Total Synthesis of Peramine†

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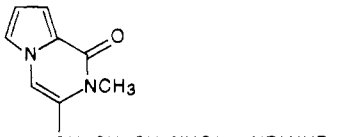
Received April 21, 1988

A facile synthesis of 1-oxo-2,3-disubstituted-pyrrolo[1,2-*a*]pyrazines, which involves the reaction of 2-(trichloroacetyl)pyrrole (**3**) with halomethyl ketones (to give pyrrolo[2,1-*c*][1,4]oxazin-1-ones) followed by successive treatment with methylamine and acid, has been developed. This methodology has been applied to the total synthesis of the insect feeding deterrent peramine (**1**).

Peramine (**1**) is an insect feeding deterrent isolated from perennial ryegrass infected with the endophyte *Acremonium loliae*.[2] The structure of this antifeedant was recently elucidated by Rowan and co-workers, who fully characterized the diacetylated derivative (**2**).[3] The interesting and novel 1-oxo-2,3-disubstituted-pyrrolo[1,2-*a*]pyrazine ring system of peramine prompted us to investigate its total synthesis.



1, R = H
2, R = $COCH_3$

Although a number of methods for the preparation of pyrrolo[1,2-*a*]pyrazines have been reported,[4] none of these are amenable to the preparation of the 1-oxo-2,3-disubstituted system found in peramine. Therefore, we first explored routes to simple 1-oxopyrrolo[1,2-*a*]pyrazines.

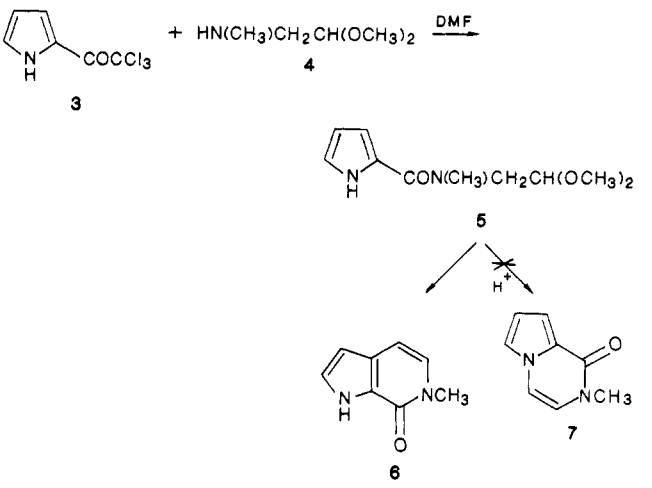
In initial experiments, the cyclization of *N*-(2,2-dimethoxyethyl)-*N*-methyl-1*H*-pyrrole-2-carboxamide (**5**), readily available from 2-(trichloroacetyl)pyrrole (**3**)[5] and *N*-methylaminoacetaldehyde dimethyl acetal (**4**), was studied (Scheme I). However, the acid-catalyzed cyclization of **5** under two sets of conditions (*p*-toluenesulfonic acid/toluene and pyridinium tosylate/water/acetone) led to the formation of pyrrolo[2,3-*c*]pyridine **6** rather than the desired pyrrolo[1,2-*a*]pyrazine **7**.

Since it has been reported that 2-(trichloroacetyl)pyrrole (**3**) is readily N-alkylated,[6] we next turned our attention to the alkylation of **3** with reagents suitable for further elaboration to pyrrolo[1,2-*a*]pyrazines. As outlined in Scheme II, chloroacetone was selected for the initial experiment since it was anticipated that treatment of alkylation product **8** with methylamine would lead directly to 1-oxo-2,3-dimethylpyrrolo[1,2-*a*]pyrazine (**11**).[7]

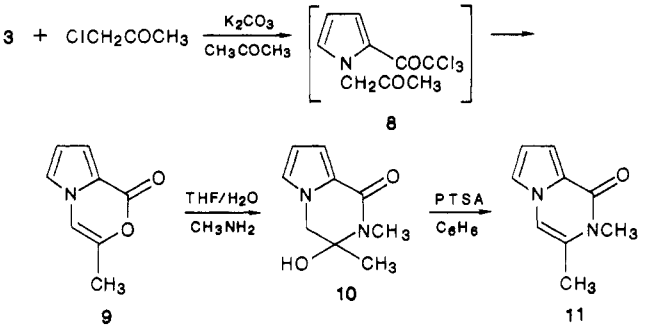
In practice, treatment of **3** with chloroacetone provided 3-methyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (**9**), presumably via the intermediacy of the initial *N*-alkylated product **8**. When a solution of **9** in tetrahydrofuran was treated with 40% aqueous methylamine a white, crystalline solid gradually separated. This was identified as aminal **10**, which was readily dehydrated to give the desired 1-oxopyrrolo[1,2-*a*]pyrazine (**11**). The ^1H NMR chemical shifts for H-4, H-6, H-7, H-8, and the NCH_3 group of **11** were in excellent agreement with those reported for peramine.[3]

