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The synthesis of the pyrrolo[1,2-*b*]cinnoline analogs **2** and **4-13** is described. The key step of this synthesis involves an intramolecular aromatic halide displacement on [2-(2-halobenzoyl)pyrrol-1-yl]carbamic acid esters. Several reactions of these cinnoline analogs with electrophilic reagents have been investigated.

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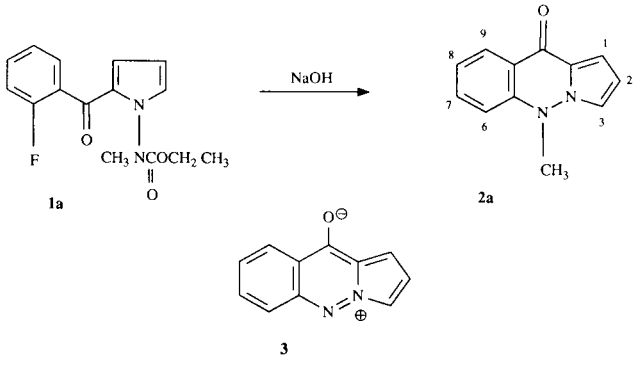
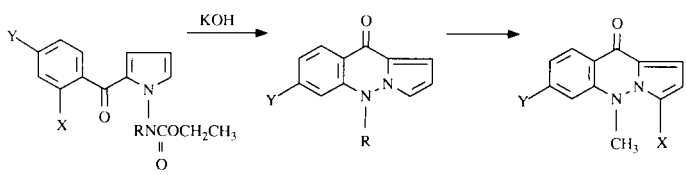
In this paper we report a further development of our research in the synthesis of aminopyrrole containing heterocycles [1-2]. During the hydrolysis of [2-(2-fluorobenzoyl)pyrrol-1-yl]methylcarbamic acid ethyl ester **1a** to the expected [2-(2-fluorobenzoyl)pyrrol-1-yl]methylamine, we noted the appearance of a second product. Analyses revealed this material to be 5-methylpyrrolo[1,2-*b*]-cinnolin-10(5*H*)-one **2a** apparently derived from displacement of the aromatic fluorine by the pendant amine. In order to further explore this unique heterocyclic system, we decided to prepare a number of derivatives and ascertain their chemical reactivity.



The only pyrrolo[1,2-*b*]cinnoline reported in the literature prior to our work is 2,3-dihydro-1*H*-pyrrolo[1,2-*b*]-cinnolium-10-oate **3** [3], by Ames *et al.*, which was prepared by a synthetic route differing substantially from the synthesis reported in this paper. These authors used a substituted cinnolinone intermediate as an A-B ring substructure, and then constructed the pyrrole C ring by alkylation. In contrast we used as starting materials the substituted 2-benzoyl-1-aminopyrrole carbamic acid esters **1a-d** as an A-C ring substructure, and then constructed ring B by aromatic halide displacement. Carbamates **1a-d** were obtained by literature methods [2,4] which involved acylation of 1-phthalimidopyrrole, followed by hydrolysis of the phthalimide protecting group [5] and then acylation. For derivatives **1a,b** there was an additional alkylation step; however, we later found it more efficient for most derivatives, to alkylate the nitrogen after cyclization.

The 5-methylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-ones **2a,b** were prepared by cyclization of carbamates **1a,b** as shown in Scheme I. Optimized cyclization conditions involved refluxing the carbamates **1a,b** in aqueous ethanol in the presence of a 3 to 5 molar excess of potassium hydroxide as a 15% solution. Attempts to cyclize either the free amine or unsubstituted carbamate with hydride bases gave less than 5% conversion to the desired cinnolines. The free amines could be prepared by hydrolysis of carbamates **1a-d** with aqueous potassium hydroxide concentrations of 3-5% without concomitant cyclization. Compounds **2a,b** behaved normally towards electrophilic substitution with *N*-halosuccinimides and acetyl nitrate [6], affording the expected 3-halo, **4a,b** and **5a,b**, or 3-nitro, **6** derivatives, respectively. However, the carbonyl functionality was inert towards reduction with sodium borohydride. Stronger reducing agents such as lithium aluminum hydride gave fission of the hydrazine bond.

