Synthesis of 2-Thiobenzimidazole Derivatives as Potential Antifilarial Agents

Siya Ram, Dean S. Wise and Leroy B. Townsend*

Department of Medicinal Chemistry, College of Pharmacy and Department of Chemistry, The University of Michigan, Ann Arbor, Michigan 48109-1065

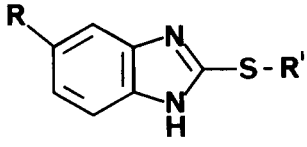
Received Januray 28, 1985

Several 5-benzoyl-2-thiobenzimidazole and 2-thiobenzimidazole aliphatic acids, esters, and *N,N*-dialkylcarboxamides and thiocarboxamides were prepared by reacting bromo aliphatic acids, bromo aliphatic esters, and *N,N*-dialkylcarbamoyl or thiocarbamoyl chlorides with 5-benzoyl-2-thiobenzimidazole or 2-thiobenzimidazole in the presence of base. 2-Thiocarbomethoxy- and 2-thiocarboethoxybenzimidazole were prepared by the reaction of 2-thiobenzimidazole with methyl or ethyl chloroformate in the presence of base. However, the reaction of 5-benzoyl-2-thiobenzimidazole with ethyl chloroformate, afforded 5-benzoyl-2-ethylthiobenzimidazole.

J. Heterocyclic Chem., **22**, 1269 (1985).

A number of 2-thiobenzimidazole derivatives have demonstrated a broad spectrum of significant biological activity, *i.e.*, plant growth inhibition [1,2], bacterial [3], fungicidal [3], virucidal [3], antioxidant [4], antiinflammatory [5], and antitumor activity [6]. We undertook the synthesis of several new 2-thio- derivatized benzimidazoles as part of a program to develop new antifilarial agents. This study was designed to investigate what effect the interchange of a sulfur atom for the 2-amino functionality in the anthelmintic benzimidazole-2-carbamates may have on the antifilarial activity associated with benzimidazole-2-carbamates, *i.e.*, mebendazole and fenbendazole [1].

This prompted us to prepare a series of type **1** compounds.



The target compounds were prepared by the alkylation of either 2-thiobenzimidazole (**2**) [2] or 5-benzoyl-2-thiobenzimidazole (**3**). The starting material **3** was prepared by the condensation of 3,4-diaminobenzophenone (**4**) with potassium ethyl xanthate in an aqueous 50% sodium hydroxide solution followed by acidification. The reaction of **2** or **3** with various *N,N*-dialkylcarbamoyl chlorides or thiocarbamoyl chlorides afforded the 2-[benzimidazol-2-yl]-thio-*N,N*-dialkylcarboxamide and thiocarboxamide derivatives **7-12**. Condensation of either **2** or **3** with various halogenated compounds, *i.e.*, bromoacetonitrile, propargyl bromide, bromoalkanes, halogenated fatty acid esters, or bromoacetic acid in the presence of alkali according to the procedure of Knobloch [4] furnished the *S*-alkylated derivatives, **13-16**, **18-19** and **20-34**. When **2** was treated with methyl or ethyl chloroformate in the presence of potassium hydroxide in ethanol the corresponding 2-*S*-carbomethoxy and 2-*S*-carboethoxy derivatives **5** and **6** were obtained. Treatment of **3** under similar reaction conditions with methyl chloroformate afforded only products of decomposition, while, the reaction of **3** with ethyl chloroformate furnished 5-benzoyl-2-ethylthiobenzimidazole (**17**) in 13% yield rather than the expected 2-*S*-carboethoxy derivative. The formation of **17** most likely results from an initial carboethoxylation at one of the benzimidazole ring nitrogens rather than at sulfur. A subsequent rearrangement then affords **17**. This mechanism is similar to that proposed by Vida [3] who has reported alkylation of various lithiated imides with alkyl chloroformates. Although the compounds **5-6**, **13-14**, and **23-24** have been reported previously [5-7] these derivatives were prepared in this study for structural activity considerations. We have included these compounds in this text since no physicochemical data was reported earlier.

