesis* **1974**, 735.

(18) Original ^1H NMR spectra of both vasicoline and vasicolinone were kindly provided by Dr. S. Johne.



thesized material. The other physical data of our compound matched those described in the literature, thus confirming the first total synthesis of vasicoline and of vasicolinone.



Experimental Section

Infrared spectra were calibrated with the 1601-cm^{-1} absorption of polystyrene. ^1H NMR spectra were measured at 200 MHz with tetramethylsilane (0.00 ppm) or chloroform (7.26 ppm) as an internal standard. ^{13}C NMR spectra were measured at 50.32 or 22.5 MHz with tetramethylsilane (0.00 ppm) or deuteriochloroform (77.0 ppm) as internal standards. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected.

Dry solvents were obtained in the following manner: tetrahydrofuran, diethyl ether, benzene, toluene, and xylene were distilled from sodium/benzophenone ketyl; methanol was distilled from magnesium methoxide; dichloromethane, diisopropylamine, triethylamine, ethanol, and acetonitrile were refluxed over calcium hydride and distilled prior to use.

Medium-pressure chromatography was performed on Altex columns packed with silica gel from E. Merck Inc. (particle size range 0.040–0.063 mm) using the solvents indicated. Baker analyzed reagent grade silica (60–200 mesh) was employed in open column chromatography. Preparative aluminum oxide plates were manufactured by Merck (aluminum oxide 150 F-254, Type T).

1-(2-Nitrobenzyl)-3-(2-nitrophenyl)pyrrolidin-2-one (7). Acetyl nitrate was generated by cautiously adding fuming nitric acid (12.03 g, 0.19 mol) to a stirring solution of acetic anhydride (19.50 g, 0.19 mol). A water bath was employed to keep the exothermic reaction at room temperature, and stirring was continued for 30 min.

1-Benzyl-3-phenylpyrrolidin-2-one (6) (2.4 g, 9.55 mmol) was dissolved in 25 mL of methylene chloride, and the resulting solution was cooled to −23 °C. Acetyl nitrate (27.1 mL, 0.19 mol) was added dropwise, and the solution was stirred at −23 °C for 2.5 h, at which point thin-layer chromatography indicated the absence of both starting material and mononitrated products. The reaction was quenched with water, followed by washing with saturated aqueous sodium bicarbonate solution until the aqueous layer was no longer acidic. The organic layer was dried over anhydrous sodium sulfate and concentrated to a viscous yellow oil (3.6 g). Half of this crude product was subjected to medium-pressure chromatography at a time, eluting with 60% ethyl acetate/hexane, to give a combined yield of 1.02 g (31.5%) of the desired bis-ortho-nitrated product 8 as the fastest eluting compound off the column: mp 126–128 °C; IR ($CHCl_3$) 3010, 1690, 1609, 1575, 1486, 1454, 1350, 1140, 1108, 1080 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02 (dd, J = 8, 1 Hz, 1 H), 7.98 (dd, J = 8, 1 Hz, 1 H), 7.36–7.71 (m, 6 H), 5.02 (d, J = 16 Hz, 1 H), 4.83 (d, J = 16 Hz, 1 H), 4.34 (t, J = 10 Hz, 1 H), 3.43–3.51 (m, 2 H), 2.67–2.82 (m, 1 H), 2.07–2.28 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 173.9, 149.6, 148.8, 134.2, 133.7, 133.5, 131.7, 131.0, 130.0, 128.6, 128.2, 125.0, 124.9, 45.5 (2 C), 44.0, 28.2; HRMS, m/z 295.1109 (calcd for $C_{17}H_{15}N_2O_3$ ($M^+ - NO_2$), m/z 295.1084).

