Synthesis of 2-Substituted Benzimidazole-5-carbamates as Potential Antifilarial Agents

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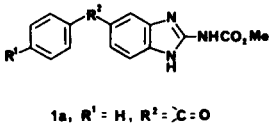
Received August 26, 1985

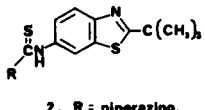
A number of 2,5-disubstituted benzimidazoles have been prepared from 2-benzyl-5-nitrobenzimidazole (**5**) and 2-*p*-fluorobenzyl-5-nitrobenzimidazole (**6**), and evaluated as potential antifilarial agents. None of the compounds prepared in this study have demonstrated any significant antifilarial activity.

J. Heterocyclic Chem., **23**, 1109 (1986).

A large group of benzimidazole derivatives are highly effective as an anthelmintics [1]. Among these, mebendazole (**1a**, methyl 5-benzoylbenzimidazole-2-carbamate) and flubendazole (**1b**, methyl 5-*p*-fluorobenzoylbenzimidazole-2-carbamate) have demonstrated a broad-spectrum of activity against helminth diseases including filarial infections [2-5]. In our continuing studies to develop new antifilarial agents [6-8], we have found that two of the metabolites of mebendazole, methyl 5-(α-hydroxylbenzyl)-benzimidazole-2-carbamate (**1c**), and, methyl 5-benzylbenzimidazole-2-carbamate (**1d**) possess antifilarial activity very similar to that of the parent drug **1a** [9]. Recently, a series of benzothiazoles, typified by structure **2**, were



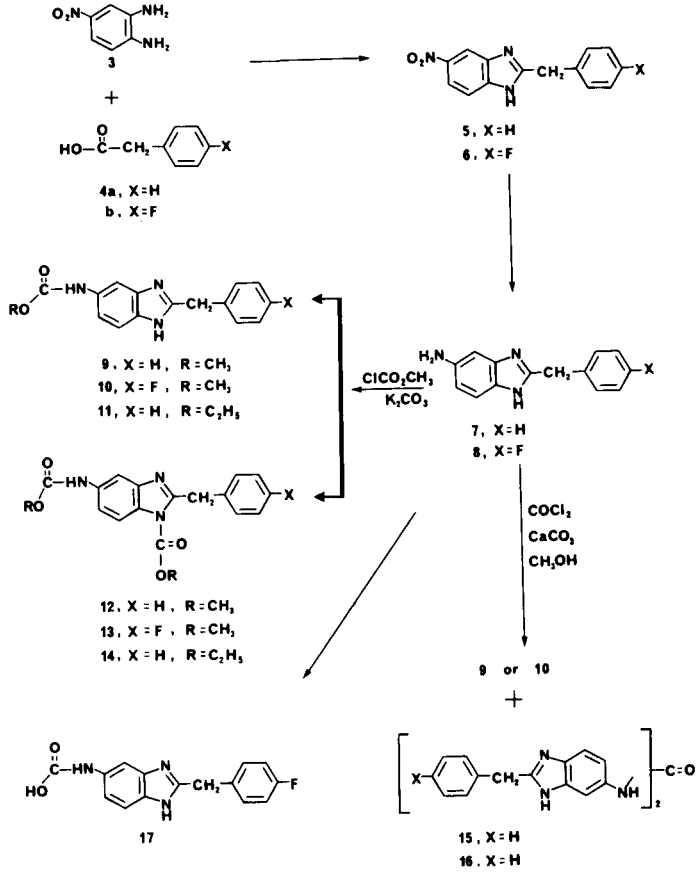
1a, R^1 = H, R^2 = >C=O
b, R^1 = F, R^2 = >C=O
c, R^1 = H, R^2 = >CHOH
d, R^1 = H, R^2 = >CH_2