Scheme 1

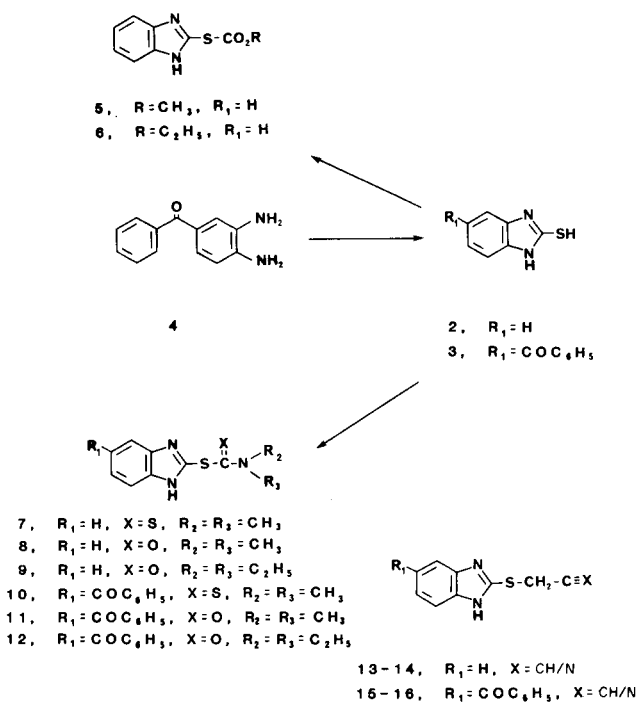


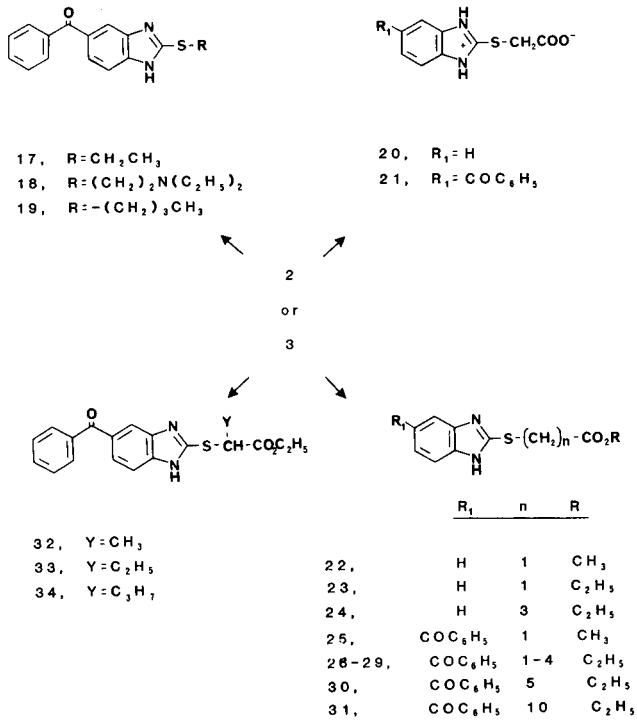
Table I

Physicochemical Data of Some Benzimidazol-2-ylthio Derivatives

C. No.	R'	R''	Molecular formula	Yield %	mp °C	Analysis Required	Found
7	H	$CSN(CH_3)_2$	$C_{10}H_{11}N_3S_2 \cdot 0.5H_2O$	63	191-193	C 48.76	48.91
						H 4.91	4.99
						N 17.06	17.14
8	H	$CON(CH_3)_2$	$C_{10}H_{11}N_3OS$	53	195-196	C 54.28	54.06
						H 5.01	5.03
						N 18.53	18.67
9	H	$CON(C_2H_5)_2$	$C_{12}H_{15}N_3OS$	64	197-198	C 57.80	57.30
						H 6.06	5.93
						N 16.85	16.67
10	COC_6H_5	$CON(CH_3)_2$	$C_{17}H_{15}N_3O_2S$	58-60	129-130	C 62.57	62.56
						H 5.42	5.47
						N 11.89	11.70
11	COC_6H_5	$CON(C_2H_5)_2$	$C_{19}H_{19}N_3O_2S$	52	54-55	C 64.57	64.62
						H 5.42	5.47
						N 11.89	11.70
12	COC_6H_5	$CSN(CH_3)_2$	$C_{17}H_{15}N_3OS_2$	56	160-162	C 59.80	59.57
						H 4.43	4.61
						N 12.31	12.08
22	H	$CH_2CO_2CH_3$	$C_{10}H_{10}N_2O_2S \cdot HBr \cdot 0.5H_2O$	64	186-190	C 38.48	38.23
						H 3.88	3.96
						N 8.96	8.81
23	H	$CH_2CO_2C_2H_5$	$C_{11}H_{12}N_2O_2S$	85	92-93	C 55.91	55.65
						H 5.11	5.07
						N 11.85	11.61
24	H	$(CH_2)_3CO_2C_2H_5$	$C_{13}H_{16}N_2O_2S$	81	83-84	C 59.07	58.89
						H 6.10	5.90
						N 10.59	10.53
25	COC_6H_5	$CH_2CO_2CH_3$	$C_{17}H_{14}N_2O_3S$	52	136-137	C 62.56	62.59
						H 4.32	4.49
						N 8.58	8.42
26	COC_6H_5	$CH_2CO_2C_2H_5$	$C_{18}H_{16}N_2O_3S \cdot HBr \cdot 0.5H_2O$	35	199-200	C 50.24	50.61
						H 4.22	3.98
						N 8.58	8.42
27	COC_6H_5	$(CH_2)_2CO_2C_2H_5$	$C_{19}H_{18}N_2O_3S \cdot HBr \cdot H_2O$	38	145-147	C 50.34	50.51
						H 4.67	4.47
						N 6.18	6.16
28	COC_6H_5	$(CH_2)_3CO_2C_2H_5$	$C_{20}H_{20}N_2O_3S \cdot HBr \cdot H_2O$	65	164-165	C 51.40	51.39
						H 4.96	4.58
						N 5.99	5.94
29	COC_6H_5	$(CH_2)_4CO_2C_2H_5$	$C_{21}H_{22}N_2O_3S$	90	84-86	C 65.95	66.06
						H 5.80	5.89
						N 7.32	7.26
31	COC_6H_5	$(CH_2)_{10}CO_2C_2H_5$	$C_{27}H_{34}N_2O_3S$	70	75-76	C 69.49	69.72
						H 7.34	7.51
						N 6.00	6.03
32	COC_6H_5	$CH(CH_3)CO_2C_2H_5$	$C_{19}H_{18}N_3O_3S$	71	79-80	C 64.39	64.22
						H 5.12	5.08
						N 7.90	7.99
33	COC_6H_5	$CH(C_2H_5)CO_2C_2H_5$	$C_{20}H_{20}N_2O_3S$	50	68-69	C 65.20	65.37
						H 5.47	5.51
						N 7.60	7.61
34	COC_6H_5	$CH(C_3H_7)CO_2C_2H_5$	$C_{21}H_{22}N_2O_3S$	87	74-75	C 65.95	65.74
						H 5.80	5.83
						N 7.32	7.22

