Imidazole Systems. I. Imidazo[2,1-*b*][1,3,5]benzothiadiazepine Derivatives as Potential Antipsychotic Agents

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Imidazo[2,1-*b*][1,3,5]benzothiadiazepine **3** constitutes a novel ring system, and its analogs **3a-i** were synthesized to investigate their potential antipsychotic activity. The synthesis of the ring system was achieved by reaction of 2-aminophenylthioimidazoles **7** with phosgene or thiophosgene and by ring closure of the 1-[2-(2-imidazolyl)thiophenyliminocarbonyl]-1-piperazines **13**. An efficient method for the conversion of thioureas **8, 12** to guanidine **3a** *via* the corresponding cyanothioamidines **11, 14** was developed.

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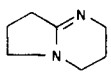
The incidence of extrapyramidal side effects, as well as the beneficial antipsychotic actions of neuroleptic drugs are believed to be due to the blockade of dopamine receptors in the brain. In our search for a neuroleptic drug that would be free of extrapyramidal side effects, we have considered an approach that is not entirely based on the dopamine hypothesis of schizophrenia. Such an alternative approach that has attracted considerable attention is based on the transmethylation hypothesis, which postulates that disturbances in the enzymatic regulation of transmethylation reactions could lead to the formation of schizotoxins [1]. Therefore, inhibition of enzymes involved in such transformations constitutes a viable approach to the therapy of schizophrenia. It has been reported [2,3] that compounds **1** and **2** are potent inhibitors of the indolamine *N*-methyltransferase, a lung enzyme that has been implicated in such transmethylation reactions [4]. In our view, to be an effective antipsychotic such an inhibitor should be able to act directly in the brain. It was of interest, therefore, to synthesize certain imidazo[2,1-*b*][1,3,5]-benzothiadiazepines **3** in which the amidine features of **1** and **2** have been incorporated into the benzodiazepine



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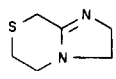

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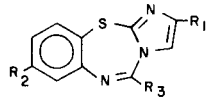


3

ring system of known antipsychotic drugs [5]. The ring system in **3** had not been reported in the literature prior to the publication of our patent applications [6]. The synthetic methods for the preparation of **3** are presented in Scheme 1.

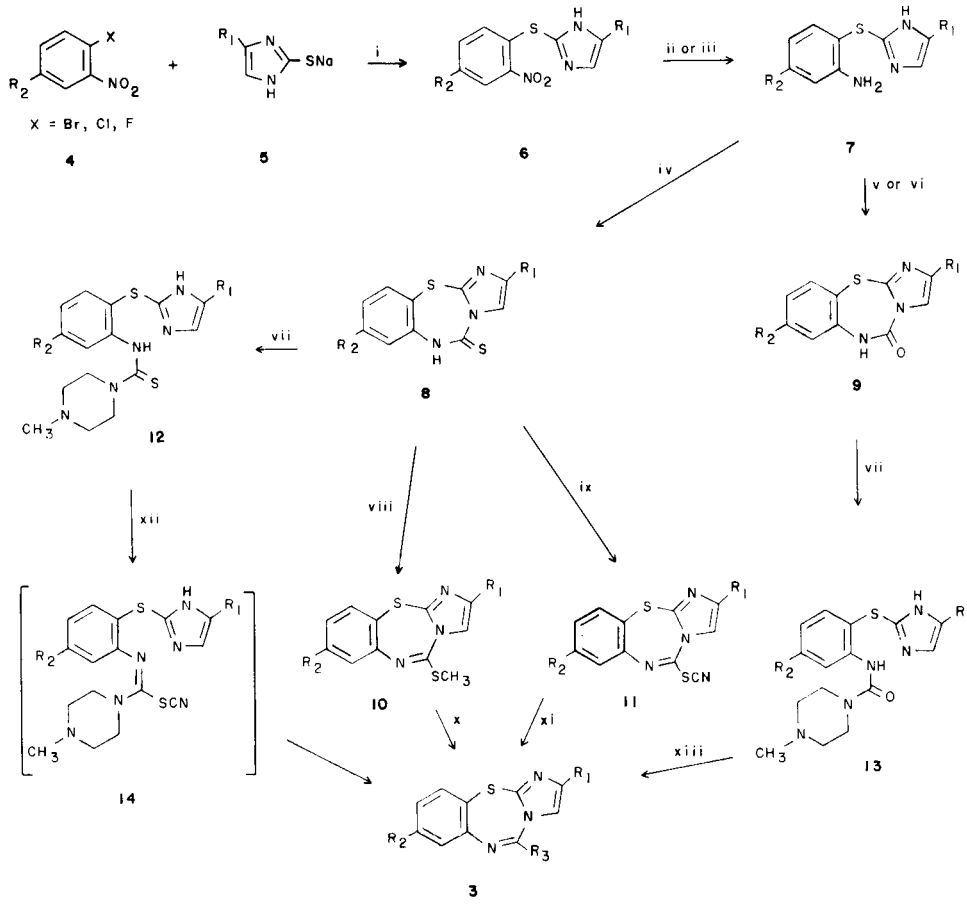
Reaction of 2-nitrohalobenzenes **4** with sodium mercaptoimidazoles **5** in refluxing ethanol gave the nitro derivatives **6** (Table I). The latter were reduced with iron or tin and hydrochloric acid in ethanol yielding the amine derivatives **7** (Table II). Treatment of **7** with thiophosgene, phosgene or a phosgene-derived reagent, *e.g.*, 1,1'-carbonyldiimidazole (CDI), gave the cyclic ureas **8** and **9** respectively. The reaction of **7f** with CDI gave compound **9d** (Table IV) along with the corresponding C_3-methyl isomer in a ratio of 6:1. The presence of a mixture of the two isomers was revealed by the pmr spectrum which showed a pair of doublets (J = 0.02 Hz) of δ 2.02 (major) and 2.28 (minor) respectively. The structural assignment of the major isomer **9d** was based only on steric considerations.