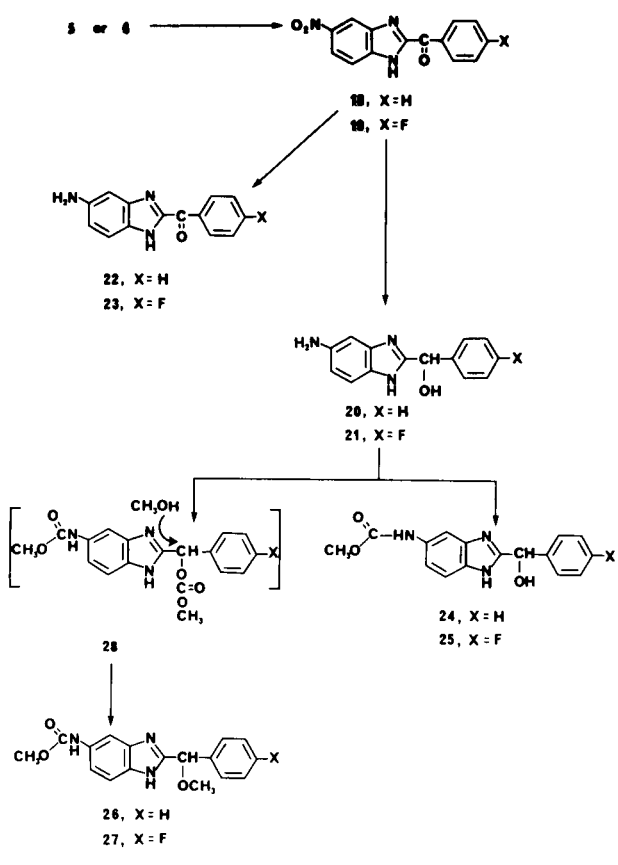
2, R = piperazino, $HO_2C(CH_2)_2S$-

reported to possess both micro- and macrofilarial activity against *B. pahangi* [10]. This interesting transposition of the hydrophilic and lipophilic groups, in relationship to those found in the methyl benzimidazole-2-carbamates, such as **1c** and **1b**, prompted us to prepare a series of methyl benzimidazole-2-carbamates in which the hydrophilic methyl carbamate group at position 2 and the lipophilic group at position 5 on the benzimidazole ring system have been transposed in order to investigate their potential as antifilarial agents.

2-Benzyl-5-nitrobenzimidazole (**5**) [11] and 2-*p*-fluorobenzyl-5-nitrobenzimidazole (**6**) were prepared by a condensation, under acidic conditions, of 4-nitro-*o*-phenylenediamine (**3a**) with phenylacetic acid (**4a**), and the *p*-fluorophenylacetic acid (**4b**) in 65% and 78% yields, respectively. The 5-nitro derivatives, **5** and **6** were submitted to catalytic hydrogenation in the presence of 5% palladium on carbon to afford near quantitative yields of 5-amino-2-benzylbenzimidazole (**7**) and 5-amino-2-*p*-fluorobenzylbenzimidazole (**8**), respectively. Subsequent treatment of



either **7** or **8** with methyl or ethyl chloroformate at room temperature in the presence of potassium carbonate yielded not only the desired methyl 5-carbamates **9-11** but also a slight amount of the diacylated methyl 1-carbomethoxybenzimidazole-5-carbamates **12-14**. If the 5-aminobenzimidazoles **7** or **8** were treated with phosgene in glyme in the presence of methanol, the yield of the desired methyl 5-carbamates **9** and **10** was decreased due to a concurrent formation of the *bis*-benzimidazole ureas **15** and **16**. Reaction of 5-amino-2-*p*-fluorobenzylbenzimidazole (**8**) with phosgene in the presence of water and calcium carbonate gave 2-*p*-fluorobenzylbenzimidazole-5-carbamic acid (**17**) in 74% yield. In our hands, the oxidation of the benzylic



methylene of either **9** or **10** using Jones reagent or chromium trioxide-acetic acid afforded only intractable complex mixtures. To circumvent this problem, we then submitted the 2-benzyl-5-nitrobenzimidazoles **5** and **6** to oxidation with chromium trioxide-acetic acid at room temperature. This oxidation proceeded very smoothly to afford the 5-nitro-2-benzoylbenzimidazole derivatives **18** and **19** in 75% and 80% yields, respectively. However, catalytic reduction of compounds **18** and **19** in the presence of either palladium on carbon (5%) or Raney-nickel in methanol gave 5-amino-2-(α-hydroxybenzyl)-benzimidazole (**20**) and 5-amino-2-(α-hydroxy-*p*-fluorobenzyl)benzimidazole (**21**) in near quantitative yield, rather than the desired products **22** and **23**. Various attempts to selectively reduce the $-NO_2$ group without concurrent reduction of the 2-carbonyl functionality either failed or afforded only compounds **20** and **21**.

