crystals: mp 173–174 °C; IR (KBr) 1680–1740 cm^{-1}; mass spectrum 496 (0.4), 105 (100); ^1H NMR δ 6.92 (1 H, s), 6.15 (1 H, ddd, J = 9.5 Hz, $J \simeq$ 2.4 Hz, $J \simeq$ 2.4 Hz), 6.01 (1 H, ddd, J = 9.5 Hz, $J \simeq$ 3.2 Hz, $J \simeq$ 3.2 Hz), 5.65 (1 H, ddd, J = 7.9 Hz, J = 5.6 Hz, J = 2.4 Hz), 4.79 (1 H, dd, J = 11.1 Hz, J = 7.1 Hz), 4.67 (1 H, dd, J = 11.1 Hz, J = 7.9 Hz), 3.86 (1 H, dd, $J \simeq$ 8.7 Hz, $J \simeq$ 8.7 Hz), 3.46 (1 H, dd, J = 9.0 Hz, J = 6.0 Hz), 2.8–2.9 (1 H, m). Anal. Calcd for $C_{29}H_{24}N_2O_6$: C, 70.15; H, 4.87; N, 5.64. Found: C, 70.40. H, 4.89; N, 5.57.

Diethyl 3-[(Carbaniloyloxy)methyl]phthalate (37b). To a stirred solution of **33b** (0.5 g, 1.55 mmol) and 10 mg of 2,6-di-*tert*-bytyl-*p*-cresol in 10 mg of dry toluene was added diethyl acetylenedicarboxylate (0.26 g, 1.55 mmol), and the mixture was refluxed under a nitrogen atmosphere for 4 days. Evaporation of the solvent gave a yellow oil. PLC of this oil afforded 0.35 g (61%) of **37b**. Recrystallization from ethanol/ethyl acetate (1:1) yielded 0.29 g (50%) of light yellow crystals: mp 105–107 °C; IR (KBr) 3420, 1720 cm^{-1}; mass spectrum 371 (20), 161 (100); ^1H NMR δ 6.94 (1 H, s), 5.25 (2 H, s), 4.41 (2 H, q, J = 7.5 Hz), 3.34 (2 H, q, J = 7.5 Hz), 1.36 (3 H, t, J = 7.5 Hz), 1.34 (3 H, t, J = 7.5 Hz). Peak matching calcd for 371.13688, found 371.13735.

Acknowledgment. Financial support from the Danish Natural Science Research Council and Thomas B. Thrige's Foundation for the purchase of the X-ray diffraction equipment is gratefully acknowledged.

A Stereospecific Total Synthesis of (3*R**,5*S**,9*S**)-Gephyrotoxin 223AB

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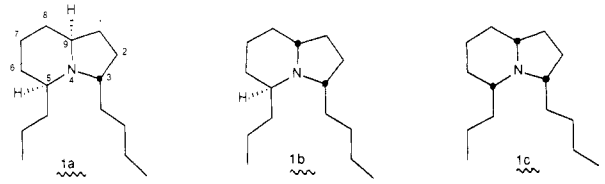
Received June 16, 1987

The title compound was synthesized stereospecifically by the nucleophilic addition of hydride ($NaCNBH_3$) to the conformationally rigid tetrahydropyridinium ion **6**. This key intermediate was obtained in six steps from the ethylene ketal of 1-chloro-4-heptanone. Biological evaluation of **1c** is also reported.

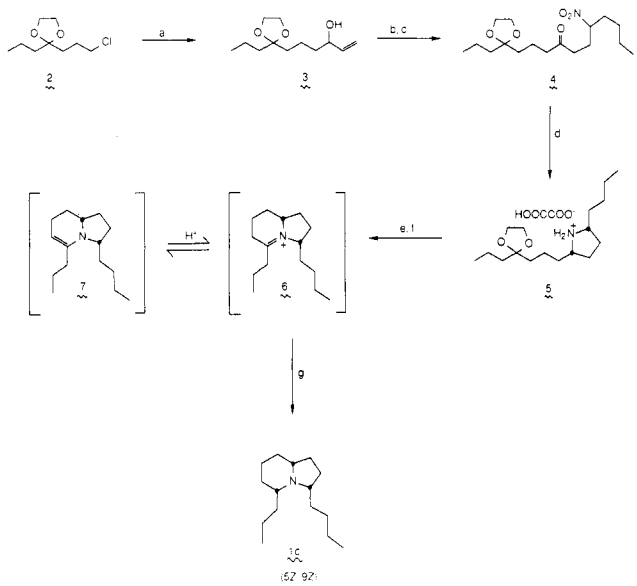
Indolizidine alkaloids isolated from the skin secretions of neotropical poison-dart frogs (family Dendrobatidae) have been the target of many synthetic efforts which have demonstrated the importance of stereoelectronic control in the design of a total synthesis.[1] In particular, gephyrotoxin 223AB (GTX 223AB) has been of interest since the relative stereochemistry of this compound remained a mystery for several years following the structure determination. The correct relative stereochemistry of GTX 223AB as structure **1a** was established in 1981,[2] and several syntheses of this natural product have since appeared.[3]