With this facile synthesis of 1-oxo-2,3-disubstituted-pyrrolo[1,2-*a*]pyrazines in hand, we turned our attention to the preparation of peramine. Although the possibility of further elaboration of compound **11** was considered, we felt that the reaction of **3** with a suitably functionalized 1-halo-2-pentanone would be more efficient, particularly in view of the numerous methods available for the preparation of halomethyl ketones.[8]

Scheme I



Scheme II



† Dedicated to Professor E. C. Taylor on the occasion of his 65th birthday.

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(2) Rowan, D. D.; Gaynor, D. L. *J. Chem. Ecol.* **1986**, *12*, 647.

(3) Rowan, D. D.; Hunt, M. B.; Gaynor, D. L. *J. Chem. Soc., Chem. Commun.* **1986**, 935.

(4) (a) Kuhla, D. E.; Lombardino, J. G. *Adv. Heterocycl. Chem.* **1977**, *21*, 31–49, and references cited therein. (b) Buchan, R.; Fraser, M.; Kong Thoo Lin, P. V. S. *J. Org. Chem.* **1985**, *50*, 1324.

(5) Bailey, D. M.; Johnson, R. E.; Albertson, N. F. *Org. Synth.* **1971**, *51*, 100.

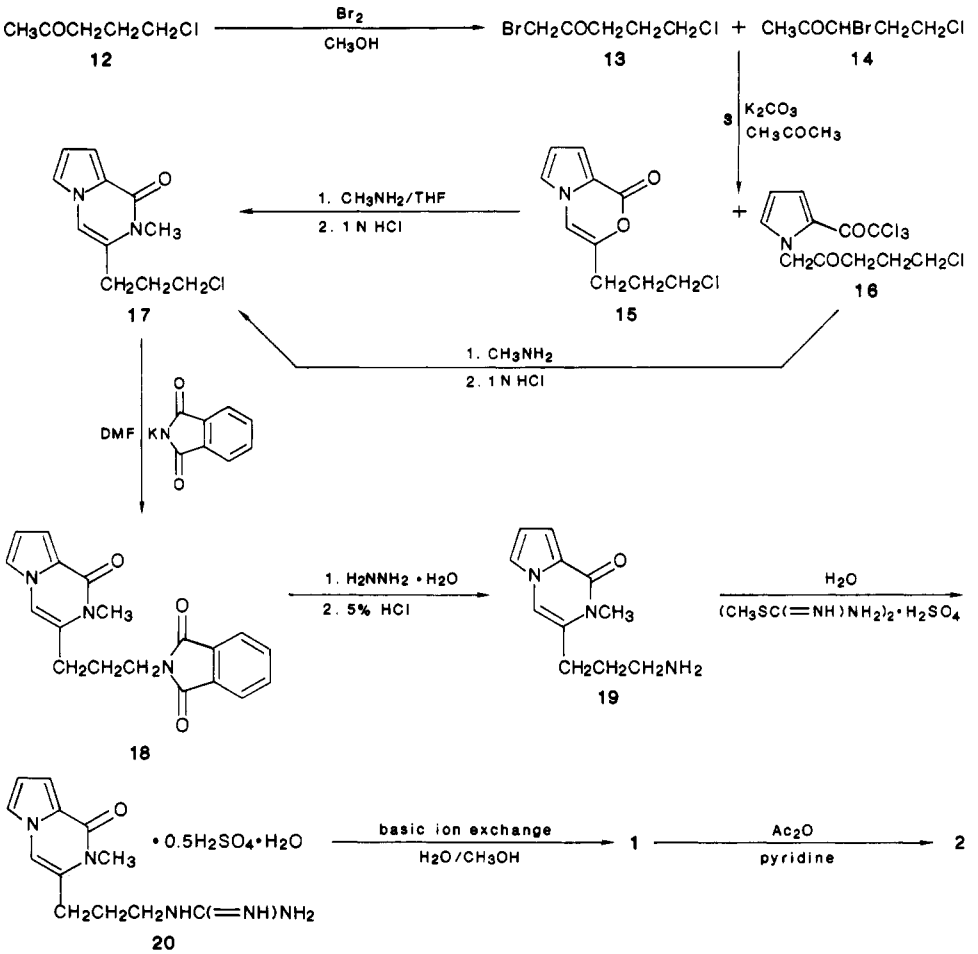
(6) Bailey, D. M.; Johnson, R. E. *J. Med. Chem.* **1973**, *11*, 1300.