Treatment of the 5-amino derivatives **20** and **21** with methyl chloroformate in glyme in the presence of potassium carbonate afforded a mixture of methyl [2-(α-hydroxybenzyl)benzimidazole-5-carbamate (**24**) and methyl [2-(α-hydroxy-*p*-fluorobenzyl)benzimidazole-5-carbamate (**25**), respectively. In addition, 5-methyl [2-(α-methoxybenzyl)methyl]benzimidazole-5-carbamate **26** and 5-methyl [2-(α-methoxy-*p*-fluorobenzyl)benzimidazole-5-carbamate (**27**) were also isolated from this reaction as side products. A suggested mechanism for the formation of **26** and **27** is incorporated into Scheme 2. The structure of all compounds was confirmed by ir, ^{1}H nmr, uv, mass spectra and analytical data.

All compounds were evaluated for antifilarial activity against both the microfilaria and adult worms of *Brugia pahangi* and *Litomosoides carinii* in jirds at 100 mg/kg administered subcutaneously for 5 days and demonstrated little or no antifilarial activity at this dosage [12, 13].

EXPERIMENTAL

The melting points were determined with a Thomas Hoover, capillary melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer 281 spectrophotometer and values are expressed in cm^{-1}. The ^{1}H nmr spectra were obtained on a Varian EM-360 (60 MHz) spectrophotometer. The chemical shifts values are reported in parts per million on the δ scale with tetramethylsilane as the internal reference. The mass spectra were recorded on a Finnigan Model 4023 GC/MS spectrometer. The microanalysis were performed by M-H-W Laboratories, Phoenix, AZ. Column chromatography was carried out on silica gel (60-200 mesh) and Kiesel gel 60 F_{254} (70-230 mesh). Ultraviolet spectra (uv) were recorded with a Hewlett-Packard 8450 uv/vs spectrophotometer. The thin layer chromatography was performed on silica gel - GF (Analtech) plates using the identical solvent systems described as eluants for column chromatography. The detection of the compounds on tlc was made by using uv light or iodine. The evaporation of solvents was carried out under reduced-pressure with a rotary evaporator using a water aspirator at steambath temperature.

2-Benzyl-5-nitrobenzimidazole (**5**) [11].

A mixture of 4-nitro-*o*-phenylenediamine (3.083 g, 0.02 mole) and phenylacetic acid (4.085 g, 0.03 mole in 4*N* aqueous hydrochloric acid, 40 ml) was stirred, and heated at 110° for 20-24 hours. The mixture was cooled to room temperature and the solid material, which separated during the reaction, was collected by filtration. The solid was washed with 10% aqueous hydrochloric acid (100-150 ml), followed by a 28% aqueous ammonium hydroxide solution (50 ml) wash, and subsequently dried. The crude product was purified by column chromatography on silica gel (60-200 mesh, Baker) eluting with chloroform:methanol (95:5, v:v). The fractions containing **5** were pooled, and upon concentration under vacuum, afforded a viscous oil which was crystallized from ethanol:water (6:4, v:v) to yield 3.30 g (75%) of **5**, mp 183-184°; ir (potassium bromide): ν max 1630, 1600, 1572, 1510, 1350-1310, 767, 737, 705 cm^{-1}; ^{1}H nmr [deuteriochloroform + DMSO-d_6 (3 drops)]: δ 4.42 (s, 2 H, CH_2-C), 7.43 (s, 5 H, Ar-H), 7.63 (d, 1 H, Ar-H), 8.30 (d, 1 H, Ar-H_6), 8.64 (bs, 1 H, Ar-H_4), 12.60 (bs, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.35; H, 4.38; N, 16.59. Found: C, 66.45; H, 4.33; N, 16.41.

2-*p*-Fluorobenzyl-5-nitrobenzimidazole (**6**).

This compound was prepared by using a method similar to that used to prepare **5**. Compound **6** was crystallized from ethanol:water; yield 78%, mp 158°; ir (potassium bromide): ν max 1630, 1515, 1345, 770, 740-732 cm^{-1}; ^{1}H nmr [deuteriochloroform + DMSO-d_6 (3 drops)]: δ 4.49 (s, 2 H, CH_2), 6.95-8.08 (m, 5 H, Ar-H), 8.34 (d, 1H, Ar-H_6), 8.70 (s, 1H, Ar-H_4).

