Synthesis of Analogs of Amrinone: 4-(3,4-Disubstitutedphenyl)pyridines and Derivatives Thereof

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4-(3,4-Dimethoxyphenyl)pyridine (**5c**) prepared by the coupling of 3,4-dimethoxyphenyldiazonium chloride with pyridine was converted to 4-(4-pyridinyl)benzene-1,2-diol (**6c**) by treating with hydrobromic acid. Diazotization of 4-(4-pyridinyl)benzeneamine (**7**) and 3-(4-pyridinyl)benzeneamine (**12**) gave the corresponding phenols **8** and **13** which were nitrated to give 2-nitro-4-(4-pyridinyl)phenol (**9**) and 2-nitro-5-(4-pyridinyl)-phenol (**14**), respectively. Reduction of these nitrophenols gave the corresponding aminophenols **10** and **16** which in turn were reacted with *N,N'*-carbonyldiimidazole to yield benzoxazolones **11** and **17**, respectively. Catalytic reduction of 2-nitro-4-(4-pyridinyl)benzeneamine (**18**) gave 4-(4-pyridinyl)benzene-1,2-diamine (**19**) which was reacted with orthoesters, urea, tetraethoxymethane, and *N,N'*-di(carbomethoxy)methylpseudothiourea to give the corresponding benzimidazole derivatives **20**, **21**, **22**, and **23**.

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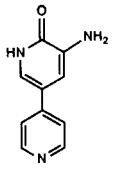
Several years ago, the search for a nonglycoside cardiotonic agent in our laboratory led to the development of amrinone (**1**) [2]. Our efforts to find an orally active and more potent compound have focused on several classes of compounds which are structurally related to amrinone. There is a structural resemblance between the bifunctional pyridinone moiety of amrinone and dopamine (**2**) [3] and dobutamine (**3**) [4]. This observation prompted the synthesis of 4-(3,4-disubstitutedphenyl)pyridines **6c**, **10**, **16** and **19**. During the course of this study, it was found that benzoxazolone **11** and its precursor, 2-aminophenol **10** have the same level of cardiotonic activity. This indicated that free hydroxy and amino groups are not essential for the cardiotonic activity. In view of this finding, diamine **19** was converted to several benzimidazole derivatives which were found to be potent cardiotonics. These compounds were prepared by synthetic sequences depicted in Schemes A, B, and C.



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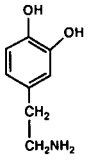

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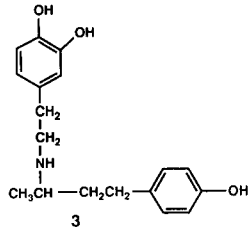

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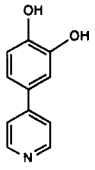
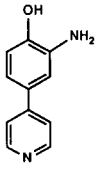


6c



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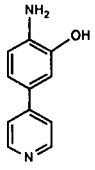

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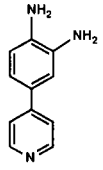
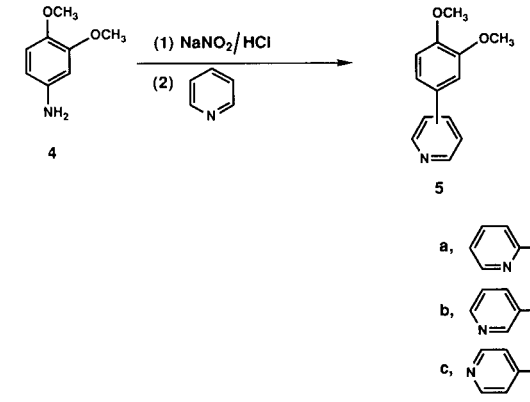
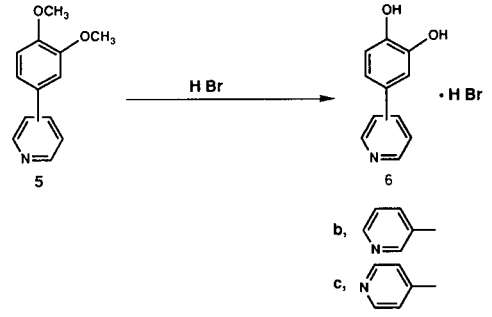