(7) A similar approach has been employed for preparation of 1,3-dialkylpyrrolo[1,2-*a*]pyrazines from 2-acylpyrroles via alkylation with bromomethyl ketones followed by cyclization with ammonium chloride. Shoedov, V. I.; Altukhova, L. B.; Bocharnikova, A. V.; Grinev, A. N. USSR Patent 237153, 1969; *Chem. Abstr.* **1969**, *71*, 13142. Shoedov, V. I.; Altukhova, L. B.; Grinev, A. N. *Khim. Geterotsiki Soedin.* **1970**, *1048*; *Chem. Abstr.* **1971**, *74*, 125628.

(8) De Kimpe, N.; De Cock, W.; Schamp, N. *Synthesis* **1987**, 188 and references cited therein.

0022-3263/88/1953-4650$01.50/0

Scheme III



1-Bromo-5-chloro-2-pentanone (**13**) was selected as the alkylating agent since it can be readily prepared by the bromination of commercially available 5-chloro-2-pentanone (**12**).[9] Although this bromination has been reported to be nonselective, giving rise to equal amounts of **13** and 3-bromo-5-chloro-2-pentanone (**14**), we reasoned that the former should be the more reactive alkylating agent and if compound **3** were employed as the limiting reagent in the subsequent alkylation step, only product arising from bromomethyl ketone **13** would be observed. As outlined in Scheme III, this proved to be the case.

In our hands, bromination of 5-chloro-2-pentanone gave an approximately 2:1 mixture of products with the desired bromomethyl ketone **13** being the major component. Treatment of the crude bromination product with an equivalent amount of **3** (based on bromomethyl ketone **13**) provided the desired pyrrolo[2,1-*c*]oxazin-1-one **15**. Products arising from the alkylation of **3** with **14** were not observed. When the reaction was carried out on a large scale, substantial quantities of the intermediate alkylation product **16** were also isolated. Compound **16** was readily converted to **15** upon reexposure to the alkylation conditions.

Treatment of either **15** or **16** with methylamine followed by exposure to aqueous hydrochloric acid gave 3-(3-chloropropyl)-2-methylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (**17**). The conversion of chloro compound **17** to the corresponding amine **19** was accomplished by using the Ing–Manske modification of the Gabriel synthesis.[10] Compound **19** was converted to peramine sulfate (**20**) on treatment with 2-methyl-2-thiopseudourea sulfate. Although this reaction was examined by using either aqueous ethanol or aqueous dioxane as the reaction medium, water proved to be the solvent of choice for this transformation. The synthesis was completed by converting sulfate **20** to the free base **1** by using ion exchange chromatography. Synthetic peramine (**1**) was converted to the corresponding diacetate **21** by the literature procedure.[2] The ^{1}H NMR ^{13}C NMR, UV, and high-resolution mass spectra of this material were in excellent agreement with those reported by Rowan and co-workers for diacetylperamine.[3]

In summary, we have developed a procedure for the synthesis of 1-oxo-2,3-disubstituted-pyrrolo[1,2-*a*]pyrazines and applied it to the preparation of the insect antifeedant peramine. Modification of this synthesis should permit the preparation of a wide variety of 1-oxopyrrolo[1,2-*a*]-pyrazines.

Experimental Section

Melting points are uncorrected and were determined on a Thomas-Hoover apparatus. Infrared spectra were recorded on a Nicolet 7199 FT-IR spectrometer. ^{1}H NMR data were obtained at either 200 MHz on a Varian XL-200 or at 300 MHz on a Varian XL-300 instrument with an internal lock on the deuterium resonance of the solvent using Me_4Si as internal standard. ^{13}C NMR data were obtained at 75.48 MHz on a Varian XL-300 instrument using Me_4Si as internal standard. High-resolution mass spectra were obtained on a Finnigan MAT8230 spectrometer. Gas chromatographs were obtained on a Hewlett-Packard 5790 instrument. Ultraviolet spectra were recorded on a Perkin-Elmer Lamda 9 spectrophotometer.

Reactions were carried out under an atmosphere of nitrogen with magnetic stirring. Reagent grade solvents were used without

(9) Semenova, N. A.; Katvalyan, G. T.; Mistryukov, E. A. *Tetrahedron Lett.* **1976**, 445.
(10) Ing, H. R.; Manske, R. H. F. *J. Chem. Soc.* **1926**, 2348.

further purification. Reactions were monitored by thin-layer chromatography, eluting with mixtures of ethyl acetate and hexane or, when the product or starting material was amine **19**, with 25:1 chloroform/isopropylamine. Thin-layer chromatography was performed on Whatman glass plates precoated with silica gel; visualization was achieved under ultraviolet light. Silica gel (230–400 mesh), obtained from the J. T. Baker Chemical Company, was used for flash column chromatographic separations. Merck Lobar LiChroprep Si 60 (40–63 μm) columns were used for medium pressure column chromatographic separations.