All of the substituted 2-thiobenzimidazole compounds which were prepared in this study were evaluated *in vivo* for antifilarial activity against the microfilariae and adult worms of *Brugia pahangi* and *Litomosoides carinii* in jirds [8]. The results of these tests indicated that none of these compounds demonstrated any significant antifilarial activity, thus indicating that the 2-NH moiety of the methyl carbamate is an essential feature for antifilarial activity.

Scheme II



EXPERIMENTAL

Melting points were determined with a Thomas Hoover, capillary melting point apparatus and are uncorrected. The ir spectra were recorded using a Perkin Elmer 281 spectrophotometer and values are expressed in cm^{-1}. The ^1H nmr spectra were obtained using a Varian EM-360, 60 MHz spectrophotometer and chemical shifts values are reported in parts per million on the δ scale with tetrmethylsilane as the internal reference. Mass spectra were run on a Finnigan Model 4023 GC/MS spectrometer. Microanalysis were performed by M-H-W Laboratories, Phoenix, AZ 85018. Column chromatography was carried out on silica gel (60-200 mesh) and Kiesel gel $60F_{254}$ (70-230 mesh) using chloroform: methanol/ethyl acetate as an eluant. Ultraviolet spectra were recorded with a Hewlett-Packard 8450 UV/VS spectrophotometer. Thin layer chromatography (tlc) was performed on silica gel-7GF (Analtech) plates using chloroform:methanol (v:v, 9:1) or (8:2) or acetone:benzene (1:3) as the eluant. Detection of compounds on tlc was made by uv light or exposure of the plate to iodine. Evaporation of solvents was, unless otherwise specified, carried out under reduced pressure using a rotary evaporator (water aspirator) at steam bath temperature.

5-Benzoyl-2-thiobenzimidazole (**3**).

A mixture of 3,4-diaminobenzophenone monohydrochloride (12.0 g, 0.0482 mole), potassium ethyl xanthate (8.49 g, 0.053 mole), and 3.96 g of sodium hydroxide in water (7.2 ml) and ethanol (50 ml) was stirred and heated at reflux for 5 hours. Additional potassium ethyl xanthate (1.80 g) was added to the reaction mixture and the mixture then heated for an additional 4 hours. The reaction mixture was allowed to stand at room temperature for 18 hours, treated with 2.4 g of charcoal and heated at reflux for 25 minutes. The hot solution was filtered through celite, and the celite pad was washed thoroughly with ethanol (100 ml). The filtrate was allowed to stand at 5° for 18 hours to give 0.8 g of a solid, which was filtered and discarded. The filtrate was evaporated to furnish a yellow colored solid which was washed with 100 ml of dry ether, and then dried under vacuum at 60° to yield 15.40 g of the potassium salt of **3**; ir (potassium bromide): ν max 3200, 1640, 1600, 785 cm^{-1}. Treatment of this potassium salt with glacial acetic acid gave **3** in 95% yield, mp 254-256°.

2-Thiocarbomethoxybenzimidazole (**5**).