One of the unnatural isomers, **1b**, has also been prepared by total synthesis utilizing the stereospecific addition of a nucleophile to a conformationally rigid tetrahydropyridinium ion.[4] We now report a variation of this approach which leads stereospecifically to the the all-cis 3*R**,5*S**,9*S** isomer of GTX 223AB, **1c**.

The Grignard reagent from the ethylene ketal of 1-chloro-4-heptanone[5] was treated with a solution of freshly distilled acrolein to give allylic alcohol **3** (Scheme I), which was oxidized with pyridinium dichromate[6] to the corresponding α,β-unsaturated ketone. Tetramethylguanidine-catalyzed Michael addition[7] of 1-nitropentane to the enone was followed by hydrogenation of the resultant nitro ketone **4** over palladium in the presence of anhydrous sodium sulfate. This procedure afforded the 2,5-disubstituted pyrrolidine, which was isolated from ether as its oxalate salt **5**. The ^{13}C NMR spectrum of the free base exhibited 16 peaks, indicating the presence of a single

Scheme I[a]



[a] (a) i, Mg/THF; ii, acrolein (30%); (b) PDC (77%); (c) 1-nitropentane, tetramethylguanidine/CH_2Cl_2 (57%); (d) i, H_2/Pd/C; MeOH, Na_2SO_4; ii, HOOCCOOH/Et_2O (59%); (e) 2 N HCl/THF; (f) 10% aqueous KOH; (g) $NaCNBH_3$/MeOH/THF; bromocresol green (62% from **5**).

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(1) (a) Macdonald, T. L. *J. Org. Chem.* **1980**, *45*, 193. (b) Stevens, R. V.; Lee, A. M. W. *J. Chem. Soc., Chem. Commun.* **1982**, 102. (c) Overman, L. E.; Fukuya, C. *J. Am. Chem. Soc.* **1980**, *102*, 1454. (d) Overman, L. E.; Bell, K. L.; Ito, F. *J. Am. Chem. Soc.* **1984**, *106*, 4192.

(2) Spande, Th. F.; Daly, J. W.; Hart, D. J.; Tsai, Y.-M.; Macdonald, T. L. *Experientia* **1981**, *37*, 1242.

(3) (a) Iida, H.; Watanabe, Y.; Kibayashi, C. *J. Am. Chem. Soc.* **1985**, *107*, 5534. (b) Roger, J.; Husson, H.-P. *Tetrahedron Lett.* **1985**, *26*, 1515.

(4) Stevens, R. V.; Lee, A. M. W. *J. Chem. Soc., Chem. Commun.* **1982**, *103*. Experimental procedure and spectral data for **1b** are available in the supplementary material for this paper.

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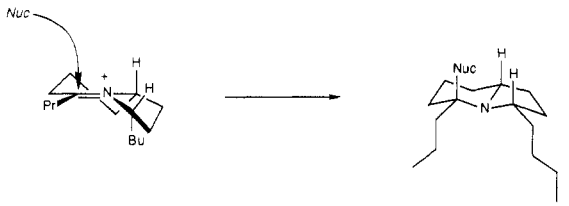
stereoisomer, and it was assumed from the literature precedent that the hydrogenation of the intermediate Δ^1-pyrrolidine had proceeded in a syn fashion.[8]

The ketal oxalate **5** was hydrolyzed in dilute aqueous hydrochloric acid followed by a basic workup to afford the unstable endocyclic enamine **6**, whose existence could be detected by the 1635-cm^{-1} absorption in the IR spectrum. In the key reaction, the unpurified enamine was subjected to treatment with sodium cyanoborohydride in methanol with bromocresol green indicator. Following Borch's procedure,[9] methanolic hydrochloric acid was added to maintain the pH of the solution between 3.8 and 5.4, and the product isolated was shown to be exclusively the all-cis stereoisomer of GTX 223AB (**1c**). In particular, the ^{13}C NMR spectrum is unique in that the C-3, C-5, and C-9 resonances occur between 60 and 70 ppm, in accord with Sonnet's ^{13}C NMR studies on selected octahydroindolizidines.[11] Indolizidines with the all-cis 5*Z*,9*Z*[10] configuration exhibit significantly lower field resonances for C-3, C-5, and C-9 than any of the other isomers.[11]