***N*-(2,2-Dimethoxyethyl)-*N*-methyl-1*H*-pyrrole-2-carboxamide (5).** A solution of 2.12 g (10 mmol) of 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone (**3**)[5] and 1.30 mL (10 mmol) of *N*-methylaminoacetaldehyde dimethyl acetal (Aldrich) in 20 mL of dimethylformamide was heated at 70–75 °C for 8 h with additional 0.20-mL (1.5 mmol) portions of *N*-methylaminoacetaldehyde dimethyl acetal being added after 4 and 6 h. The solution was allowed to cool, poured on ice, and extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed successively with water (3 × 25 mL) and brine (25 mL), dried over $MgSO_4$, and concentrated under reduced pressure to a brown oil which was purified by flash column chromatography, eluting with 40% EtOAc/hexane to give 0.89 g (42%) of an amber oil which slowly solidified: mp 47–49 °C. Recrystallization from hexane (carbon) provided the analytical sample as fluffy white needles: mp 47–50 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.35 (br s, 3 H), 3.44 (s, 6 H), 3.68 (br d, 2 H, J = 5.3 Hz), 4.62 (t, 1 H, J = 5.3 Hz), 6.26 (6 lines (ddd), 1 H, J = 3.7 Hz, J = 2.6 Hz, and J = 2.6 Hz), 6.64 (7 lines (ddd), 1 H, J = 3.7 Hz, J = 2.5 Hz, and J = 1.3 Hz), 6.94 (6 lines, (ddd), 1 H, J = 2.6 Hz, J = 2.6 Hz, and J = 1.3 Hz), 10.12 (br s, 1 H); IR (KBr) 3265, 2940, 1593, 1545, 1490, 1455, 1408, 1112, 1078, 1050, 762, 745 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}N_2O_3$: C, 56.59; H, 7.60; N, 13.20. Found: C, 56.58; H, 7.50; N, 13.21.

6-Methyl-1*H*-pyrrolo[2,3-*c*]pyridin-7(6*H*)-one (6). Method A. A mixture of 1.06 g (5 mmol) of *N*-(2,2-dimethoxyethyl)-*N*-methyl-1*H*-pyrrole-2-carboxamide (**5**), 10 mg of *p*-toluenesulfonic acid monohydrate, and 20 mL of toluene was heated at 100 °C for 3 h. While still hot, the toluene solution was decanted from an insoluble brown gum. The gummy crystals that formed on cooling were collected and recrystallized from toluene (carbon) to give 0.24 g (32%) of off-white clusters: mp 190–192 °C; ^1H NMR ($CDCl_3$, 300 MHz), δ 3.68 (s, 3 H), 6.35 (dd, 1 H, J = 2.8 Hz and J = 2.1 Hz), 6.56 (br d, 1 H, J = 7.0 Hz), 6.92 (d, 1 H, J = 7.0 Hz), 7.30 (3 lines (dd), 1 H, J = 2.8 Hz and J = 2.8 Hz), 12.98 (br s, 1 H); IR (KBr) 3180, 3155, 1652, 1585, 1398, 1277, 786 cm^{-1}.

Anal. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.69; H, 5.58; N, 18.63.

Method B. A solution of 0.30 g (1.4 mmol) of **5**, 0.15 g (0.6 mmol) of pyridinium tosylate, and 5 mL of 95% aqueous acetone was heated to reflux for 10 h. On cooling, the solvent was removed under reduced pressure and the residue partitioned between water and ethyl acetate. The organic layer was washed with water and dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was triturated with 1-chlorobutane to give 0.05 g (24%) of tan solid: mp 188–190 °C. The product was identical with that obtained by method A as judged by NMR, IR, and TLC.