A mixture of 2-mercaptobenzimidazole (2.5 g, 0.017 mole) and potassium hydroxide (1.0 g, 0.018 mole) in ethanol (32.0 ml) was heated briefly to effect solution, and then cooled to 0°. To this cold solution, methyl chloroformate (2.0 ml) was added dropwise. At the end of the addition, tlc analysis in acetone/benzene 1:1 indicated that only a partial reaction had occurred. An additional amount of methyl chloroformate (5.0 ml) was added and the reaction mixture was refluxed with stirring for 12 hours. The mixture was cooled, and the precipitated inorganic salt was removed by filtration. The filtrate on evaporation afforded a viscous solid, which was crystallized from ethanol. The yield of **5** was 1.2 g (33%), mp 188°, (product and starting material have the same R_f value); ir (potassium bromide): ν max 2670, 1618, 1515, 732 cm^{-1}; ^1H nmr (DMSO-d_6 + deuteriochloroform): δ 3.1 (s, 3 H, CO_2CH_3), 7.28-8.0 (m, 4 H, Ar-H), 11.57 (bs, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for ($C_9H_8N_2O_2S \cdot H_2O$): C, 47.78; H, 4.43; N, 12.40. Found: C, 48.04; H, 4.15; N, 13.23.

2-Thiocarboethoxybenzimidazole (**6**).

2-Mercaptobenzimidazole (**2**, 1.20 g, 0.08 mole), sodium ethoxide (0.54 g, 0.008 mole) and ethyl chloroformate (2.0 ml) were combined in ethanol (30 ml) and heated under reflux with stirring for 5 to 6 hours. Analysis (tlc) (acetone:benzene) indicated that at this time, the reaction was incomplete, thus, an additional amount of ethyl chloroformate (5.0 ml) was added to the reaction mixture and the refluxing was continued for an additional 15 hours. After cooling, the precipitated inorganic salt was removed by filtration, and, the filtrate was evaporated to dryness. The resulting residue was recrystallized from an ethanol:ethyl acetate:hexane mixture to yield, 1.27 g (71%), of **6**, mp 132°; ir (potassium bromide): ν max 3360, 2060-2500, 1620, 1510, 800, 755 cm^{-1}; ^1H nmr (DMSO-d_6 + deuteriochloroform): δ 1.50 (t, 3H, CCH_3), 3.67 (q, 2 H, $-OCH_2$), 7.28-8.10 (m, 4 H, Ar-H), 10.06 (bs, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for ($C_{10}H_{10}N_2O_2S \cdot H_2O$): C, 49.99; H, 5.03; N, 12.60. Found: C, 50.29; H, 5.02; N, 12.86.

General Procedure for the Synthesis of 2-Thio[dimethyl/diethyl]carboxamide/(dimethyl)thiocarboxamide Benzimidazoles and 5-Benzoylbenzimidazoles **7-12**.

An appropriate dialkylcarbamoyl chloride (0.015 mole-0.021 mole) was added dropwise to a cold stirred mixture of benzimidazole **2** or **3** (0.01 mole) and anhydrous potassium carbonate (0.005 mole) in dry THF (30 ml) [in the reactions to prepare compounds **11** and **12**, the potassium salt of **3** was used and no potassium carbonate was added to the reaction]. The resulting mixture was stirred at reflux temperature for 36-48 hours, cooled and the solid which separated during the course of the reaction, or upon cooling (the dimethylthiocarbamoyl derivatives precipitated from the reaction mixture upon stirring for 2-3 days at room temperature) was collected by filtration. The solid was redissolved in ethyl acetate and was washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to afford the desired products. Purification was accomplished by either crystallization from ethyl acetate or by column chromatography on silica gel using chloroform:methanol as eluant.

2-Propynylthiobenzimidazole (**13**).

Propargyl bromide (0.595 g, 0.005 mole) was added dropwise to a stirred cold solution of **2** (0.601 g, 0.004 mole) in absolute ethanol (15 ml) and then heated at reflux temperature for 3-4 hours. On cooling, light yellowish needle crystals of **13** precipitated from the reaction mixture. These crystals were collected by filtration, and dried under vacuum at room temperature to yield 1.0 g of **13**, mp 200-202°; ir (potassium bromide): ν max 3220, 2920, 2840, 1510, 780, 735 cm^{-1}; ^1H nmr (DMSO-d_6 + deuteriochloroform): δ 4.50 (s, 2 H, $S-CH_2$), 7.28-8.17 (m, 4 H, Ar-H), 12.53 (bs, 2 H, C=CH and NH [NH exchangeable with deuterium oxide]).