Anal. Calcd. for $C_{14}H_{10}FN_3O_2$: C, 61.99; H, 3.72; N, 15.49. Found: C, 61.91; H, 3.87; N, 15.41.

5-Amino-2-benzylbenzimidazole (**7**).

A solution of **5** (3.04 g) in methanol (40 ml) was hydrogenated in a Parr apparatus at 50-60 psi of hydrogen in the presence of palladium on carbon (1.5 g, 5%) for 18 hours at room temperature. The catalyst was removed by filtration through a celite pad, and the pad was washed with hot methanol (50 ml). The combined filtrates were concentrated, under

reduced pressure, to furnish crude **7**. This material was purified by silica gel chromatography on silica gel $60F_{254}$ (30 g, 70-230 mesh; column size, 30 x 2.5 cm) using ethyl acetate:methanol (95:5 v:v) as an eluant. The yield of **7** was 2.60 g (96%), mp 83-84° (shrinking starts after 75°); ir (potassium bromide): ν max 3370, 3200-2980, 1632, 805, 720-710, 690 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.05 (s, 2 H, CH_2), 4.80-6.32 (bm, 3H, NH_2 and NH, exchangeable with deuterium oxide), 6.35-7.40 (m, 8H, Ar-H).

Anal. Calcd. for $C_{14}H_{13}N_3$: C, 75.31; H, 5.87; N, 18.82. Found: C, 75.24; H, 6.00; N, 18.55.

5-Amino-2-*p*-fluorobenzylbenzimidazole (**8**).

This compound was prepared by a method similar to that used to prepare **7**, yield 94%, mp 65-67°; ir (potassium bromide): ν max 3400-3300, 1635, 820, 765, 732 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.22 (s, 2 H, CH), 4.82-6.35 (bm, 3 H, NH_2 and NH, exchangeable with deuterium oxide), 6.35-7.70 (m, 7 H, Ar-H).

Anal. Calcd. for $C_{14}H_{12}FN_3$: C, 69.70; H, 5.01; N, 17.42. Found: C, 70.00; H, 5.25; N, 17.17.

Methyl 2-Benzylbenzimidazole-5-carbamate (**9**) and Methyl 2-Benzyl-1-carbomethoxybenzimidazole-5-carbamate (**12**).

Method 1.

Methyl chloroformate (0.8 ml, 0.01 mole) was added dropwise to a cold solution of 5-amino-2-benzylbenzimidazole (2.01 g, 0.009 mole) and potassium carbonate (0.691, 0.005 mole) in dry glyme (30 ml). The mixture was stirred for 5 hours at room temperature, absolute methanol (30 ml) was added to the mixture, and the stirring was continued for 3 hours, and, then the solvent was then removed. The tlc analysis indicated that this material was comprised of two components. These two products were separated by column chromatography on silica gel $60F_{254}$ (30 g, 70-230 mesh; column size 30 x 2.5 cm) eluting with chloroform:methanol (9:1, v:v). The initial fractions, containing reaction products, to elute from the column were comprised of mainly **12**, contaminated with a small quantity of **9**. The fractions containing pure **9**, as determined by tlc, were pooled and evaporated to furnish 2.18 g (85%) of **9**, mp 124-127°; ir (potassium bromide): ν max 1735-1710, 1635, 1605, 768, 725, 695 cm^{-1}; ^1H nmr (deuteriochloroform + 3 drops of DMSO-d_6): δ 4.0 (s, 3 H, $-CH_3$), 4.56 (s, 2 H, $-CH_2$), 6.84-8.35 (m, 8 H, Ar-H), 8.90 (bs, 1H, NH, exchangeable with deuterium oxide), 10.9-11.7 (bs, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{16}H_{15}N_3O_2 \cdot 3/4\ H_2O$: C, 65.18; H, 5.64; N, 14.25. Found: C, 64.90; H, 5.54; N, 14.20.