3-Methyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (9). A solution of 6.30 mL (75 mmol) of 95% chloroacetone (Fluka) in 50 mL of acetone was added dropwise to a slurry of 10.60 g (50 mmol) of 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone (**3**), 20.7 g (0.15 mol) of potassium carbonate, and 150 mL of acetone, and the resulting mixture was stirred at ambient temperature for 20 h. The solids were then removed by filtration and washed with acetone. The filtrates were concentrated under reduced pressure, the residue was partitioned between 200 mL of water and 200 mL of ethyl acetate, the layers were separated, and the aqueous layer was extracted with 100 mL of ethyl acetate. The combined organic layers were washed successively with water (3 × 100 mL) and brine (100 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure to leave 11.0 g of oily brown solid which was purified by flash column chromatography, eluting with 2:1 hexane:ethyl acetate to give 4.36 g (58%) of yellow solid: mp 88–90 °C. Recrystallization from 1-chlorobutane/hexane (carbon) provided the analytical sample as colorless blades: mp 92–94 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.16 (d, 3 H, J = 1.2 Hz), 6.51 (dd, 1 H, J = 4.1 Hz and J = 2.5 Hz), 6.80 (m, 1 H), 7.04 (dd, 1 H, J = 2.5 Hz and J = 1.4 Hz), 7.21 (ddd, 1 H, J = 4.1 Hz, J = 1.4 Hz, and J = 0.7 Hz); IR (KBr) 3110, 1748, 1720, 1708, 1690, 1532, 1480, 1410, 1393, 1376, 1355, 1291, 1220, 1080, 1063, 992, 739, 730 cm^{-1}.

Anal. Calcd for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.20; H, 4.68; N, 9.50.

3,4-Dihydro-3-hydroxy-2,3-dimethylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (10). A solution of 1.10 g (7.4 mmol) of 3-methyl-1*H*-pyrrolo[2,1-*c*][1,4]oxazin-1-one (**9**) in 7.5 mL of tetrahydrofuran was cooled in an ice bath and 2.3 mL (~30 mmol) of 40% aqueous methylamine added. The cooling bath was removed and the reaction mixture stirred at room temperature for 4 h. The resulting suspension was cooled in an ice bath and the white solid collected and washed with 1-chlorobutane to give 0.82 g (61%) of the desired product: mp 169–171 °C. Recrystallization from ethanol provided an analytical sample: mp 169–172 °C; ^1H NMR (DMSO-d_6, 300 MHz) δ 1.41 (s, 3 H), 2.89 (s, 3 H), 4.05 (d, 1 H, J = 12.9 Hz), 4.15 (d, 1 H, J = 12.9 Hz), 6.13 (dd, 1 H, J = 3.7 Hz and J = 2.5 Hz), 6.36 (s, 1 H), 6.59 (dd, 1 H, J = 3.7 Hz and J = 1.6 Hz), 6.94 (dd, 1 H, J = 2.5 Hz and J = 1.6 Hz); IR (KBr) 3280, 1616, 1551, 1494, 1430, 1410, 1368, 1268, 1156, 1116, 1110, 1074, 875, 761, 751 cm^{-1}.

Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.54. Found: C, 59.75; H, 6.53; N, 15.65.

2,3-Dimethylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (11). A mixture of 0.58 g (3.2 mmol) of 3,4-dihydro-3-hydroxy-2,3-dimethylpyrrolo[1,2-*a*]pyrazin-1(2*H*)-one (**10**), 5 mg of *p*-toluenesulfonic acid monohydrate, and 10 mL of benzene was heated to reflux for 1 h. The resulting solution was allowed to cool and the crystals that formed were collected and washed with benzene to give 0.29 g (55%) of off-white product: mp 179–183 °C. Recrystallization from benzene provided the analytical sample as pale yellow crystals: mp 181–183 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.20 (d, 3 H, J = 1.2 Hz), 3.44 (s, 3 H), 6.50 (dd, 1 H, J = 4.0 Hz and J = 2.5 Hz), 6.81 (m, 1 H), 6.99 (dd, 1 H, J = 2.5 Hz and J = 1.5 Hz), 7.04 (ddd, 1 H, J = 4.0 Hz, J = 1.5 Hz, J = 0.7 Hz); IR (KBr) 1677, 1620, 1478, 1422, 1373, 770, 760, 738 cm^{-1}.

Anal. Calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.22; N, 17.27. Found: C, 66.69; H, 6.17; N, 17.23.

1-Bromo-5-chloropentan-2-one (13) and 3-Bromo-5-chloropentan-2-one (14). To a solution of 3.4 mL (~32 mmol) of 90% technical grade 5-chloro-2-pentanone (**12**) in 36 mL of methanol was added 1.6 mL (~31 mmol) of bromine dropwise over 10 min. An exotherm from 23 °C to 37 °C was noted. After an additional 1 h, 7.5 g of potassium carbonate was added and the mixture stirred for an additional 1 h. The reaction mixture was filtered, the solids washed with methanol, and the filtrates were concentrated under reduced pressure. The residue was partitioned between 50 mL of CH_2Cl_2 and 50 mL of water, the layers were separated, and the organic layer was washed with 50 mL of saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure to leave 5.0 g of golden oil: VPC (6 ft, SP2100, 100 °C) analysis of the product showed, in order of elution, 9.4% 5-chloro-2-pentanone, 28.0% **14**, and 62.4% **13**. ^1H NMR ($CDCl_3$, 200 MHz): δ 3.90 (s, $COCH_2Br$ of **13**).