Table II

Infrared and ^{1}H NMR Data of Some Benzimidazol-2-ylthio Derivatives

C.No.	IR [a]	^{1}H NMR [b]
7	1505, 805, 744	[deuteriochloroform + DMSO-d_6]: 3.45 [s, 6 H, N(CH_3)$_2$], 7.13-7.96 (m, 4 H, Ar-H), 8.28 (bs, 1 H, NH)
8	2940, 1680, 752	[deuteriochloroform]: 3.07 [s, 6 H, N(CH_3)$_2$], 7.1-8.88 (m, 4 H, Ar-H), 10.67 (bs, 1 H, NH)
9	2970-2940, 1662, 850, 747	[deuteriochloroform + DMSO-d_6]: 1.27 (t, 3 H, (CH_3)$_2$], 3.47 (q, 4 H, OCH_2), 7.2-7.8 (m, 4 H, Ar-H), 8.4-9.9 (bs, 1 H, NH)
10	3310, 3050, 2920, 1650-1690, 780, 720, 705	[deuteriochloroform]: 3.1 (s, 6 H, N(CH_3)$_2$), 7.2-8.2 [m, 9 H, Ar-H and NH, (exchangeable with deuterium oxide)]
11	3300, 2970, 1675-1670, 1612, 848, 785, 712	[deuteriochloroform]: 1.3 (t, 6 H, N(CH_3)$_2$), 3.5 [q, 4 H, N(CH_2)$_2$], 7.22-8.28 (m, 9 H, Ar-H and NH, exchangeable with deuterium oxide)
12	3140, 1640, 1600, 880, 812, 710-702	[deuteriochloroform + DMSO-d_6]: 3.53 [s, 6 H, N(CH_3)$_2$], 7.3-8.42 (m, 8 H, Ar-H), 9.6 (bs, 1 H, NH exchangeable with deuterium oxide)
22	2920, 2840-2800, 1730, 890, 765, 740	[DMSO-d_6]: 3.77 (s, 3 H, CH_3), 4.63 (s, 2 H, SCH_2), 7.2-8.18 (m, 4 H, Ar-H), 12.23 (bs, 1 H, NH)
23	2960, 2800, 1620, 745	[deuteriochloroform + DMSO-d_6]: 1.20 (t, 3 H, CH_3), 3.9-4.77 (m, 4 H, OCH_2 and SCH_2), 6.8-7.9 (m, 4 H, Ar-H), 9.67 (bs, 1 H, NH, exchangeable with deuterium oxide)
24	2960, 2800, 1720, 745	[deuteriochloroform]: 1.25 (t, 3 H, CH_3), 1.79-1.73 (m, 4 H, $CH_2CH_2CO_2$), 3.33 (s, 2 H, S-CH_2), 4.17 (q, 2 H, OCH_2), 7.1-7.75 (m, 4 H, Ar-H), 10.03 (bs, 1 H, NH)
25	3030, 2930, 1730, 1650, 1612, 882, 822, 785, 712	[deuteriochloroform]: 3.78 (s, 3 H, CO_2CH_3), 4.08 (s, 2 H, SCH_2), 7.20-8.17 (m, 9 H, Ar-H and NH, exchangeable with deuterium oxide)
26	3100-2500, 1725, 1660, 890, 787, 745, 710	[deuteriochloroform]: 3.78 (s, 3 H, CO_2CH_3), 4.23 (q, 2 H, OCH_2), 4.57 (s, 2 H, SCH_2), 7.3-8.25 (m, 8 H, Ar-H), 10.77 (bs, 2 H, 2NH, exchangeable with deuterium oxide)
27	2750, 1730, 1655, 1617, 885, 825, 770, 701	[deuteriochloroform]: 1.25 (t, 3 H, CH_3), 2.18 (t, 2 H, CH_2), 2.63 (t, 2 H, CCH_2, OCH_2), 7.17-8.50 (m, 8 H, Ar-H), 13.07 (bs, 1 H, NH, exchangeable with deuterium oxide)
28	2780-2740, 1725, 1655, 1615, 885, 755, 702	[deuteriochloroform]: 1.25 (t, 3 H, CH_3), 2.18 (t, 2 H, CH_2), 2.63 (t, 2 H, CH_2CO), 3.76 (t, 2 H, SCH_2), 4.18 (q, 2 H, OCH_2), 7.2-8.68 (m, 8 H, Ar-H), 13.90 (bs, 1 H, NH, exchangeable with deuterium oxide)
29	2930, 1728, 1660, 880, 815, 712	[deuteriochloroform]: 1.27 (t, 3 H, CCH_3), 1.57-2.17 (m, 4 H, Ar-H), 2.40 (t, 2 H, CH_2CO), 3.97 (t, 2 H, S-CH_2), 7.18-8.26 (m, 8 H, Ar-H), 14.00 (bs, 1 H, NH, exchangeable with deuterium oxide)
31	2910, 2850, 1722, 1655, 880, 710	[deuteriochloroform]: 1.23 (m, 19 H, $C(CH_2)_8CH_3$), 2.32 (t, 2 H, -CH_2CO), 3.37 (t, 2 H, SCH_2), 4.18 (q, 2 H, OCH_2), 7.18-8.20 (m, 8 H, Ar-H), 11.00 (bs, 1 H, NH, exchangeable with deuterium oxide)
32	2930, 1730, 1655, 885, 710	[deuteriochloroform]: 1.27 (t, 3 H, CH_3), 1.69 (d, 3 H, CCH_3), 4.28 (q, 2 H, CH_2), 7.18-8.32 (m, 8 H, Ar-H), 13.20 (bs, 1 H, NH, exchangeable with deuterium oxide)
33	2970-2930, 1730, 1655, 1612, 885, 822, 715, 710	[deuteriochloroform]: 0.78-1.57 (m, 6 H, CH_3), 2.02 (q, 2 H, CCH_2), 3.73-4.56 (m, 3 H, SCH, OCH_2), 7.11-8.32 (m, 8 H, Ar-H), 11.67 (bs, 1 H, NH, exchangeable with deuterium oxide)
34	2930, 1725, 1650, 1612	[deuteriochloroform + DMSO-d_6]: 0.90-1.36 (m, 6 H, (CH_3)$_2$), 1.48-2.37 (m, 4 H, (CH_2)$_2$), 4.20 (q, 2 H, OCH_2), 4.63 (t, 1 H, SCHCO), 7.23-8.23 (m, 8 H, Ar-H), 12.48 (bs, 1 H, NH, exchangeable with deuterium oxide)