The observed stereospecificity of hydride addition to the tetrahydropyridinium ion can be attributed to the principles of stereoelectronic control, in which nucleophilic addition occurs (to the most stable chair-like transition state) so as to maintain maximum orbital overlap between the incoming nucleophile and the developing lone electron pair on nitrogen.[12]



After the successful completion of the synthesis, both of the stereoisomers of GTX 223AB which had been synthesized via this route (**1b** and **1c**) were sent to NIH for biological testing under the supervision of Dr. J. W. Daly. Both isomers inhibited the binding of [^{3}H]perhydrohistrionicotoxin to sites within the ion channel associated with the nicotinic receptor.[13] The IC_{50} values are ca. 1–2 μM for *Torpedo electroplax*, suggesting that these indolizidines, like the histrionicotoxins,[14] pumiliotoxins,[15] gephyrotoxins,[16] and other drugs[17] will prove to be useful and potent antagonists of the nicotonic receptor channel involved in neuromuscular transmission.

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 F254, Type T).

2-Propyl-2-(3-chloropropyl)-1,3-dioxolane (2). A solution of 1-chloro-4-heptanone (25.0 g, 0.17 mol), *p*-toluenesulfonic acid monohydrate (0.095 g, 0.5 mmol), and ethylene glycol (12.9 g, 0.21 mol) in 150 mL of benzene was refluxed by using a Dean–Stark apparatus for 12 h, at which time IR analysis indicated the absence of starting ketone. The mixture was washed first with aqueous bicarbonate and then with brine. Evaporation of the solvent followed by distillation (90 °C, 0.3 mm) afforded 28.9 g of ketal **2** as a colorless oil (90%): IR (film) 2955, 2870, 1462, 1445, 1323, 1077, 945 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.93 (s, 4 H), 3.55 (t, J = 7 Hz, 2 H), 1.75–1.95 (m, 4 H), 1.54–1.65 (m, 2 H), 1.30–1.45 (m, 2 H), 0.92 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 111.2, 64.9, 45.2, 39.5, 34.2, 27.1, 17.1, 14.3; HRMS, m/z 149.0366 (calcd for $C_6H_{10}O_2Cl$, m/z 149.0370).

2-Propyl-2-(4-hydroxy-5-hexenyl)-1,3-dioxolane (3). A solution of **2** (10.0 g, 0.052 mol) and 0.20 mL of 1,2-dibromoethane in 10 mL of THF was added dropwise to a refluxing suspension of finely cut magnesium ribbon (1.68 g, 0.069 mol) in 10 mL of THF. An additional 50 mL of THF were introduced, and refluxing was continued until thin-layer chromatography indicated that no starting material remained. After cooling to room temperature, the Grignard reagent was cannulated into a −78 °C solution of freshly distilled acrolein (3.64 g, 0.064 mol) in 100 mL of THF. The mixture warmed to room temperature and after 2 h, was poured onto 150 mL of ice-cooled saturated aqueous ammonium chloride. The aqueous layer was extracted twice with ether, and the combined organic extracts were washed with brine and dried over sodium sulfate to give 10.61 g of a yellow oil, which afforded pure **3** (3.11 g, 28%) after medium-pressure chromatography eluting with 30% ethyl acetate/hexane: IR (film) 3350, 3065, 2860–2940, 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.87 (ddd, J = 17, 10, 6 Hz, 1 H), 5.22 (ddd, J = 17, 1.5, 1.5 Hz, 1 H), 5.10 (ddd, J = 10, 1.5, 1.5 Hz, 1 H), 4.09–4.12 (m, 1 H), 3.93 (s, 4 H), 1.31–1.68 (m, 10 H), 0.91 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 141.2, 114.4, 111.6, 72.9, 64.8, 39.3, 37.1, 36.8, 19.6, 17.0, 14.3; HRMS, m/z 171.1020 (calcd for $C_9H_{15}O_3$, m/z 171.1021).