1-(2-Nitrobenzyl)-3-(4-nitrophenyl)pyrrolidin-2-one (8). Compound 8 was eluted next and was isolated in 14% (0.47 g) yield: mp 102–104 °C; IR ($CHCl_3$) 3005, 1605, 1575, 1520, 1489, 1455, 1430, 1348, 1285, 1143, 1110, 1085, 852 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.22 (d, J = 8.5 Hz, 2 H), 8.01 (dd, J = 8, 1 Hz, 1 H), 7.64 (dd, J = 8, 8 Hz, 1 H), 7.49 (d, J = 8.5 Hz, 2 H), 7.44–7.50 (m, 2 H), 4.99 (d, J = 16 Hz, 1 H), 4.82 (d, J = 16 Hz, 1 H), 3.90 (t, J = 9 Hz, 1 H), 3.46–3.53 (virtual q, 2 H), 2.56–2.73 (m, 1 H), 2.12–2.32 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 174.1, 149.1, 147.3, 146.8, 133.9, 131.7, 130.2, 129.1 (2 C), 128.9, 125.1, 124.1 (2 C), 47.7, 45.8, 44.1, 27.8; HRMS, m/z 295.1097 (calcd for $C_{17}H_{15}N_2O_3$ ($M^+ - NO_2$), m/z 295.1084).

1-(3-Nitrobenzyl)-3-(2-nitrophenyl)pyrrolidin-2-one (10). Compound 10 was the third fastest eluting compound off the column and was isolated in 9% (0.31 g) yield: mp 94–95 °C; IR ($CHCl_3$) 3005, 1690, 1610, 1580, 1527, 1492, 1460, 1430, 1352, 1288, 1146, 1112, 1090, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.18 (br s, 2 H), 7.98 (d, J = 8 Hz, 1 H), 7.37–7.72 (m, 5 H), 4.76 (d, J = 15 Hz, 1 H), 4.55 (d, J = 15 Hz, 1 H), 4.34 (t, J = 9.6 Hz, 1 H), 3.40–3.48 (m, 2 H), 2.65–2.76 (m, 1 H), 2.12–2.27 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 173.6, 149.5, 148.5, 138.5, 134.3, 134.1, 133.6, 131.0, 128.2, 125.2, 122.9 (2 C), 46.6, 45.6, 28.0 (one carbon unresolved); HRMS, m/z 341.1013 (calcd for $C_{17}H_{15}N_3O_5$, m/z 341.1012).

1-(4-Nitrobenzyl)-3-(2-nitrophenyl)pyrrolidin-2-one (9). Compound 9 was the fourth compound off the column and was isolated in 29% (0.86 g) yield: mp 116–118 °C; IR ($CHCl_3$) 3000, 1685, 1605, 1575, 1520, 1490, 1455, 1435, 1412, 1350, 1280, 1110, 1085, 855 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.24 (d, J = 8 Hz, 2 H), 8.00 (dd, J = 8, 1 Hz, 1 H), 7.63 (ddd, J = 7.6, 7.6, 1 Hz, 1 H), 7.50 (d, J = 8.5 Hz, 2 H), 7.45–7.49 (m, 1 H), 7.38 (ddd, J = 8, 7.6, 1 Hz, 1 H), 4.78 (d, J = 15 Hz, 1 H), 4.55 (d, J = 15 Hz, 1 H), 4.32 (t, J = 10 Hz, 1 H), 3.34–3.45 (m, 2 H), 2.64–2.80 (m, 1 H), 2.01–2.28 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 173.5, 149.5, 147.6, 143.8, 134.1, 133.5, 131.0, 128.9 (2 C), 128.3, 125.2, 124.0 (2 C), 46.6, 45.7, 45.0, 27.9; HRMS, m/z 341.1007 (calcd for $C_{17}H_{15}N_3O_5$, m/z 341.1012).

1-(2-Aminobenzyl)-3-(2-aminophenyl)pyrrolidin-2-one (11). Bis(*o*-nitrophenyl)pyrrolidone 7 (0.30 g, 0.88 mmol) was dissolved in 120 mL of absolute ethanol and 0.06 g of Adam's platinum catalyst was added. This solution was hydrogenated at 47 psi for 2 h and then filtered through a pad of Celite. Removal of the solvent afforded 0.23 g (94%) of 11 as a light brown foam. This material could be further purified by preparative thin-layer chromatography (alumina) eluting with 60% ethyl acetate/hexane: IR ($CHCl_3$) 3330, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.03–7.16 (m, 4 H), 6.62–6.80 (m, 4 H), 4.41 (d, J = 15 Hz, 1 H), 4.32 (d, J = 15 Hz, 1 H), 4.00 (br s, 4 H), 3.90 (t, J = 4 Hz, 1 H), 3.42 (m, 2 H), 2.34 (virtual q, 2 H); ^{13}C NMR ($CDCl_3$) δ 175.5, 145.8, 145.6, 131.3, 129.4, 128.0, 126.9, 124.3, 119.1, 119.0, 117.3, 117.2, 115.5, 45.3, 44.7, 43.8, 24.0; HRMS, m/z 281.1526 (calcd for $C_{17}H_{19}N_3O$, m/z 281.1530).