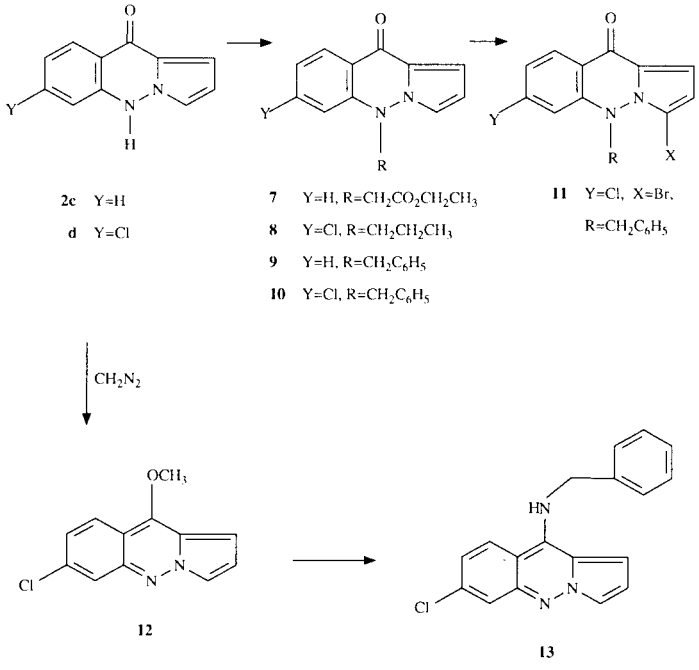
Scheme I



1a	X=F, Y=H, R=CH_3	**2a**	Y=H, R=CH_3	**4a**	Y=H, X=Cl
b	X=Cl, Y=Cl, R=CH_3	**b**	Y=Cl, R=CH_3	**b**	Y=Cl, X=Cl
c	X=F, Y=H, R=H	**c**	Y=H, R=H	**5a**	Y=H, X=Br
d	X=Cl, Y=Cl, R=H	**d**	Y=Cl, R=H	**b**	Y=Cl, X=Br
				6	Y=H, X=NO_2

Ring closure of carbamates **1c,d** in the same manner as **1a,b**, gave rise to high melting, light sensitive solids which defied rigorous purification. These solids were tentatively assigned structures **2c,d**. As seen in Scheme II these solids readily alkylated on the secondary nitrogen in the presence of potassium carbonate with a variety of alkyl halides to give cinnolines **7-10**. Compound **10** was subsequently brominated to give cinnoline **11**. These reactions support our assignment of **2c** and **2d** as pyrrolo[1,2-*b*]-cinnolin-10(5*H*)-ones.

Scheme II



The proton nmr spectra also support this assignment. Compounds **4-11** all display a characteristic doublet or doublet of doublets at δ 8.1-8.3 which is assigned to the strongly deshielded H-9 proton. This telltale downfield doublet is also seen in compounds **2a-d** but not in the uncyclized carbamates **1a-d**. That electrophilic substitution on the ring occurs specifically at position 3 is seen by collapse of the H-2 doublet of doublets at δ 6.5 and the shifted appearance of a characteristic set of doublets assigned to protons H-2 and H-1 at δ 6.4 and δ 7.1 respectively. The overlap of aromatic absorptions with the weak carbonyl absorptions (1610-1635 cm^{-1}) makes the infrared spectra an unreliable indicator in this series.