19

Scheme A

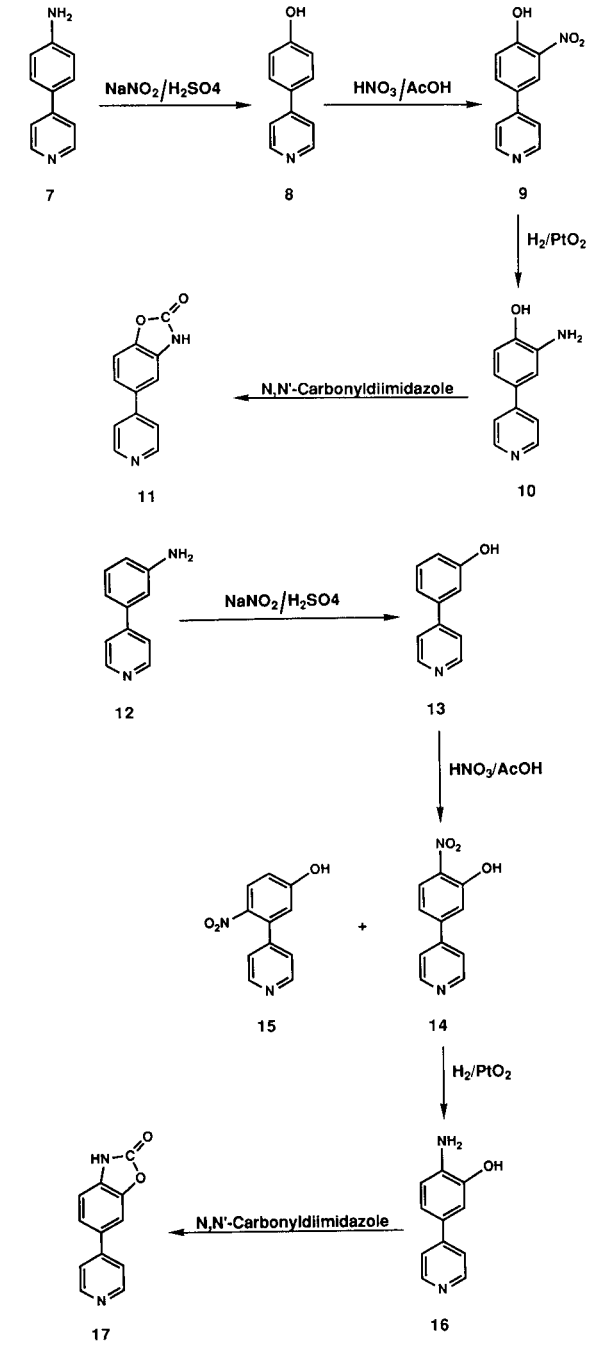




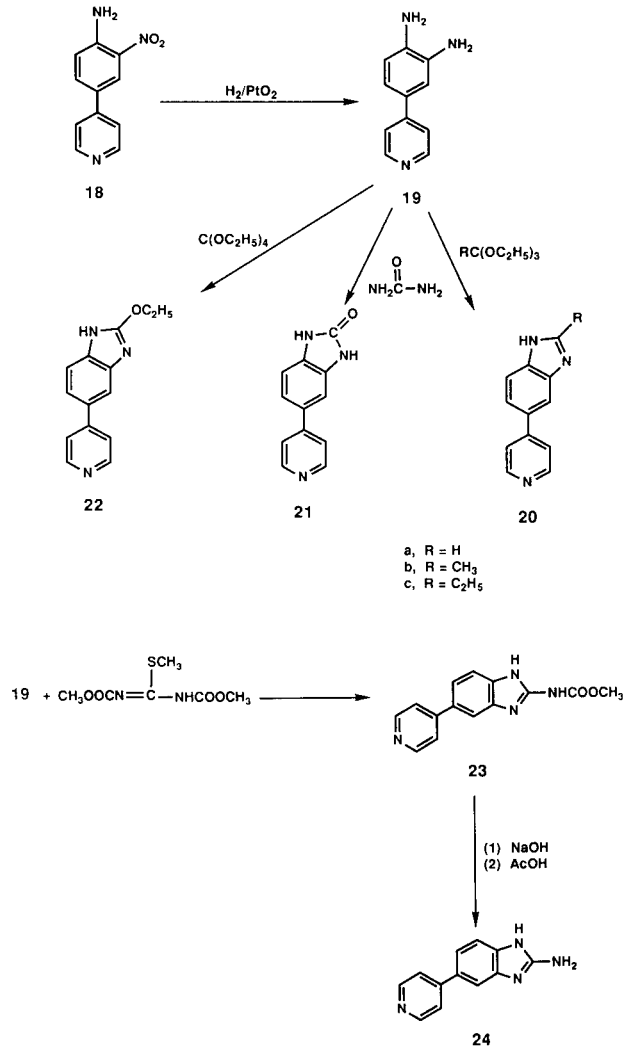
Results and Discussion.