2-(1,2,3,9-Tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)-benzenamine (12). The bis(*o*-aminophenyl)pyrrolidone 11 (0.42 g, 0.15 mmol) was purified prior to use and dissolved in 2 mL of dry xylene. Phosphorus oxychloride (1.0 mL) was added to give a fluffy white precipitate, and the reaction mixture was heated to 130 °C under a nitrogen atmosphere. The reaction was refluxed for 4 h and then distilled to remove the xylene and phosphorus oxychloride. The residual oil was treated with ice and then with ammonium hydroxide until the solution was strongly basic. This mixture was extracted once with ether and then twice with methylene chloride. The organic layers were combined and dried over anhydrous sodium sulfate and concentrated to afford the cyclized product 12 (0.036 g, 91.0%).

If a low yield was obtained by using this procedure, the aqueous layer was acidified with concentrated hydrochloric acid and refluxed for 12 h. The solution was once again made basic with ammonium hydroxide and extracted with ether and methylene chloride to give the remainder of the product: IR ($CHCl_3$) 1621,

1593, 1570 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70–7.14 (m, 8 H), 4.60 (s, 2 H), 4.47 (br s, 2 H, varies in position between 3.0 and 5.0 ppm), 4.11 (dd, J = 8 Hz, 1 H), 3.51 (ddd, J = 9.5, 8, 8 Hz, 1 H), 3.33 (ddd J = 9.5, 7, 5 Hz, 1 H), 2.36 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 163.7, 146.4, 143.1, 128.2, 127.8, 126.4, 125.7, 125.5, 124.4, 123.9, 119.3, 118.6, 117.3, 50.2, 47.3, 43.8, 25.5; HRMS, m/z 263.1422 (calcd for $C_{17}H_{17}N_3$, m/z 263.1424).

***N,N*-Dimethyl-2-(1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazolin-3-yl)benzenamine, Vasicoline (1).** The quinazoline **12** was purified prior to use by preparative thin-layer chromatography (alumina) eluting with 60% ethyl acetate/hexane. All solvents and reagents were degassed before use by bubbling argon through the solutions for several minutes.

A 1 N ethanolic potassium hydroxide solution was generated and added (0.41 mL, 0.41 mmol) to a solution of iron pentacarbonyl (0.027 g, 0.137 mmol) in 0.16 mL of ethanol in a 10-mL round-bottomed flask fitted with a rubber septum. The system was connected with a gas bubbler and carbon monoxide was introduced and maintained at a slight positive pressure. This mixture was allowed to stir for 2 h at room temperture. Formaldehyde (0.023 g, 0.301 mmol) was then introduced, followed by addition of an ethanolic solution of the quinazoline **12** (0.036 g, 0.137 mmol). The septum was replaced with a reflux condenser, and the reaction mixture was heated at 60 °C under a slightly positive pressure of carbon monoxide for 48 h. The solution was acidified with a few drops of 3 N hydrochloric acid and concentrated to give the hydrochloride salt of **1**, which was liberated after a basic workup using ammonium hydroxide. Following extraction with ether and drying over anhydrous sodium sulfate, removal of the solvent afforded 0.041 g (99%) of **1** as a light yellow oil. Due to its extreme susceptibility toward oxidation, the product was handled under a nitrogen atmosphere at all times: IR ($CHCl_3$) 3050, 2930, 2850, 2820, 2780, 1621, 1593, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.92–7.25 (m, 8 H), 4.70 (d, J = 10 Hz, 1 H), 4.62 (d, J = 10 Hz, 1 H), 4.54 (dd, J = 9, 8 Hz, 1 H), 3.36 (m, 2 H), 2.71 (s, 6 H), 2.35–2.60 (m, 1 H), 1.95 (ddd, J = 15, 13, 7.6, 1 H); ^{13}C NMR ($CDCl_3$) δ 164.9, 153.1, 143.6, 137.6, 128.9, 128.2, 127.6, 124.5, 123.7, 120.8, 119.3, 50.0, 47.6, 46.0 (2 C), 43.8, 29.8 (two carbons unresolved); HRMS, m/z 291.1730 (calcd for $C_{19}H_{21}N_3$, m/z 291.1737).