Somewhat surprisingly, treatment of the parent pyrrolo[1,2-*b*]cinnolin-10(5*H*)-one **2d** with a freshly distilled diazomethane solution gave only the *O*-methyl ether **12**. This assignment is based upon the upfield shift of the characteristic doublet at δ 8.1 to δ 7.8 and the compound's physical dissimilarity to the *N*-methylcinnoline **2b**. This structure is further supported by subsequent displacement of the methyl ether with benzylamine in the presence of mercuric acetate [7] to give *N*-benzyl-7-chloropyrrolo[1,2-*b*]cinnolin-10-amine **13** as seen in Scheme II. The lack of a doublet between δ 8.1-8.3 as well as its dissimilarity to the *N*-benzylcinnoline **10** is in agreement with the indicated structure.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Mass spectral data were determined on a Finnigan 4023 GC/MS/DS equipped with a INCOS data system. The ^1H nmr spectra were obtained at 200 MHz using a Varian 200 XL with tetramethylsilane as an internal standard. The infrared spectra were recorded on a Pye Unicam SP3-200. Elemental analyses were performed by Micro Tech Laboratories, Skokie, Illinois. Flash chromatographic separations were performed using silica gel 60 as the solid phase (230-400 mesh) from EM Laboratories, Elmsford, NY. The hplc purifications were performed on a Waters Prep LC/System 500A with silica gel cartridges.

5-Methylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**2a**).

A solution of [2-(2-fluorobenzoyl)-1*H*-pyrrol-1-yl)methylcarbamic acid ethyl ester (**1a**) (23.5 g, 0.081 mole) and potassium hydroxide (16.8 g, 0.3 mole) in aqueous ethanol was heated under reflux for 16 hours then evaporated. The yellow residue was taken up in water and washed with ether. The aqueous phase was adjusted to *p*H 5 with 6*N* hydrochloric acid and the precipitated product was collected and air dried. The solid was recrystallized from dichloromethane to give 8.0 g (50%) of **2a** as yellow crystals, mp 154-156°; ir (chloroform): 1635 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.80 (s, N-CH_3), 6.55 (dd, H-2), 6.9-7.7 (m, 5H aromatic), 8.41 (dd, H-9); ms: (m/e) 198 (M^+).

Anal. Calcd. for $C_{12}H_{10}N_2O$: C, 72.70; H, 5.08; N, 14.13. Found: C, 72.36; H, 5.33; N, 14.08.

3-Chloro-5-methylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**4a**).

A solution of 5-methylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**2a**) (5.0 g, 0.025 mole) in tetrahydrofuran was treated with *N*-chlorosuccinimide (3.4 g, 0.026 mole) and stirred at room temperature for 6 hours then evaporated. The residue was purified by flash chromatography (dichloromethane) and the resulting solid washed with hexane to give 2.8 g (45%) of **4a** as white crystals, mp 88-90°; ir (chloroform): 1650 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.45 (s, N-CH_3), 6.36 (d, H-2), 7.12 (d, H-1), 7.2-7.7 (m, 3H aromatic), 8.26 (dd, H-9); ms: (m/e) 232 (M^+).

Anal. Calcd. for $C_{12}H_9ClN_2O$: C, 61.94; H, 3.89; N, 12.04. Found: C, 61.69; H, 4.05; N, 12.14.

3-Bromo-5-methylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**5a**).

A solution of 5-methylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**2a**) (3.8 g,

0.019 mole) in tetrahydrofuran was treated with *N*-bromosuccinimide (3.5 g, 0.020 mole) and stirred at room temperature for 16 hours then evaporated. The residue was purified by hplc (dichloromethane) and the resulting solid was recrystallized from ether to give 3.6 g (67%) of **5a** as pale yellow crystals, mp 103-105°; ir (chloroform): 1645 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.44 (s, N-CH_3), 6.45 (d, H-2), 7.13 (d, H-1), 7.2-7.7 (m, 3H aromatic), 8.22 (dd, H-9); ms: (m/e) 277 (M^+).

Anal. Calcd. for $C_{12}H_9BrN_2O$: C, 52.00; H, 3.27; N, 10.11. Found: C, 51.61; H, 3.30; N, 10.17.

5-Methyl-3-nitropyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**6**).

Acetyl chloride (1.2 g, 0.015 mole) was added dropwise to a mixture of 5-methylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**2a**) (3.0 g, 0.015 mole) and silver nitrate (2.5 g, 0.015 mole) in acetonitrile then stirred at room temperature for 2 hours. This mixture was diluted with water and the precipitated product was collected and air dried. Recrystallization from acetonitrile gave 3.0 g (62%) of **6** as yellow crystals, mp 263-265°; ir (potassium bromide): 1635 cm^{-1} (C=O); ^1H nmr (dimethylsulfoxide-d_6): δ 4.12 (s, N-CH_3), 7.28 (dd, H-8), 7.38 (d, H-1), 7.6-7.9 (m, 2H aromatic), 7.98 (d, H-2), 8.22 (dd, H-9); ms: (m/e) 243 (M^+).