[a] Values are expressed in cm^{-1}. [b] Values are expressed in δ.

Anal. Calcd. for ($C_{10}H_8N_2S$·HBr): C, 44.61; H, 3.37; N, 10.40. Found: C, 44.42; H, 3.46; N, 10.16.

5-Benzoyl-2-propynylthiobenzimidazole (**15**).

A mixture of **3** (1.0 g, 0.004 mole), propargyl bromide (0.52 g, 0.0043 mole) and potassium carbonate (0.276 g, 0.002 mole) in dry tetrahydrofuran (20 ml) was stirred at room temperature for 80-96 hours. The solvent was evaporated and the resulting residue was dissolved in water and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried over anhydrous sodium sulfate. After filtration the solution was evaporated to furnish a semi-viscous solid, which on trituration with ethyl acetate: hexane gave a colorless solid. The solid was collected by filtration and recrystallized from an ethyl acetate: hexane mixture to give 2.2 g (96%) of **15**, mp 151°; ir (potassium bromide): ν max 3210-3110, 1635, 1062-1015, 825 , 785, 705, 690 cm^{-1}, ^{1}H nmr (deuteriochloroform): δ 4.08 (d, 2 H, S-CH_2), 7.2-8.20 (m, 9 H, Ar-H and C=CH), 10.00 (bs, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for ($C_{17}H_{12}N_2OS$): C, 69.84; H, 4.14; N, 9.50. Found: C, 69.68; H, 4.31; N, 9.35.

2-(5-Benzoylbenzimidazol-2-yl)thioacetonitrile (**16**).

A mixture of **3** (1.0 g, 0.004 mole), bromoacetonitrile (0.52 g, 0.0043 mole) and potassium carbonate (0.276 g, 0.002 mole) in dry tetrahydrofuran (20 ml) was stirred at room temperature for 80-96 hours. The solvent was removed by evaporation and the resulting residue was diluted with water, and extracted with ethyl acetate. The organic layer was washed with water, and dried over anhydrous sodium sulfate. After filtration, the filtrate was evaporated to furnish a semi-viscous solid. This mixture on trituration with ethyl acetate:hexane gave a colorless solid; yield 1.1 g, (96%), mp 151-152°; ir (potassium bromide): ν max 3140-3120, 2240, 1642, 1595, 890, 815, 785, 720, 705 cm^{-1}; ^{1}H nmr (DMSO-d_6 + deuteriochloroform): δ 4.25 (s, 2 H, S-CH_2), 7.27-8.30 (m, 8 H, Ar-H), 12.83 (bs, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for ($C_{16}H_{11}N_3OS$): C, 65.51; H, 3.78; N, 14.35. Found: C, 65.70; H, 3.85; H, 14.11.

2-(Benzimidazol-2-yl)thioacetonitrile (**14**).

Compound **14** prepared by a procedure similar to that which afforded **16**. The yield of **14** was 85%, mp 169°; ir (potassium bromide): ν max

3120-3115, 1130, 875, 740 cm^{-1}, ^1H nmr (DMSO-d_6): δ 4.33 (s, 2 H, S-CH_2), 7.02-8.0 (m, 5 H, Ar-H and NH, exchangeable with deuterium oxide).

Anal. Calcd. for ($C_9H_7N_3S$): C, 57.12; H, 3.72; N, 22.20. Found: C, 56.92; H, 3.82; N, 21.98.

5-Benzoyl-2-ethythiobenzimidazole (**17**).