The fractions containing both **9** and **12** were pooled, evaporated and rechromatographed on silica gel $60F_{254}$ (20 g) using chloroform:methanol (99:1, v:v) as eluant. Fractions containing pure **12** (R_f = 0.58) were pooled and evaporated to give a semisolid residue. Trituration of this residue with ether:hexane (1:1, v:v) furnished a solid, which was collected by filtration, to yield 0.22 g (7.5%) of **12**, mp 162°, ir (potassium bromide): ν max 1760-1740, 1625-1610, 765, 715, 692 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.77 (s, 3 H, CO_2CH_3), 3.98 (s, 3 H, CO_2CH_3), 4.56 (s, 2 H, $-CH_2$), 6.73-8.30 (m, 9 H, Ar-H and NH, NH exchangeable with deuterium oxide).

Anal. Calcd. for $C_{18}H_{17}N_3O_4$: C, 63.71; H, 5.05; N, 12.38. Found: C, 63.60; H, 5.09; N, 12.47.

Methyl 2-Benzylbenzimidazole-5-carbamate (**9**) (Method 2), and N^1,N^3-*bis*-(2-Benzylbenzimidazole-5-yl)urea (**15**).

Phosgene (5.32 ml of a 12.5% solution of phosgene in toluene, 0.0067 mole) was added dropwise to a stirred ice cold mixture of **7** (1.50 g, 0.0067 mole) and calcium carbonate (0.673 g, 0.0067 mole) in glyme (18 ml) and methanol (12 ml). The reaction mixture was stirred 3 hours at room temperature and then evaporated to dryness. The resulting residue was dissolved in methanol (40 ml) and heated at reflux temperature for 2 hours. After cooling, the solvent was evaporated and the residue, on trituration with water, furnished a solid, which was collected by filtration, and dried. The solid, which consisted of a mixture of **9** and **15**, was dissolved in methanol (40 ml), by heating at reflux, and then the solution was subsequently cooled and diluted with anhydrous diethyl ether (60 ml). A solid precipitated from the mixture which was collected by filtration. This solid was comprised mainly of **15** contaminated with a small amount of **9**. The filtrate was concentrated to remove the solvent and the resulting residue was chromatographed on silica gel (Baker 60-20 mesh, 40 g, column size 30 x 2.5 cm) eluting with chloroform:methanol (95-90:5-10, v:v). Fractions containing **9** were pooled, and, upon evaporation furnished 0.80 g (42%) of pure **9**, which was identical in all respects with **9** prepared in Method 1. The solid which contained mostly **15** was dissolved in hot dimethylsulfoxide, filtered and then the mixture was poured into water to precipitate pure **15**. This solid was collected by filtration to yield 0.38 g (12%) of **15**, mp 207-211°; ir (potassium bromide): ν max 3280-3030, 1682-1670, 1650, 1615, 770, 725, 692 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.25 (s, 2 H, $-CH_2$), 5.67-6.86 (m, 2H, Ar-H, OH, exchangeable with deuterium oxide), 8.50 (bs, 2 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{29}H_{24}N_6O \cdot H_2O$: C, 70.99; H, 5.34; N, 17.13. Found: C, 70.49; H, 5.47; N, 16.79.

Ethyl 2-Benzylbenzimidazole-5-carbamate (**11**), and Ethyl 2-Benzyl-1-carboethoxybenzimidazole-5-carbamate (**14**).

Ethyl chloroformate (0.574 ml, 0.006 mole) was added dropwise to a cold solution of **7** (1.25 g, 0.0056 mole) and potassium carbonate (0.415 g, 0.003 mole) in dry glyme (20 ml). The mixture was stirred 3 hours at room temperature, then absolute ethanol (35 ml) was added and stirring was continued for an additional 3 hours, then the solvent was evaporated. Tlc analysis on silica gel using a chloroform:methanol (9:1) solvent system indicated the residue was comprised of two components. Therefore the crude material was submitted to chromatography on silica gel $60F_{254}$ (30 g, 70-230 mesh; column size 30 x 2.5 cm). Elution of the column with hexane:ethyl acetate (1:1, v:v), furnished **14** upon evaporation of the appropriate fractions. This residue was crystallized from ethyl acetate:hexane (1:1, v:v) to yield 0.220 g (11%) of pure **14**, mp 116°; ir (potassium bromide): ν max 3300, 2980, 1760-1735, 1625, 1610, 768, 710, 692 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.37 (m, 6 H, 2 CH_3), 4.30 (q, 4 H, 2x $-OCH_2$), 4.64 (s, 2 H, C-CH_2), 6.82-8.43 (m, 9 H, Ar-H and NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{20}H_{21}N_3O_4$: C, 65.38, H, 5.76; N, 11.44. Found: C, 65.43; H, 5.75; N, 11.42.