3-(3-Chloropropyl)-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (15). A solution of 3.20 g (15 mmol) of 2,2,2-trichloro-1-(1*H*-pyrrol-2-yl)ethanone (**3**) in 20 mL of acetone was added dropwise over 10 min to a slurry of 5.0 g (~15 mmol) of 62% crude 1-bromo-5-chloro-2-pentanone and 6.20 g (45 mmol) of potassium carbonate in 40 mL of acetone. The mixture was stirred at room temperature for 18 h and filtered and the solids were washed with acetone. The filtrate was concentrated under reduced pressure, the residue partitioned between 50 mL of ethyl acetate and 50 mL of water, and the aqueous layer extracted with ethyl acetate (2 × 25 mL). The combined extracts were washed successively with water (3 × 50 mL) and brine (50 mL), dried over $MgSO_4$, and concentrated under reduced pressure to a brown oil which was purified by flash column chromatography, eluting with 22% ethyl acetate/hexane to give 1.97 g (62%) of off-white solid after trituration with hexane: mp 38–40 °C. The anlaytical sample was obtained as a white solid (mp 43–45 °C) by medium pressure liquid chromatography, eluting with 22% EtOAc/hexane. This material slowly decomposed on

standing at room temperature: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (m, 2 H), 2.63 (t, 2 H, J = 7.1 Hz), 3.61 (t, 2 H, J = 6.1 Hz), 6.54 (dd, 1 H, J = 4.1 Hz and J = 2.5 Hz), 6.89 (d, 1 H, J = 0.8 Hz), 7.07 (dd, 1 H, J = 2.5 Hz and J = 1.4 Hz), 7.22 (ddd, 1 H, J = 4.1 Hz, J = 1.4 Hz, and J = 0.8 Hz); IR (KBr) 1747, 1728, 1478, 1408, 1390, 1365, 1215, 1078, 735 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62. Found: C, 56.38; H, 4.84; N, 6.43.

When the above reaction was carried out on a 92-mmol scale by using 2.3 instead of 3.0 equiv of potassium carbonate, 4.96 g (25%) of **15** was obtained along with 7.71 g (25%) of the faster eluting 5-chloro-1-[2-(trichloroacetyl)-1*H*-pyrrol-1-yl]-2-pentanone (**16**): mp 63–65 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (br quintet, 2 H), 2.77 (t, 2 H, J = 6.9 Hz), 3.61 (t, 2 H, J = 6.2 Hz), 5.07 (s, 2 H), 6.34 (dd, 1 H, J = 4.4 Hz and J = 2.5 Hz), 6.96 (dd, 1 H, J = 2.5 Hz and J = 1.5 Hz), 7.59 (dd, 1 H, J = 4.4 Hz, and J = 1.5 Hz); IR (KBr) 1730, 1660, 1522, 1468, 1422, 1400, 1383, 1335, 1239, 1093, 846, 805, 740, 688 cm^{-1}.

Anal. Calcd for $C_{11}H_{11}Cl_4NO_2$: C, 39.91; H, 3.35; N, 4.23. Found: C, 39.93; H, 3.24; N, 4.22.

3-(3-Chloropropyl)-2-methylpyrrolo[1,2-*a*]pyrazin-1-(2*H*)-one (17). Method A. A solution of 4.60 g (22 mmol) of 3-(3-chloropropyl)-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (**15**) in 35 mL of tetrahydrofuran was cooled in an ice bath and 5 mL (~0.11 mol) of condensed methylamine added. The cooling bath was then removed and the solution allowed to warm to ambient temperature. After a total reaction time of 3 h, the solvent was removed under reduced pressure and the resulting green syrup stirred for 2 h with 40 mL of 1 N HCl. The solid that formed was collected, washed with water, and then dissolved in 700 mL of ethyl acetate. This solution was washed twice with water and once with brine and dried over $MgSO_4$ and the solvent was removed under reduced pressure. Trituration of the residue with 1-chlorobutane provided 2.24 g (45%) of white microcrystals: mp 138–140 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.08 (m, 2 H), 2.72 (t, 2 H, J = 7.5 Hz), 3.47 (s, 3 H), 3.64 (t, 2 H, J = 6.0 Hz), 6.53 (dd, 1 H, J = 4.0 Hz and J = 2.5 Hz), 6.85 (d, 1 H, J = 0.8 Hz), 7.03 (dd, 1 H, J = 2.5 Hz and J = 1.5 Hz), 7.06 (ddd, 1 H, J = 4.0 Hz, J = 1.5 Hz, and J = 0.8 Hz); IR (KBr) 3105, 1673, 1622, 1480, 1428, 1367, 770, 758, 743 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.83; N, 12.47. Found: C, 58.79; H, 5.76; N, 12.40.