Ethyl chloroformate (2.17 g, 0.02 mole) was added dropwise to a stirred cold solution of **3** (2.54 g, 0.01 mole) and sodium ethoxide (0.68 g, 0.01 mole) in absolute ethanol (30-35 ml). After the addition was complete the reaction mixture, was stirred and heated at reflux for 4 hours. Thin layer chromatography analysis showed only partial reaction had taken place, thus, an additional amount of ethyl chloroformate (0.02 mole) was added to the reaction mixture and heating was continued for 2 hours. The tlc analysis, was repeated and a third charge of ethyl chloroformate (0.02 mole) was added to the mixture. The reaction was continued for 24 hours. The solvent was evaporated and the resulting semi-solid residue on trituration with water, afforded a solid, which was collected by filtration, dried, and purified by silica gel chromatography using ethyl acetate:hexane mixture (v:v, 2:2) as an eluant, yield 0.36 g (13%), mp 138-139°; ir (potassium bromide): ν max 3180, 1645-1600, 885, 818, 785, 715, 705 cm^{-1}; ^1H nmr (DMSO-d_6 + deuteriochloroform): δ 1.47 (t, 3 H, CH_3), 3.37 (q, 2 H, CH_2), 7.25-8.14 (m, 8 H, Ar-H), 9.0 (bs, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for ($C_{16}H_{14}N_2OS$): C, 68.07; H, 5.00; N, 9.92. Found: C, 67.90; H, 5.08; N, 9.91.

1-*N,N*-Diethylamino-2-(5-benzoylbenzimidazol-2-yl)thioethane, Dihydrochloride Salt (**18**).

A mixture of **3** (2.03 g, 0.008 mole), 2-diethylaminoethyl chloride hydrochloride (1.72 g, 0.01 mole) and anhydrous potassium carbonate (1.25 g, 0.009 mole) in ethanol (40 ml) was heated under reflux for 48 hours. The ethanol was evaporated and the resulting residue diluted with water and the mixture extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, filtered and evaporated to furnish a viscous solid. The solid was purified by chromatography on silica gel $60F_{254}$ (50 g) using ethyl acetate:methanol (v:v, 95:5) as an eluant, yield 1.51 g as a thick oil. Compound **18** was converted to its hydrochloride salt by treatment with ethanolic-hydrogen chloride or ethereal-hydrogen chloride to yield 1.8-1.90 g (56%); mp 172°; ir (potassium bromide): ν max 3000-2200, 1660, 1630, 882-895, 750, 720-705 cm^{-1}; ^1H nmr (deuterium oxide): δ 1.10-1.67 [m, 6 H, 2 (CH_3)], 3.0-4.0 (m, 8 H, S-CH_2, N(CH_2)$_3$], 7.0-8.07 (m, 8 H, Ar-H).

Anal. Calcd. for ($C_{20}H_{23}N_3O_5 \cdot 2$ HCl): C, 56.34; H, 5.91; N, 9.86. Found: C, 56.14; H, 5.79; N, 9.59.

5-Benzoyl-2-[butylthiobenzimidazol-2-yl]thiobutane (**19**).

A mixture of **3** (2.03 g, 0.008 mole), 1-bromobutane (1.65 g, 0.012 mole) and anhydrous potassium carbonate (0.55 g, 0.004 mole) in absolute ethanol (40 ml) was stirred and heated at reflux for 48 hours. The solvent was evaporated and the resulting residue was diluted with water, and the compound **19** was extracted from the mixture with ethyl acetate. The organic layer was washed with water and dried over anhydrous sodium sulfate. After filtration, and evaporation of the solvent a crude brown red viscous oil was obtained which was purified by column chromatography on silica gel $60F_{254}$ using chloroform:methanol (v:v, 98:2) as the eluant. The yield was 2.22 g (90%), mp 96-97°; ir (potassium bromide): ν max 3020, 2920, 2840, 2780, 1655, 1612, 1600, 782, 712 cm^{-1}; ^1H nmr (deuteriochloroform): δ 0.89 (t, 3 H, CH_3), 1.1-2.07 [m, 4 H, (CH_2)$_2$], 3.34 (t, 2 H, S-CH_2), 7.20-8.20 (m, 8 H, Ar-H), 11.03 (bs, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for ($C_{12}H_{18}N_2OS$): C, 69.65; H, 5.85; N, 9.03. Found: C, 69.55; H, 6.00; N, 8.83.

(Benzimidazol-2-yl)thioacetic Acid (**20**).

A mixture of **2** (1.5 g, 0.01 mole), bromoacetic acid (0.96 g, 0.01 mole), and fused sodium acetate (0.82 g, 0.01 mole) in absolute ethanol was stirred at reflux temperature for 4 hours. Analysis (tlc) on silica [acetone:-benzene (1:3)] indicated the reaction was incomplete, thus, an additional amount of bromoacetic acid (0.0114 mole) was added to the reaction mixture and the heating was continued for 3 hours. The solvent was removed by evaporation and the resulting residue, on trituration with water, gave a colorless solid which was collected by filtration, and dried under reduced pressure at room temperature. The solid was recrystallized from methanol to give 1.30 g, (79%) of **20**, mp 212-213°; ir (potassium bromide): ν max 3400, 2910, 1570, 741 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.16 (s, 2 H, CH_2), 7.63-8.58 [m, 5 H, Ar-H, and -COO*H*, (COO*H* exchangeable with deuterium oxide)].