Continued elution of the column with ethyl acetate:methanol (88:12, v:v) afforded **11**, yield 1.1 g (65%); mp 79-83°; ir (potassium bromide): ν max 1708, 1605, 800, 750, 718, 688 cm^{-1}; ^1H nmr (deuteriochloroform): 1.27 (t, 3 H, $-CH_3$), 4.12 [q (merged with benzylic-CH_2), 4 H, $-OCH_2$, C-CH_2], 6.82-7.83 (m, 8 H, Ar-H), 10.10 (bs, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{17}H_{17}N_3O_2 \cdot 1/2\ H_2O$: C, 67.09; H, 5.96; N, 13.81. Found: C, 67.14; H, 6.07; N, 13.88.

Methyl 2-*p*-Fluorobenzylbenzimidazole-5-carbamate (**10**), and, Methyl 1-Carbomethoxy-2-*p*-flourobenzylbenzimidazole-5-carbamate (**13**).

These compounds were prepared by a method similar to that used to prepare **11** and **14**. The compounds **10** and **13** were separated and purified by column chromatography on silica gel 60 F_{254} (50 g, 70-230 mesh, column size 30 x 2.5 cm) using hexane: chloroform (3:7) as eluant collecting 20 ml fractions. Fractions containing **13** as determined by tlc were pooled, and upon evaporation furnished compound **13**, yield 0.200 g (5%), mp 160-162°; ir (potassium bromide): ν max 1760, 1740, 1610, 815, 770 cm^{-1}; ^1H nmr (deuteriochloroform): 3.83 (s, 3 H, N^1-CO_2CH_3), 3.94 (s, 3 H, $-OCH_3$), 4.47 (s, 2 H, CH_2), 6.6-8.28 (m, 7 H, Ar-H).

Anal. Calcd. for $C_{18}H_{16}FN_3O_4 \cdot 1/4\ H_2O$: C, 59.75; H, 4.60; N, 11.61. Found: C, 59.75; H, 4.82; N, 11.48.

Changing the elution solvent system to chloroform:methanol (9:1, v:v) afforded after evaporation pure **10** in 76% yield, mp 94-97°; ir (potassium bromide): ν max 3300, 2960, 1745-1705, 1600, 805, 768 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.73 (s, 3H, $-OCH_3$), 4.02 (s, 2 H, CCH_2), 6.50-8.28 (m, 8 H, Ar-H, and NH, exchangeable with deuterium oxide),

10.23 (bs, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{16}H_{14}FN_3O_2$: C, 64.21; H, 4.72; 14.04. Found: C, 64.01; H, 4.70; N, 13.91.

2-(*p*-Fluorobenzyl)benzimidazole-5-carbamic acid (**17**).

Phosgene (3.2 ml, of a 12.4% solution in toluene 0.004 mole) was added dropwise to an ice-cold stirred solution of **8** (0.965 g, 0.004 mole) and calcium carbonate (0.4 g, 0.004 mole) in glyme (12 ml) and water (8.0 ml). The mixture was stirred for 2.5 hours at room temperature and the solvent evaporated. The resulting solid was heated at reflux with stirring in methanol (50 ml) for 1.5 hours. The solvent was then evaporated and the residue was diluted with water (150 ml) and stirred for 15 minutes. The solid which formed was collected by filtration, then washed with water and dried to yield 0.870 g (74%) of **17**, mp < 300; ir (potassium bromide): ν max 1715, 1645, 1635, 860-805, 782 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.35 (s, 2 H, CH_2), 6.78-8.23 (m, 7 H, Ar-H), 9.93 (bs, 2 H, NH, COOH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{15}H_{12}FN_3O_2 \cdot 1/2\ H_2O$: C, 61.22; H, 4.45; N, 14.29. Found: C, 60.90; H, 4.37; N, 14.41.

2-Benzoyl-5-nitrobenzimidazole (**18**).