The coupling of 3,4-dimethoxybenzenediazonium chloride with pyridine, shown in Scheme A, gave a mixture of three isomeric pyridine derivatives **5**. The least polar and the most abundant 2-isomer **5a** was separated by column chromatography. The mixture of the remaining two isomers was separated by fractional crystallization. Dimethoxybenzene derivatives **5b** and **5c** were converted to catechols, **6b** and **6c**, respectively, by heating with 48% aqueous hydrobromic acid. After we had completed this

Scheme B



Scheme C



work, Brossi *et al.* [5] reported the preparation of **6c** by the aromatization of 4-(3,4-dimethoxyphenyl)-1,2,3,6-tetrahydropyridine.

Diazotization of benzeneamines **7** [6] and **12** [7] in aqueous sulphuric acid gave the corresponding phenols **8** and **13** (Scheme B). Treatment of **8** with stoichiometric amount of 95% nitric acid in acetic acid yielded nitrophenol **9** in a high yield. Nitration of phenol **13** under similar conditions gave a mixture from which nitrophenol **14** and nitrophenol **15** were isolated by repeated crystallizations. Catalytic reduction of **9** and **14** gave the corresponding aminophenols **10** and **16** which in turn were reacted with *N,N'*-carbonyldiimidazole to give benzoxazolones **11** and **17**, respectively.

Catalytic reduction of 2-nitro-4-(4-pyridinyl)benzeneamine (**18**) [6] gave diamine **19**. Reaction of **19** with orthoesters, urea, tetraethoxymethane, and *N,N'*-di(carbomethoxy)methylpseudothiourea gave benzimidazoles **20**, benzimidazolone **21**, 2-ethoxybenzimidazole derivative **22**, and carbamate **23**, respectively. Hydrolysis of carbamate **23** with aqueous sodium hydroxide gave amino compound **24**.

The *in vitro* cardiotonic activity of catechol **6c**, aminophenol **10**, phenylenediamine **19**, benzoxalone **11**, and benzimidazole derivatives **20**, **21** and **22** is equal to that of amrinone.

EXPERIMENTAL

Melting points were determined in open capillaries in an oil bath and are uncorrected. The ^{1}H nmr spectra were obtained in deuteriotrifluoroacetic acid, unless indicated otherwise, on Varian HA-100 spectrometer.

Coupling of 3,4-Dimethoxybenzenediazonium Chloride with Pyridine.