3-[2-(Dimethylamino)phenyl]-2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one, Vasicolinone (2). Vasicoline (0.030 g, 0.10 mmol) was allowed to stand in a solution of chloroform exposed to air for 3 days, at which point ^1H NMR indicated complete conversion to the oxidized product **2**. This compound could be chromatographed on silica, eluting with 40% ethyl acetate/hexane to afford 0.030 g of pure vasicolinone (95%): IR ($CHCl_3$) 1666, 1612, 1464, 1334 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.31 (d, J = 8 Hz, 1 H, (7.58–7.72 (m, 2 H), 7.43 (ddd, J = 8, 8, 1.8 Hz, 1 H), 7.27–7.31 (m, 2 H), 7.10–7.14 (m, 2 H), 5.04 (t, J = 9 Hz, 1 H), 4.42 (ddd, J = 13, 9, 4 Hz, 1 H), 4.15 (ddd, J = 13, 8, 8 Hz, 1 H) 2.71–2.86 (m, 1 H), 2.65 (s, 6 H), 2.24 (ddd, J = 18, 13, 9 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 161.7, 161.2, 153.2, 149.5, 136.7, 133.8, 129.1, 128.4, 127.2, 126.2, 126.0, 125.0, 121.6, 120.4, 46.0 (2 C), 45.6, 45.0, 29.7; HRMS, m/z 305.1550 (calcd for $C_{19}H_{19}N_3O$, m/z 305.1530).

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Registry No. (±)-**1**, 113010-09-6; (±)-**2**, 113010-10-9; (±)-**6**, 113010-11-0; (±)-**7**, 113010-12-1; (±)-**8**, 113010-13-2; (±)-**9**, 113010-14-3; (±)-**10**, 113010-15-4; (±)-**11**, 113010-16-5; (±)-**12**, 113010-17-6.

Nucleophilic Addition to Oxazolium Salts: Stabilized Azomethine Ylides via 2-Substituted 4-Oxazolines

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Treatment of oxazolium salts with cyanide generates 4-oxazolines **2** in situ. Ring opening to azomethine ylides **3** occurs spontaneously and 2 + 3 cycloadducts are obtained in the presence of acrylate, propiolate, or acetylenedicarboxylate dipolarophiles. In the case of acetylenic dipolarophiles, loss of HCN occurs under the reaction conditions and leads directly to pyrroles **5**. The propiolate experiments are complicated by the formation of six-membered adducts **17** in some cases. This reaction pathway is explained by the addition of the acetylide anion derived from propiolate to the dipole, followed by cyclization. Sulfide nucleophiles can also be used to generate 4-oxazolines, but the yields of cycloadducts are lower.

In previous papers, we have described a versatile method for carbonyl-stabilized axomethine ylide generation from oxazolium salts by the nucleophilic addition of hydride.[1] The resulting 4-oxazolines open spontaneously to ylides provided that the C_4 position is unsubstituted, and the nitrogen substituent is a relatively compact alkyl group. A useful variant of this reaction would involve addition of nucleophiles other than hydride. As an initial step toward this goal, we chose cyanide as the attacking nucleophile due to its minimal steric demands and its potential to act as a leaving group in the product pyrrolines or pyrrolidines. Cyano-stabilized azomethine ylides have

Table I

entry	R_2	R_5	product	yield, % TMSCN/CsF	yield, % Et_4NCN
a	Ph	Ph	**5a**	80	50
b	Ph	OEt	**5b**	95	
c	Ph	Me	**5c**	57	
d	Me	Ph	**5d**	16[a]	
e	Me	OEt	**5e**	74	67
f	H	Ph	**5f**	79	59
g	H	OEt	**5g**	95	

[a] 10% recovered oxazole; low material balance may be due to competing methyl deprotonation in the dipole (see ref 1).

(1) (a) Vedejs, E.; Grissom, J. W. *J. Am. Chem. Soc.* **1986**, *108*, 6433. (b) Vedejs, E.; Grissom, J. W., submitted for publication in *J. Am. Chem. Soc.* (c) Vedejs, E.; Grissom, J. W. *J. Org. Chem.*, following paper in this issue.

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