Anhydrous chromium trioxide (36 g, 0.36 mole) was added to a stirred suspension of **5** (8.8 g, 0.035 mole) in glacial acetic acid (300 ml) and the mixture was stirred at room temperature for 24 hours. Upon addition of water (1000 ml) to the solution a solid separated which was collected by filtration, washed with water (100 ml) and dried to furnish 7.42 g (80%) of analytically pure **18**, mp 254°; ir (potassium bromide): 3280, 1640, 1625, 1535, 1330, 815, 740-728; ^1H nmr (DMSO-d_6) 3.5 (bs, 1 H, NH), 7.12-9.40 (m, 8 H, Ar-H).

Anal. Calcd. for $C_{14}H_9N_3O_3$: C, 62.92; H, 3.40; N, 15.72. Found: C, 63.03; H, 3.45; N, 15.70.

2-*p*-Fluorobenzoyl-5-nitrobenzimidazole (**19**).

Anhydrous chromium trioxide (15.0 g, 0.15 mole) was added to a stirred suspension of **6** (3.16 g, 0.0117 mole) in glacial acetic acid (160 ml). The reaction mixture was stirred for 28 hours at room temperature. Water (1000 ml) was added to this solution, at which time a solid separated from the mixture. The solid was collected by filtration, washed with water (100 ml) and dried to yield 2.50 g (75%) of **19**, mp 268-269°; ir (potassium bromide): ν max 3290, 1640-1635, 1605, 1535, 1345, 1330, 780, 735 cm^{-1}; ^1H nmr (DMSO-d_6): δ 6.9-9.4 (m, 7 H, Ar-H), 14.00 (s, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{14}H_8FN_3O_3$: C, 58.95; H, 2.83; N, 14.73. Found: C, 58.86; H, 2.88; N, 14.69.

5-Amino-2-(α-hydroxy-*p*-fluorobenzyl)benzimidazole (**21**).

A suspension of **19** (2.49 g, 0.0093 mole) in methanol (75 ml) was catalytically reduced in a hydrogen atmosphere in a Parr apparatus at 50 psi in the presence of Raney-Ni (1.0-1.20 g wet) for 5-6 hours. The catalyst was removed by filtration through a celite pad, which was washed with hot methanol (3 x 10 ml). The filtrate on evaporation gave **21** as a light yellow solid, yield 2.2 g (98%), mp 109-112°; ir (potassium bromide): ν max 3450-3000, 1635, 1605, 830, 805 cm^{-1}; ^1H nmr (DMSO-d_6): 4.80 (bs, 2 H, NH_2, exchangeable with deuterium oxide), 5.80 (s, 1 H, CH-O), 6.36-6.59 (m, 3 H, Ar-H), 7.14-7.52 (m, 5 H, Ar-H and OH exchangeable with deuterium oxide), 11.75 (bs, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{14}H_{12}FN_3O \cdot 1/4\ H_2O$: C, 64.24; H, 4.81; N, 16.05. Found: C, 64.60; H, 4.81; N, 15.75.

5-Amino-2-(α-hydroxybenzyl)benzimidazole (**20**).

This compound was prepared by a method similar to that used to prepare **21**, yield 90%. The compound was characterized as a dihydrochloride salt, mp > 300°; ir (potassium bromide): (free base) ν max 3245, 1642, 800, 760, 700 cm^{-1}; ^1H nmr (DMSO-d_6) (free base): δ 4.80 (bs, 2 H, NH_2, exchangeable with deuterium oxide), 5.80 (s, 1 H, CH-O), 6.36-6.59 [m, 3 H, Ar-H, and OH, exchangeable with deuterium oxide], 7.14-7.52 (m, 6 H, Ar-H), 11.75 (bs, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{14}H_{13}N_3O \cdot 2HCl \cdot 1/2\ H_2O$: C, 52.68; H, 5.05; N, 13.16. Found: C, 52.99; H, 5.01; N, 13.14.

Methyl 2-(α-Hydroxy-*p*-fluorobenzyl)benzimidazole-5-carbamate (**25**) and Methyl 2-(α-Methoxy-*p*-fluorobenzyl)benzimidazole-5-carbamate (**27**).