3,4-Dimethoxybenzenediazonium chloride solution prepared from [3,4-dimethoxybenzeneamine (200 g, 1.3 moles), 30% aqueous hydrochloric acid (500 ml), and sodium nitrite (102 g, 1.5 moles) dissolved in water (200 ml)] was stirred into pyridine (2 l) preheated to 40° over 2.5 hours. External heating was stopped and the internal temperature stayed at 45-55° due to exothermic nature of the reaction. After 1 hour of heating on a steam bath, the reaction mixture was concentrated under reduced pressure. The black semisolid residue was partitioned between 15% aqueous hydrochloric acid (1 l) and chloroform (600 ml). The organic layer was discarded and the aqueous phase was made basic by treating with concentrated aqueous ammonia. The resulting dark brown oil was extracted with chloroform (500 ml). Removal of chloroform under reduced pressure gave 165.7 g of a viscous dark brown oil which was separated into two fractions by column chromatography (silica gel 1.2 kg, 1:1 hexane/ether-ether). The less polar fraction was recrystallized from ether-hexane to afford 67.8 g (24%) of cottony white needles of 2-(3,4-dimethoxyphenyl)pyridine (**5a**), mp 76-78°; ^{1}H nmr (deuteriochloroform): δ 8.8-6.8 (m, 7H, 3ArH + -C_5H_4N), 4.0 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3).

Anal. Calcd. for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.67; H, 6.15; N, 6.39.

The more polar fraction was recrystallized from ether to give 24.8 g (9%) of 4-(3,4-dimethoxyphenyl)pyridine (**5c**) as a white solid, mp 101-103° (lit mp 245-247° (hydrobromide salt) [5]); ^{1}H nmr (deuteriochloroform): δ 8.64, 7.48 (A_2B_2, 4H, -C_5H_4N), 7.4-6.9 (m, 3H, ArH), 3.98 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3).

The residue from the mother liquor of the more polar fraction was dissolved in 6*N* aqueous hydrochloric acid (200 ml). The resulting solution was treated with charcoal and then concentrated to dryness under reduced pressure to give a greenish solid residue which was recrystallized from 2-propanol to give 33 g (10%) of light green crystals of hydrochloride salt of 3-(3,4-dimethoxyphenyl)pyridine (**5b**), mp 198-200°; ^{1}H nmr: δ 9.18-7.16 (m, 7H, 3ArH, -C_5H_4N), 4.12 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3).

Anal. Calcd. for $C_{13}H_{13}NO_2$·HCl: C, 62.03; H, 5.61; N, 5.56. Found: C, 62.24; H, 5.70; N, 5.52.

4-(4-Pyridinyl)-1,2-benzenediol Hydrobromide Salt (**6c**).

A mixture of **5c** (10.3 g, 0.047 mole) and 48% aqueous hydrobromic acid (75 ml) was heated under reflux for 5 hours and then allowed to stand at room temperature overnight. The product that crystallized as yellow needles was collected to give 11.8 g (94%) of **6c**, mp 214-217° (lit mp 206-209° [5]); ^{1}H nmr: δ 8.9, 8.6 (A_2B_2, 4H, -C_5H_4N), 7.3-7.1 (m, 3H, ArH).

4-(3-Pyridinyl)-1,2-benzenediol Hydrobromide Salt (**6b**).

Following the procedure for the preparation of **6c**, **6b** was prepared in 79% yield as a yellow solid, mp 288-290°; ^{1}H nmr: δ 9.04-7.18 (m, 7H).

Anal. Calcd. for $C_{11}H_9NO_2$·HBr: C, 49.28; H, 3.76; N, 5.22. Found: C, 49.62; H, 3.74; N, 5.28.

4-(4-Pyridinyl)phenol (**8**).

To a stirred mixture of amine **7** [6] (85 g, 0.5 mole) and 20% aqueous sulphuric acid (500 ml) cooled in an ice bath was added a solution of sodium nitrite (35 g, 0.5 mole) in water (100 ml) dropwise over a period of 2 hours below 5°. The resulting dark solution was allowed to stand at room temperature overnight and then filtered. The filtrate was heated on a steam bath for 4 hours and then neutralized by treating with concentrated aqueous ammonia. The resulting yellow precipitate was collected and recrystallized from methanol to yield 75.8 g (89%) of a light solid, mp 240-244°; ^{1}H nmr: δ 8.73, 8.27 (A_2B_2, 4H, C_5H_4N), 7.9, 7.25 (A_2B_2, 4H, -C_6H_4-).

Anal. Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.34; H, 5.46; N, 8.20.

3-(4-Pyridinyl)phenol (**13**).