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.25; H, 3.73; N, 17.28. Found: C, 59.51; H, 3.49; N, 17.42.

7-Chloro-5-methylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**2b**).

A solution of [2-(2,4-dichlorobenzoyl)-1*H*-pyrrol-1-yl]methylcarbamic acid ethyl ester (**1b**) (25.1 g, 0.07 mole) and potassium hydroxide (15.6 g, 0.28 mole) in aqueous ethanol was heated under reflux for 5 hours then evaporated. The yellow residue was taken up in water and washed with ether. The aqueous phase was adjusted to *p*H 5 with 6*N* hydrochloric acid and the precipitated product was collected and air dried. This solid was recrystallized from ethanol to give 6.6 g (41%) of **2b** as yellow crystals, mp 172-173°; ir (chloroform): 1630 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.88 (s, N-CH_3), 6.59 (dd, H-2), 7.1-7.3 (m, 4H aromatic), 8.32 (d, H-9); ms: (m/e) 233 (M^+).

Anal. Calcd. for $C_{12}H_9ClN_2O$: C, 61.67; H, 4.31; N, 11.99. Found: C, 62.06; H, 3.97; N, 12.12.

3,7-Dichloro-5-methylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**4b**).

A solution of 7-chloro-5-methylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**2b**) (3.0 g, 0.013 mole) in tetrahydrofuran was treated with *N*-chlorosuccinimide (1.7 g, 0.013 mole) and stirred at room temperature for 24 hours then evaporated. The residue was purified by hplc (dichloromethane) and the resulting solid was recrystallized from ethanol to give 2.2 g (64%) of **4b** as pale yellow crystals, mp 129-131°; ir (chloroform): 1650 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.48 (s, N-CH_3), 6.39 (d, H-2), 7.12 (d, H-1), 7.3-7.4 (m, 2H aromatic), 8.18 (d, H-9); ms: (m/e) 267 (M^+).

Anal. Calcd. for $C_{12}H_8Cl_2N_2O$: C, 53.95; H, 3.02; N, 10.49. Found: C, 53.96; H, 2.94; N, 10.46.

3-Bromo-7-chloro-5-methylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**5b**).

A solution of 7-chloro-5-methylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**2b**) (6.0 g, 0.026 mole) in tetrahydrofuran was treated with *N*-bromosuccinimide (4.6 g, 0.026 mole) and stirred at room temperature for 24 hours then evaporated. The residue was purified by hplc (dichloromethane) and the resulting powder was recrystallized from ethanol to give 5.7 g (70%) of **5b** as yellow fibers, mp 133-135°; ir (chloroform): 1645 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 3.46 (s, N-CH_3), 6.48 (d, H-2), 7.12 (d, H-1), 7.3-7.4 (m, 2H aromatic), 8.16 (d, H-9); ms: (m/e) 311 (M^+).

Anal. Calcd. for $C_{12}H_8BrClN_2O$: C, 46.26; H, 2.59; N, 9.03. Found: C, 46.31; H, 2.81; N, 9.03.

Pyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**2c**).

A solution of [2-(2-fluorobenzoyl)-1*H*-pyrrol-1-yl]carbamic acid ethyl ester (**1c**) (60.0 g, 0.22 mole) and potassium hydroxide (61 g, 1.1 mole) in aqueous ethanol was heated under reflux for 1 hour then evaporated. The residue was taken up in water and washed with ether. The aqueous phase was adjusted to *p*H 5 with 6*N* hydrochloric acid and the precipitated product collected and air dried to give 20.0 g (49%) of **2c** as a yellow powder, mp >300°; ir (potassium bromide): 1635 cm^{-1} (C=O); ^1H nmr (dimethylsulfoxide-d_6): δ 6.60 (dd, H-2), 6.92 (dd, H-1), 7.0-7.7 (m, 4H aromatic), 8.12 (dd, H-9), 12.7 (s, broad, N-H); ms: (m/e) 184 (M^+).