2-Propyl-2-(4-oxo-5-hexenyl)-1,3-dioxolane. Pyridinium dichromate (2.50 g, 6.64 mmol) and Celite (2.50 g) were added to a stirring solution of **3** (0.86 g, 4.01 mmol) in 50 mL of methylene chloride at room temperature. After 24 h the mixture was taken up in ether and filtered through a short column of Celite. Concentration of the filtrate yielded the enone (0.652 g, 77%) as a light yellow oil, which was taken on to the next reaction without further purification: IR (film) 2870–2960, 1680, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.36 (dd, J = 17, 10 Hz, 1 H), 6.20 (dd J = 17, 2 Hz, 1 H), 5.80 (dd, J = 10, 2 Hz, 1 H), 3.92 (s, 4 H), 2.61 (t, J = 7 Hz, 2 H), 1.55–1.76 (m, 6 H), 1.25–1.45 (m, 2 H), 0.91 (t, J = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 220.6, 136.5, 127.8, 111.5, 64.9, 39.6, 39.4, 18.3, 17.1, 14.4; HRMS, m/z 169.0863 (calcd for $C_9H_{13}O_3$ ($M^+ - C_3H_7$), m/z 169.0865).

2-Propyl-2-(4-oxo-7-nitroundecyl)-1,3-dioxolane (4). A mixture of the enone (1.04 g, 4.88 mmol), 1-nitropentane (0.63 g, 5.37 mmol), and tetramethylguanidine (0.06 g, 0.50 mmol) in

(5) Julia, S.; Julia, M.; Brasseur, L. *Bull. Soc. Chim. Fr.* **1962**, *1634*.
(6) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.
(7) Pollini, G. P.; Barco, A.; DeGiuli, G. *Synthesis* **1972**, 44.
(8) Benezva, L. L.; DePablo, S.; Osgood, E. R. Ger. Offen. 2 344 509, 1974, *Chem. Abstr.* **1974**, *81*, 146009h.
(9) Borch, R. F.; Bernstein, M. D.; Durst, H. D. *J. Am. Chem. Soc.* **1971**, *93*, 2897.
(10) *E* and *Z* refer to the configuration of the hydrogens (trans or cis) with respect to the hydrogen at C-3.
(11) Sonnet, P. E.; Netzel, D. A.; Mendoza, R. *J. Heterocyl. Chem.* **1979**, *16*, 1040.
(12) (a) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Organic Chemistry Series; Baldwin, J. E., Ed.; Pergamon: Press: Oxford, 1983; Vol. 1, p 211 and references cited therein. (b) Maruoka, K.; Miyazaki, T.; Ando, M.; Matsumura, Y.; Sakane, S.; Hattori, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1983**, *105*, 2831. (c) Stevens, R. V. *Acc. Chem. Res.* **1984**, *8*, 289.
(13) Aronstam, R. S.; Daly, J. W.; Spande, T. F.; Narayanan, P. K.; Albuquerque, E. X. *Neurochem. Res.* **1986**, *11*, 1227.
(14) Spivak, C. E.; Maleque, M. A.; Oliveira, A. C.; Masukawa, L. M.; Tokuyama, T.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharmacol.* **1982**, *21*, 351.
(15) Warnick, J. E.; Jessup, P. J.; Overman, L. E.; Elderfrawi, M. E.; Nimit, Y.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharmacol.* **1982**, *22*, 565.
(16) Aronstam, R. S.; Eldefrawi, A. T.; Pessah, I. N.; Daly, J. W.; Albuquerque, E. X.; Elderfrawi, M. E. *J. Biol. Chem.* **1981**, *256*, 2843.
(17) Souccar, C.; Varanda, W. A.; Aronstam, R. S.; Daly, J. W.; Albuquerque, E. X. *Mol. Pharmacol.* **1984**, *25*, 395.

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).

Acknowledgment. We thank Dr. John W. Daly at the National Institutes of Health, Bethesda, MD, for his interest in this project and for his helpful communications. Support was provided by the National Institutes of Health (GM 28122).

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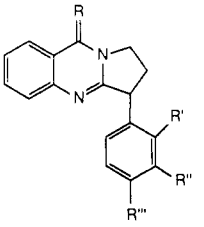
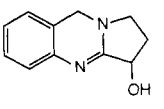
Bis-ortho-nitration of α-phenyl-*N*-(phenylmethyl)-γ-butanelactam (**6**) using acetyl nitrate followed by reduction and regiospecific dehydrative cyclization afforded quinazoline **12**. The aniline moiety in **12** could be dimethylated by using aqueous formaldehyde and $KHFe(CO)_4$, affording vasicoline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

0022-3263/88/1953-1873$01.50/0