Following the procedure for the preparation of phenol **8**, amine **12** [7] was converted to phenol **13** in 94% yield, mp 220-224°; ^{1}H nmr: δ 8.84, 8.32 (A_2B_2, 4H, -C_5H_4N), 7.7-7.2 (m, 4H, ArH).

Anal. Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.95; H, 5.16; N, 7.98.

2-Nitro-4-(4-pyridinyl)phenol (**9**).

To a stirred mixture of phenol **8** (17.1 g, 0.1 mole) and glacial acetic acid (250 ml) was added a solution of nitric acid (4.5 ml, d, 1.5) in glacial acetic acid (15 ml) over a 20 minute period whereupon a yellow solid crystallized. The resulting mixture was heated on a steam bath for 2 hours. The solid dissolved resulting in a deep red solution which was poured into ice cold water (500 ml). Neutralization with concentrated aqueous ammonia gave an orange solid which was recrystallized from DMF to afford 17.1 g (79%) of orange needles, mp 208-210°; ^{1}H nmr: δ 8.93, 8.44 (A_2B_2, 4H, -C_5H_4N), 8.82 (dd, 1H), 8.24 (dd, 1H), 7.54 (dd, 1H).

Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 60.90; H, 3.83; N, 12.96.

Nitration of 3-(4-pyridinyl)phenol (**13**).

To a stirred mixture of phenol **13** (242 g, 1.4 moles) and glacial acetic acid (1 l) was added dropwise a solution of nitric acid (60 ml, d = 1.5) in glacial acetic acid (200 ml) over a period of 40 minutes below 15°. The resulting mixture was stirred at room temperature for 1 hour, heated on a steam bath for 4 hours and then acetic acid ($\approx$ 700 ml) was removed under reduced pressure. The deep red residual mixture was poured into ice cold water (1 l) and neutralized by treating with concentrated aqueous ammonia. The resulting red precipitate was collected and separated by fractional crystallization (methanol-acetic acid) to give nitrophenol **14** and nitrophenol **15**.

Compound **14** had mp 177-178°, yield 64 g (21%); ^{1}H nmr: δ 9.06-7.45 (m, 7H).

Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.11; H, 3.63; N, 12.91.

Compound **15** had mp >300°, yield 50.4 g (16%); ^{1}H nmr: δ 8.88, 8.08 (A_2B_2, 4H, -C_5H_4N), 8.37 (dd, 1H), 7.27 (dd, 1H), 6.98 (dd, 1H).

Anal. Calcd. for $C_{11}H_8N_2O_3$: C, 61.11; H, 3.73; N, 12.96. Found: C, 61.38; H, 3.69; N, 12.98.

2-Amino-4-(4-pyridinyl)phenol (**10**).

A mixture of nitrophenol **9** (21.6 g, 0.1 mole), platinum oxide (1 g), and 75% aqueous acetic acid (200 ml) was reduced on a Parr hydrogenator. The catalyst was removed by filtration through a celite pad. The filtrate was concentrated to dryness under reduced pressure and the solid residue was recrystallized as a dihydrochloride salt from methanol to give 22.4 g (89%) of greenish needles, mp >300°; ^{1}H nmr (deuterium oxide): δ 9.13, 8.55 (A_2B_2, 4H, -C_5H_4N), 8.3 (dd, 1H), 8.21 (dd, 1H), 7.52 (dd, 1H).

Anal. Calcd. for $C_{11}H_{10}N_2O \cdot 2HCl$: C, 50.99; H, 4.67; N, 10.81. Found: C, 50.87; H, 4.72; N, 10.57.

2-Amino-5-(4-pyridinyl)phenol (**16**).

Following the procedure for the reduction of nitrophenol **9**, aminophenol **16** was obtained in 73% yield, mp 212-215°; ^{1}H nmr: δ 8.95, 8.4 (A_2B_2, 4H, -C_5H_4N), 7.95-7.45 (m, 3H).

Anal. Calcd. for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 71.12; H, 5.36; N, 15.06.

5-(4-Pyridinyl)benzoxazol-2(3*H*)-one (**11**).