Method B. Using the procedure described above, treatment of 3.31 g (10 mmol) of 5-chloro-1-[2-(trichloroacetyl)-1*H*-pyrrol-1-yl]-2-pentanone (**16**) with 2.2 mL of methylamine (approximately 50 mmol) provided 1.16 g (51%) of the product: mp 135–137 °C.

2-[3-(1,2-Dihydro-2-methyl-1-oxopyrrolo[1,2-*a*]pyrazin-3-yl)propyl]-1*H*-isoindole-1,3(2*H*)-dione (18). A mixture of 5.05 g (22.5 mmol) of 3-(3-chloropropyl)-2-methylpyrrolo[1,2-*a*]-pyrazin-1(2*H*)-one (**17**), 4.63 g (25 mmol) of potassium phthalimide (Aldrich), and 50 mL of dimethylformamide was heated at 77–82 °C for 1.5 h. The resulting yellow slurry was allowed to cool and then poured over 100 mL of ice water. The yellow precipitate was collected, washed thoroughly with water, and recrystallized from ethanol to give 6.10 g (81%) of white microcrystals: mp 175–176 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.03, (br quintet, 2 H), 2.59 (t, 2 H, J = 7.5 Hz), 3.44 (s, 3 H), 3.82 (t, 2 H, J = 6.9 Hz), 6.50 (dd, 1 H, J = 3.9 Hz and J = 2.6 Hz), 6.92 (d, 1 H, J = 0.7 Hz), 7.02 (m, 2 H), 7.73 (m, 2 H), 7.85 (m, 2 H); IR (KBr) 1769, 1710, 1678, 1630, 1429, 1400, 1361, 746, 722 cm^{-1}.

Anal. Calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.10; H, 5.10; N, 12.58.

3-(3-Aminopropyl)-2-methylpyrrolo[1,2-*a*]pyrazin-1-(2*H*)-one (19). A slurry of 11.80 g (35 mmol) of phthalimide **18**, 350 mL of ethanol, and 5.10 mL (0.105 mol) of hydrazine hydrate was heated to reflux for 30 min. After cooling to room temperature, 350 mL of 1 N HCl was added to the thick slurry and the resulting mixture was heated at reflux until a clear solution was obtained (approximately 2 min). The solid that crystallized on cooling was removed by filtration and washed with water. The filtrates were concentrated to one-half of their original volume under reduced pressure and extracted with 200 mL of $CHCl_3$. The aqueous layer was saturated with NaCl and extracted eight more times with 200-mL portions of $CHCl_3$. The combined extracts were dried ovver K_2CO_3, concentrated under reduced pressure, and recrystallized from 1-chlorobutane (carbon) to give 3.75 g of pale yellow crystals, mp 94–100 °C. The filtrates were concentrated under reduced pressure and the residue triturated with hexane to give an additional 2.28 g (84% total yield) of white solid: mp 106–110 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.43 (br s, 3 H), 1.75 (br quintet, 2 H), 2.59 (br t, 2 H, J = 7.7 Hz), 2.83 (t, 2 H, J = 6.9 Hz), 3.47 (s, 3 H), 6.52 (dd, 1 H, J = 4.0 Hz and J = 2.5 Hz), 6.82 (d, 1 H, J = 0.8 Hz), 7.01 (dd, 1 H, J = 2.5 Hz and J = 1.5 Hz), 7.05 (ddd, 1 H, J = 4.0 Hz, J = 1.5 Hz, and J = 0.8 Hz); IR (Nujol) 3515, 3420, 3355, 3100, 1676, 1590, 1480, 1426, 1375, 1355, 1210, 1180, 1080, 1050, 885, 870, 782, 770, 740 cm^{-1}; high-resolution MS calcd for 205.1215, found 205.1240.

Bis[[3-(1,2-dihydro-2-methyl-1-oxopyrrolo[1,2-*a*]pyrazin-3-yl)propyl]guanidine] Hydrogen Sulfate Complex Dihydrate (Peramine sulfate) (20). A solution of 3.59 g (17.5 mmol) of amine **19**, 4.42 g (17.5 mmol) of 2-methyl-2-thiopseudourea sulfate (Aldrich, 98%), and 35 mL of water was heated at 90 °C for 15 h. The solid that formed on cooling was collected, washed with water, and recrystallized from water to give 2.71 g (49%) of off-white blades: mp >250 °C; IR (Nujol) 3370, 3160, 3115, 1678, 1655, 1630, 1610, 1485, 1470, 1426, 1380, 1110, 1085, 778, 772, 738 cm^{-1}.