Methyl chloroformate (0.473 g, 0.005 mole) was added to a cold stirred solution of **21** (1.20 g, 0.0047 mole) and potassium carbamate (0.410 g, 0.003 mole) in dry glyme (30 ml). The resulting solution was stirred at room temperature for 6 hours. The solvent was then evaporated and the resulting residue was dissolved in ethyl acetate:methanol (1:1, v:v). The insoluble material was removed by filtration and discarded. The filtrate was evaporated and the resulting residue was chromatographed on silica gel 60 F_{254} (35-40 g, 70-230 mesh, column size 30 x 2.5 cm) eluting with chloroform:methanol (95:5, v:v) to furnish **27**, 0.120 g (7.5%); ir (potassium bromide): ν max 2950, 1725-1712, 1632, 1605, 805, 765 cm^{-1}; ^1H nmr (deuteriochloroform): 3.43 (s, 3 H, O-CH_3), 3.80 (s, 3H, CO_2CH_3), 5.55 (s, 1H, CH-O), 6.70-7.93 (m, 9 H, Ar-H, and NH, exchangeable with deuterium oxide); ms: m/e 329 (M^+-9, 30).

Anal. Calcd. for $C_{17}H_{16}FN_3O_3 \cdot 1/2\ H_2O$: C, 60.35; H, 5.07; N, 12.42. Found: C, 60.43; H, 5.05; N, 12.01.

Increasing the polarity of the elution solvent to chloroform:methanol (9:1) afforded the product **25**, yield 0.62 g (42%), mp 126-130° (shrinking starts after 115°); ir (potassium bromide): ν max 3300, 1725-1708, 1610, 840, 770, 760 cm^{-1}; ^1H nmr (deuteriochloroform + 2 drops of DMSO-d_6): δ 3.73 (s, 3 H, -CO_2CH_3), 6.0 (s, 1 H, -CH-O-), 6.68-7.97 (m, 9 H, Ar-H, NHCO and OH, exchangeable with deuterium oxide), 8.53 (s, 1 H, NH exchangeable with deuterium oxide).

Anal. Calcd. for $C_{16}H_{14}FN_3O_3 \cdot 1/2\ H_2O$: C, 59.25; H, 4.66; N, 12.96. Found: C, 59.11; H, 4.51; N, 12.86.

Methyl 2-(α-Methoxybenzyl)benzimidazole-5-carbamate (**26**) and, Methyl 2-(α-Hydroxybenzyl)benzimidazole-5-carbamate (**24**).

These products were prepared by a procedure similar to that used to prepare **25**. Purification was accomplished by column chromatography on silica gel 60F_{254} (50 g, 70-230 mesh, column size 35 x 2.5 cm) using dichloromethane:methanol (97:3, v:v) as eluant. The fractions containing **26** were pooled and evaporated to furnish **26** which contained a small amount of an impurity. The product was rechromatographed using a chloroform:methanol gradiant (100:0; 97.5:2.5; 90:10, v:v) solvent system as eluant, yield 0.411 g (14%), mp 94-96°; ir (potassium bromide): ν max 2730, 1715, 1630, 1605, 810, 795 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.40 (s, 3H, CH_3), 3.73 (s, 3 H, -OCH_3), 5.55 (s, 1 H, CH-O), 6.80-8.0 (m, 10 H, Ar-H, NH and OH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.40. Found: C, 65.05; H, 5.47; N, 13.40.

Upon further elution of the initial column with dichloromethane:methanol (90:10), the fractions containing **24** were pooled and evaporated to afford 1.9 g (75%) of the desired **24**, mp 143-148° (shrinking starts after 140°); ir (potassium bromide): ν max 3300, 1720, 1625, 1608, 805, 760, 695 cm^{-1}; ^1H nmr (deuteriochloroform + 2 drops of DMSO-d_6): δ 3.70 (s, 3 H, -OCH_3), 6.07 (s, 1 H, CH), 6.92-8.10 (m, 8 H, Ar-H), 8.60 (bs, 3 H, NH, water, and OH, exchangeable with deuterium oxide) 9.19 (s, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for $C_{16}H_{15}N_3O_3 \cdot 1/2\ H_2O$: C, 59.20; H, 5.55; N, 12.95. Found: C, 59.59; H, 5.16; N, 12.98.

Acknowledgments.

We are grateful to Dr. D. A. Denham, London School of Hygiene and Tropical Medicine and Dr. J. W. McCall, University of Georgia, for the antifilarial testing data and Ms. Deanna VanSickle for help in the preparation of this paper. This investigation was supported by the Filariasis Component of the World Bank/UNDP/WHO Special Program for Research and Training in Tropical Diseases (I.D. 840398 and 840124).

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