A mixture of aminophenol **10** (18.6 g, 0.1 mole), *N,N'*-carbonyldiimidazole (18.9 g, 0.11 mole), and DMF (200 ml) was stirred at room temperature for 18 hours and then concentrated under reduced pressure. The solid residue was washed with water and recrystallized from 2-propanol to afford 12.9 g (61%) of a tan solid, mp 223-225°; ^{1}H nmr (DMSO-d_6): δ 10.4 [s (br), 1H, NH], 8.62 (d, 2H, pyridine H-2, H-6), 7.6-7.24 (m, 5H, 3ArH + pyridine H-3, H-5).

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.69; H, 3.79; N, 13.29.

6-(4-Pyridinyl)benzoxazol-2(3*H*)-one (**17**).

Amino phenol **16** was converted to **17** in a manner similar to the conversion of **10** to **11**, giving tan crystals in 76% yield, mp >300°; ^{1}H nmr: δ 8.88, 8.39 (A_2B_2, 4H, -C_5H_4N), 8.0-7.8 (m, 2H), 7.64 (dd, 1H).

Anal. Calcd. for $C_{12}H_8N_2O_2$: C, 67.92; H, 3.80; N, 13.20. Found: C, 67.97; H, 3.76; N, 13.25.

4-(4-Pyridinyl)-1,2-benzenediamine (**19**).

A mixture of 2-nitro-4-(4-pyridinyl)benzeneamine **18** [6] (115 g, 0.53 mole), platinum oxide (1.2 g), and 70% aqueous acetic acid (1.1 l) was reduced on a Parr hydrogenator. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The brown solid residue was basified by treating with concentrated aqueous ammonia, filtered off, washed with water, and recrystallized from ethanol to afford 50.4 g (51%) of a light brown solid, mp 260-267°; ^{1}H nmr: δ 9.2-7.8 (m, 7H).

Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.28; H, 6.63; N, 22.58.

5-(4-Pyridinyl)-1*H*-benzimidazole Dimethanesulfonate Salt (**20a**).

A mixture of diamine **19** (4 g, 20 mmoles), trimethyl orthoformate (3.5 ml, 33 mmoles), and ethanol (30 ml) was heated under reflux for 8 hours and then concentrated under reduced pressure. The solid residue was recrystallized as a dimethanesulfonate salt from ethanol to yield 6.2 g (80%) of tan crystals, mp 233-235°; ^{1}H nmr: δ 9.7 (s, 1H, H-2), 9.25-8.35 (m, 7H, 3ArH + -C_5H_4N), 3.25 (s, 6H, 2 x CH_3SO_3-).

Anal. Calcd. for $C_{12}H_9N_3 \cdot 2CH_3SO_3H$: C, 43.40; H, 4.22; N, 10.85. Found: C, 43.08; H, 4.30; N, 10.46.

2-Methyl-5-(4-pyridinyl)-1*H*-benzimidazole Dimethanesulfonate Salt (**20b**).

A mixture of **19** (11.8 g, 64 mmoles), triethyl orthoacetate (20 ml), and ethanol (100 ml) was heated under reflux for 24 hours and then concentrated under reduced pressure. The solid residue was recrystallized as a dimethane sulfonate salt from isopropanol yielding 21.5 g (90%) of tan crystals, mp 226-228°; ^{1}H nmr: δ 8.95 (d, 2H, pyridine H-2, H-6), 8.47 (m, 3H), 8.13 (m, 2H), 3.25 (s, 6H, 2 x CH_3SO_3-), 3.15 (s, 3H, -CH_3).

Anal. Calcd. for $C_{13}H_{11}N_3 \cdot 2CH_3SO_3H$: C, 44.88; H, 4.77; N, 10.47. Found: C, 45.30; H, 4.67; N, 10.64.

2-Ethyl-5-(4-pyridinyl)-1*H*-benzimidazole Dimethanesulfonate Salt (**20c**).

Replacement of triethyl orthoacetate by triethyl orthopropionate in the above example (**20b**) gave **20c** in 92% yield, mp 182-184°; ^{1}H nmr: δ 9.0-8.0 (m, 7H, 3ArH + -C_5H_4N), 3.47 (q, 2H, -CH_2CH$_3$), 3.18 (s, 6H, 2 x CH_3SO_3-), 1.68 (t, 3H, -CH_2CH_3).