Anal. Calcd for $C_{12}H_{17}N_5O{\cdot}H_2O{\cdot}0.5H_2SO_4$: C, 45.85; H, 6.41; N, 22.27; H_2O, 8.60. Found: C, 45.93; H, 6.44; N, 22.54; H_2O, 8.47.

[3-(1,2-Dihydro-2-methyl-1-oxopyrrolo[1,2-*a*]pyrazin-3-yl)propyl]guanidine (Peramine) (1). A slurry of 1.89 g (3.0 mmol) of peramine sulfate (**20**) in 90 mL of water was warmed to 90 °C and diluted with 90 mL of methanol. The resulting warm (60–65 °C) solution was loaded on a column packed with 10 g of basic ion exchange resin (AG 1-X8, 20–50 mesh, Bio-Rad) and eluted with 50% aqueous methanol. All fractions containing UV-active material were combined and the solvent was removed under reduced pressure. The residue was dissolved in methanol, a small amount of solid was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was triturated with 1-chlorobutane to give 1.45 g (98%) of white powder: mp 160–162 °C; ^{1}H NMR (D_2O, 300 MHz) δ 1.10 (br quintet, 2 H), 1.81 (t, 2 H, J = 7.6 Hz), 2.53 (t, 2 H, J = 6.6 Hz), 2.62 (s, 3 H), 5.93 (dd, 1 H, J = 4.1 Hz and J = 2.5 Hz), 6.25 (br d, 1 H, J = 4.1 Hz), 6.38 (s, 1 H), 6.54 (dd, 1 H, J = 2.5 Hz and J = 1.4 Hz); IR (Nujol) 3485, 3440, 3360, 3250, 3215, 3120, 1675, 1620, 1598, 1540, 1472, 1428, 1370, 1215, 1080, 1040, 786, 752 cm^{-1}; high-resolution MS calcd for 247.1433, found 247.1419.

[(Acetylamino)[3-(1,2-dihydro-2-methyl-1-oxopyrrolo-[1,2-*a*]pyrazin-3-yl)propylamino]methylene]acetamide. (Diacetylperamine, 2). A slurry of 0.75 g (3.0 mmol) of peramine (1), 7.5 mL of pyridine, and 7.5 mL of acetic anhydride was warmed to 88 °C, and the resulting solution was allowed to cool, diluted with an equal volume of toluene, and concentrated under reduced pressure. The residue was repeatedly stripped from toluene until most of the excess reagents were removed. The residue was triturated with 1-chlorobutane to give 0.74 g of tan solid, which was dissolved in 100 mL of warm ethyl acetate and filtered from a small amount of solid and the filtrate was concentrated to ~5 mL. The clusters of crystals that formed on standing were collected to give 0.48 g (48%) of off-white product: mp 149–150.5 °C. The spectral sample was purified by MPLC, eluting with ethyl acetate to give a white solid: mp 150–152 °C (lit.[2] mp 141–142 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.95 (br quintet, 2 H), 2.13 (s, 3 H), 2.18 (s, 3 H), 2.59 (t, 2 H, J = 7.6 Hz), 3.46 (s, 3 H), 3.56 (br q, 2 H), 6.53 (dd, 1 H, J = 3.97 Hz and J = 2.56 Hz), 6.87 (d, 1 H, J = 0.7 Hz), 7.03 (dd, 1 H, J = 2.56 Hz and J = 1.52 Hz), 7.05 (ddd, 1 H, J = 3.97 Hz, J = 1.52, and J = 0.7 Hz), 9.15 (br s, 1 H), 13.15 (br s, 1 H); ^{13}C NMR ($CDCl_3$) δ 25.1, 27.6, 27.9, 28.7, 29.0, 39.7, 106.1, 109.8, 112.3, 117.5, 123.0, 127.3, 155.7, 157.1, 172.8, 186.0; IR (KBr) 3290, 1694, 1673, 1623, 1558, 1427, 1374, 1323, 1210, 741 cm^{-1}; high-resolution MS calcd for 331.1644, found 331.1640; UV (CH_3OH) λ_{max} 229 (ϵ 35 200), 257 (17 300), 290 sh (7400).

Acknowledgment. I express my appreciation to Dr. Gary D. Annis, Dr. Rafael Shapiro, and Dr. Mark E. Thompson for helpful discussions during the course of this work.