10-Oxopyrrolo[1,2-*b*]cinnolineacetic Acid Ethyl Ester (**7**).

Ethyl bromoacetate (10.7 g, 0.064 mole) was added dropwise to a mixture of pyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**2c**) (11.7 g, 0.064 mole) and potassium carbonate (26.5 g, 0.192 mole) in methyl ethyl ketone and stirred at room temperature for 3 hours then evaporated. The residue was partitioned between dichloromethane and water then separated. The organic phase was evaporated and the residue purified by flash chromatography (dichloromethane) to give an orange solid. This solid was recrystallized from ethanol to give 10.8 g (63%) of **7** as yellow crystals, mp 130-131°; ir (chloroform): 1635, 1740 (C=O) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.23 (t, CH_3), 4.22 (q, O-CH_2), 4.96 (s, N-CH_2), 6.52 (dd, H-2), 7.0-7.7 (m, 5H aromatic), 8.39 (dd, H-9); ms: (m/e) 270 (M^+).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.35; H, 5.36; N, 10.41.

5-Benzylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**9**).

Benzyl bromide (4.0 g, 0.024 mole) was added dropwise to a mixture of pyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**2c**) (4.0 g, 0.02 mole) and potassium carbonate (11.2 g, 0.08 mole) in methyl ethyl ketone and stirred at 60° for 4 hours. This mixture was quenched with water then extracted with dichloromethane. The organic extracts were evaporated and this residue purified by flash chromatography (dichloromethane) to give a yellow solid. This solid was recrystallized from dichloromethane to give 3.5 g (65%) of **9** as yellow crystals, mp 146-148°; ir (chloroform): 1638 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 5.42 (s, N-CH_2), 6.46 (dd, H-2), 7.10-7.64 (m, 10H aromatic), 8.40 (dd, H-9); ms: (m/e) 274 (M^+).

Anal. Calcd. for $C_{18}H_{14}N_2O$: C, 78.80; H, 5.14; N, 10.21. Found: C, 79.10; H, 5.38; N, 10.40.

7-Chloropyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**2d**).

A solution of [2-(2,4-dichlorobenzoyl)-1*H*-pyrrol-1-yl]carbamic acid ethyl ester (**1d**) (102.4 g, 0.31 mole) and potassium hydroxide (84 g, 1.5 mole) in aqueous ethanol was heated under reflux for 1 hour then evaporated. The residue was taken up in water and washed with ether. The aqueous phase was adjusted to *p*H 5 with 6*N* hydrochloric acid and the precipitated product was collected and air dried to give 68 g (98%) of **2d** as a yellow powder, mp >300°; ir (potassium bromide): 1630 cm^{-1} (C=O); ^1H nmr (dimethylsulfoxide-d_6): δ 6.60 (dd, H-2), 6.8 (s, broad, N-H) 6.9-7.6 (m, 4H aromatic), 8.08 (d, H-9); ms: (m/e) 218 (M^+).

7-Chloro-5-propylpyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**8**).

1-Bromopropane (10.1 g, 0.08 mole) was added dropwise to a mixture of 7-chloropyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**2d**) (9.0 g, 0.04 mole) and potassium carbonate (11.3 g, 0.08 mole) in dimethylformamide and stirred at room temperature for 48 hours. The reaction was quenched with water and extracted with dichloromethane. The combined organic extracts were evaporated and the residue purified by hplc (dichloromethane) to an orange powder. This solid was recrystallized from ether to give 3.4 g (32%) of **8** as yellow crystals, mp 107-108°; ir (chloroform): 1635 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 1.04 (t, -CH_3), 1.76 (m, -CH_2-CH_3), 4.22 (t, N-CH_2), 6.60 (dd, H-2), 7.12-7.32 (m, 4H aromatic), 8.34 (d, H-9); ms: (m/e) 260 (M^+).

Anal. Calcd. for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 5.02; N, 10.75. Found: C, 64.59; H, 4.99; N, 10.72.

5-Benzyl-7-chloropyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**10**).