Anal. Calcd. for $C_{14}H_{13}N_3 \cdot 2CH_3SO_3H$: C, 46.25; H, 5.09; N, 10.11. Found: C, 45.94; H, 5.08; N, 10.25.

5-(4-Pyridinyl)-1*H*-benzimidazol-2-one (**21**).

A mixture of **19** (11.1 g, 60 mmoles), urea (22.5 g, 0.38 mole), and DMF (200 ml) was heated under reflux with stirring for 5 hours and then concentrated under reduced pressure. The residual solid was treated with water, filtered off and recrystallized from DMF to give 10 g (79%) of a white solid, mp >300°; ^{1}H nmr: δ 8.84, 8.36 (A_2B_2, 4H, -C_5H_4N), 8.04 (dd, 1H), 7.85 (dd, 1H), 7.65 (dd, 1H).

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.24; H, 4.30; N, 19.89. Found: C, 68.31; H, 4.42; N, 19.68.

2-Ethoxy-5-(4-pyridinyl)-1*H*-benzimidazole (**22**).

A mixture containing **19** (13.5 g, 73 mmoles), tetraethoxymethane (90 ml), and acetic acid (3 ml) was stirred at room temperature for 2 hours, heated on a steam bath for 2.15 hours and then concentrated under reduced pressure. The gummy residue was treated with 10% aqueous potassium carbonate, collected and crystallized from acetone after treating with charcoal to give 10.5 g (60%) of **22**, mp 108-110°; ^{1}H nmr: δ 8.9, 8.41 (A_2B_2, 4H, -C_5H_4N), 8.2-7.81 (m, 3H, ArH), 5.03 (q, 2H, O-CH_2CH$_3$), 1.8 (t, 3H, -OCH$_2$CH_3).

Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.29; H, 5.43; N, 17.57. Found: C, 70.15; H, 5.51; N, 17.41.

Methyl *N*-[5-(4-Pyridinyl)-1*H*-benzimidazol-2-yl]carbamate (**23**).

A mixture of **19** (14.2 g, 0.08 mole), *N,N'*-di(carbomethoxy)-methylpseudothiourea [8] (15.8 g, 0.08 mole), and methanol (300 ml) was heated under reflux with stirring overnight and then allowed to stand at room temperature for several hours. The light tan solid which crystallized was collected to yield 14.6 g (68%) of **23**, mp >290° dec; ^{1}H nmr: δ 8.9 (d, 2H, pyridine H-2, H-6), 8.55-8.0 (m, 5H, 3ArH + pyridine H-3, H-5), 4.15 (s, 3H, OCH_3).

Anal. Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.67; H, 4.50; N, 20.90.

2-Amino-5-(4-pyridinyl)-1*H*-benzimidazole Dimethane Sulfonate Salt (**24**).

A solution of carbamate **23** (11.2 g, 40 mmoles), 35% aqueous sodium hydroxide (50 ml) and methanol (200 ml) was heated under reflux for 3 hours and then concentrated under reduced pressure. The residue was treated with 30% aqueous acetic acid (100 ml) and cooled in an ice bath whereupon a greenish product crystallized. This solid was collected, washed with water, dried, and recrystallized as a dimethanesulfonate salt from ethanol to afford 8.5 g (53%) of light green hydroscopic crystals, mp 248-250°; ^{1}H nmr: δ 8.87, 8.39 (A_2B_2, 4H, -C_5H_4N), 8.11 (dd, 1H), 7.92 (dd, 1H), 7.73 (dd, 1H), 3.18 (s, 6H, 2 x CH_3SO_3-).

Anal. Calcd. for $C_{12}H_{10}N_4 \cdot 2CH_3SO_3H$: C, 41.78; H, 4.51; N, 13.92. Found: C, 41.60; H, 4.71; N, 13.88.

Acknowledgement.

We are grateful to Dr. Donald F. Page for the preparation of compounds **21** and **22** and the Department of Molecular Characterization for the ^{1}H nmr spectra.

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