Anal. Calcd. for ($C_9H_8N_2O_2S$): C, 51.91; H, 3.87; N, 13.45. Found: C, 51.69; H, 4.06; N, 13.23.

(5-Benzoylbenzimidazol-2-yl)thioacetic Acid (**21**).

Bromoacetic acid (1.85 g, 0.0133 mole) was added to a stirred suspension of the potassium salt of 2-mercapto-5-benzoylbenzimidazole (2.4 g, 0.0085 mole) in dry tetrahydrofuran (30 ml).The reaction mixture was stirred and refluxed for 7 hours. The solvent was removed under reduced pressure, and the resulting residue was diluted with water, and the mixture extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and filtered. The filtrate was evaporated to furnish a solid, which was collected and dried at 60° for 5 hours, yield 2.0 g (76%), mp 178-179°; ir (potassium bromide): ν max 3300-2800, 1730-1712, 1660, 840, 785, 750, 720, 700 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.2 (s, 2 H, S-CH_2), 7.08-8.4 (m, 8 H, Ar-H).

Anal. Calcd. for ($C_{16}H_{12}N_2O_3S$): C, 61.55; H, 3.87; N, 8.97. Found: C, 61.80; H, 3.86; N, 8.68.

General Method of Preparation of 2- and 2,5-Disubstituted Benzimidazole Derivatives. Ethyl or Methyl Benzimidazol-2-ylthio- and [5-benzoylbenzimidazol-2-yl]thio Fatty Acid Esters **22-29**, **31-34**.

A mixture of either **2** or **3** (0.01 mole), a bromo fatty acid ester (0.01-0.02 mole), and anhydrous potassium carbonate (0.005 mole) in absolute ethanol or methanol was stirred and heated under reflux for 8-30 hours. The solvent was evaporated under reduced pressure and the resulting residue was diluted with water (30 ml) and extracted with ethyl acetate or chloroform. The organic layer was washed with water, dried over anhydrous sodium sulfate and filtered. Evaporation of the filtrate furnished a solid which was purified by either recrystallization from an ethyl acetate; hexane mixture or by column chromatography on silica gel using a chloroform:methanol mixture as the eluant. Some products, were characterized as hydrobromide salts.

6-[5-Benzoylbenzimidazol-2-yl-thio]hexanoic Acid (**30**).

Compound **30** was prepared by a method similar to that which afforded **21**. Purification was accomplished by column chromatography on silica gel using chloroform:methanol (v:v, 98-95:2-5) as eluant, yield 39%, mp 69-71°; ir (potassium bromide): ν max 3200, 2930, 1700, 1660-1640, 880, 820, 700 cm^{-1}; ^1H nmr (deuteriochloroform + DMSO-d_6): δ 1.23-2.05 (m, 6 H, -(CH_2)$_3$-), 2.2 (t, 2 H, -CH_2CO), 3.37 (t, 2 H, S-CH_2), 7.23-8.24 (m, 8 H, Ar-H), 9.1 (bs, 1 H, COOH, exchangeable with deuterium oxide), 12.51 (bs, 1 H, NH, exchangeable with deuterium oxide).

Anal. Calcd. for ($C_{20}H_{20}N_2O_3S$): C, 65.20; H, 5.47; N, 7.60. Found: C, 65.25; H, 5.47; N, 7.33.

Acknowledgement.

The authors would like to thank Dr. J. W. McCall, University of Georgia and Dr. D. A. Denham, London School of Hygiene and Tropical Medicine for antifilarial testing and Ms. Deanna VanSickle for help in the preparation of this manuscript. This investigation was supported by the filariasis component of the UNDP/World Bank/WHO special program for Research and Training in Tropical Diseases (I. D. 840398, and 840124).

REFERENCES AND NOTES

[1] H. V. den Bossche, F. Rochette and C. Horig, *Adv. Pharmacol. Chemother.*, **19**, 67 (1982).

[2] J. A. Van Allan and B. D. Deacon, *Org. Synth. Coll.*, Vol. IV, 569, (1963).

[3] J. A. Vida, *Tetrahedron Letters*, 3921 (1972).

[4] W. Knobloch, G. Winkelmann and K. Rintelen, *Arch. Pharm.*, **291**, 113 (1958).

[5] A. N. Krasovskii, A. B. Roman, V. I. Linenko, V. I. Proskurnya, I. I. Soroka, *Khim Farm Zh.*, **12**, 72 (1978) (Russ); *Chem. Abstr.*, **88**, 152568w (1978).

[6] G. Rovnyah, V. L. Narayanan, R. D. Haugwitz and C. M. Cimarusti, U. S. Patent 3,927,014 (1975); *Chem. Abstr.*, **84**, 105596m (1976).

[7] A. Fredga, *Acta Chem. Scand. Ser. B*, **31**, 869 (1977).

[8] J. W. McCall and H. H. Crouthannel, *J. Parasitol.*, **62**, 844 (1976).