Benzyl bromide (44.4 g, 0.26 mole) was added dropwise to a mixture of 7-chloropyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**2d**) (35.0 g, 0.16 mole) and potassium carbonate (66.3 g, 0.48 mole) in methyl ethyl ketone and was stirred at 50° for 2 hours. This mixture was quenched with water and extracted with chloroform. The combined organic layers were evaporated and the residue purified by flash chromatography (dichloromethane) to

an orange powder. This powder was recrystallized from ethanol to give 12.0 g (22%) of **10** as yellow crystals, mp 163-165°; ir (chloroform): 1638 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 5.43 (s, N-CH_2), 6.46 (dd, H-2), 7.08-7.44 (m, 9H aromatic), 8.34 (d, H-9); ms: (m/e) 308 (M^+).

Anal. Calcd. for $C_{18}H_{13}ClN_2O$: C, 70.02; H, 4.24; N, 9.08. Found: C, 70.07; H, 4.31; N, 9.15.

5-Benzyl-3-bromo-7-chloropyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**11**).

A solution of 5-benzyl-7-chloropyrrolo[1,2-*b*]cinnolin-10(5*H*)-one (**10**) (4.5 g, 0.015 mole) in tetrahydrofuran was treated with *N*-bromosuccinimide (2.6 g, 0.015 mole) and stirred at room temperature for 16 hours then evaporated. The residue was purified by hplc (dichloromethane) to give a green powder which was recrystallized from ethanol to give 3.7 g (66%) of **11** as yellow fibers, mp 138-140°; ir (chloroform): 1635 cm^{-1} (C=O); ^1H nmr (deuteriochloroform): δ 5.32 (s, N-CH_2), 6.50 (d, H-2), 7.00 (d, H-1), 7.10-7.44 (m, 7H aromatic), 8.28 (d, H-9); ms: (m/e) 388 (M^+).

Anal. Calcd. for $C_{18}H_{12}BrClN_2O$: C, 55.62; H, 3.11; N, 7.21. Found: C, 55.88; H, 3.13; N, 7.10.

7-Chloro-10-methoxypyrrolo[1,2-*b*]cinnoline (**12**).

A solution of diazomethane (16.2 g, 0.30 mole) prepared from 64 g of Diazald®) in ether was added to a solution of 7-chloropyrrolo[1,2-*b*]-cinnolin-10(5*H*)-one (**2d**) (37.0 g, 0.17 mole) in tetrahydrofuran and allowed to stand for 48 hours then evaporated. The residue was purified by flash chromatography (dichloromethane) to give an orange powder. This powder was recrystallized from ether to give 18.0 g (46%) of **12** as orange fibers, mp 128-129°; ^1H nmr (deuteriochloroform): δ 4.56 (s, O-CH_3), 6.84 (dd, H-8), 7.12 (s, broad H-1, H-2), 7.46 (s, H-6), 7.86 (d, H-9), 8.03 (s, H-3); ms: (m/e) 232 (M^+).

Anal. Calcd. for $C_{12}H_9ClN_2O$: C, 61.94; H, 3.90; N, 12.04. Found: C, 61.94; H, 3.80; N, 11.94.

N-Benzyl-7-chloropyrrolo[1,2-*b*]cinnolin-10-amine (**13**).

A mixture of 7-chloro-10-methoxypyrrolo[1,2-*b*]cinnoline (**12**) (8.1 g, 0.34 mole), mercuric acetate (1.7 g, 0.005 mole), and benzylamine (107 g, 1.0 mole) was heated at 55° for 2 hours then evaporated under high vacuum. The residue was first triturated with cold ether then recrystallized from hot ether to give 9.7 g (92%) of **13** as orange crystals, mp 184-186°; ^1H nmr: δ 5.14 (d, N-CH_2), 5.52 (s, broad, N-H), 6.74 (d, H-8), 6.92-7.04 (m, H-1, H-2), 7.36-7.52 (m, 7H aromatic), 7.92 (dd, H-3); ms: (m/e) 307 (M^+).

Anal. Calcd. for $C_{18}H_{14}ClN_3$: C, 70.24; H, 4.58; N, 13.65. Found: C, 70.20; H, 4.52; N, 13.62.

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