Because of the weak bonding between the imidazole nitrogen and the urea carbonyl, compounds **8** and **9** reacted as expected with *N*-methylpiperazine at room temperature to give the ring-opened ureas **12** and **13** (Table III) respectively.

Reaction of **8** with sodium hydride and methyl iodide in tetrahydrofuran gave the methylthio derivative **10** which, in contrast to the reactivity of **8** and **9**, was found to be surprisingly stable to nucleophilic attack. Compound **10a** (Table IV) was recovered quantitatively even after prolonged refluxing in *N*-methylpiperazine. In the presence of one equivalent of hydrochloric acid, however, compound **10a** reacted with *N*-methylpiperazine in refluxing amyl alcohol to give the desired product **3a**, along with a considerable amount of tarry side products. Nevertheless, this method was used successfully in the preparation of analogs **3b, d, e**, and **g** in moderate yields (Table IV).

At this point it became apparent that in order to suppress the side reactions and improve the yields of **3**, a better leaving group than the methylthio group, was desirable. The cyanothio group in compound **11** was considered such a leaving group, since the nucleophilic displacement of thiocyanate ion would be energetically more favorable. Indeed, compound **11**, which was conveniently prepared by reaction of **8a** with sodium hydride and cyanogen bromide, reacted at 0° with *N*-methylpiperazine to give a mixture of the desired product **3a** and the thiourea **8a**. Apparently, the reaction proceeds in two different directions resulting from nucleophilic displacement at the amidine carbon to give **3a** or at the cyanide carbon to give **8a**. A solvent effect that could suppress formation of **8a** was investigated by employing a variety of solvents in this

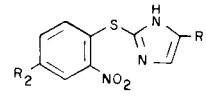
Scheme I [a,b]



[a] For R_1, R_2, R_3 and n see Tables I-IV. [b] (i) EtOH/Δ: Method A. (ii) Fe/HCl: Method B. (iii) Sn/HCl: Method C. (iv) $CSCl_2/CH_2Cl_2$: Method D. (v) $COCl_2/CH_2Cl_2$: Method E. (vi) CDI/CH_2Cl_2: Method F. (vii) Amine/CH_2Cl_2. (viii) NaH/MeJ: Method G. (ix) NaH/BrCN: Method H. (x) Amine/HCl: Method I. (xi) Amine/HMPA: Method J. (xii) $BrCN/K_2CO_3$: Method K. (xiii) $POCl_3/PCl_5$; $NEt_3/CHCl_2$: Method L.

Table I [a]

2-(2-Nitrophenylthio)imidazoles

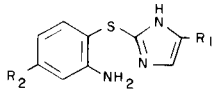


6	R_1	R_2	Mp °C	Crystallization Solvent	% Yield	Empirical Formula	Analyses % Calcd./Found C	H	N
6α	H	H	179-181	Ethanol	83	$C_9H_7N_3O_2S$	48.86	3.19	18.99
							48.73	3.23	18.87
6b	H	Cl	184-186	Ethanol	81	$C_9H_6ClN_3O_2S$	42.28	2.37	16.43
							42.50	2.50	16.09
6c	H	F	167-169	Ether	85	$C_9H_6FN_3O_2S$	45.19	2.53	17.57
							45.21	2.60	17.55
6d	H	CF_3	158-161	Ether	91	$C_{10}H_6F_3N_3O_2S$	41.53	2.09	14.53
							41.67	2.04	14.30
6e	H	OCH_3	187-190	Ethanol	68	$C_{10}H_9N_3O_3S$	47.80	3.61	16.72
							47.89	3.58	16.69
6f	CH_3	H	149-152	Dichloromethane-ether	81	$C_{10}H_9N_3O_2S$	51.05	3.86	17.86
							50.66	3.97	17.54

[a] These compounds were prepared according to Method A.

Table II

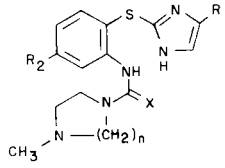
2-(2-Aminophenylthio)imidazoles



7	R_1	R_2	Method	Mp °C	Crystallization Solvent	% Yield	Empirical Formula	Analyses % Calcd./Found C	H	N
7a	H	H	B	135-137	Ethanol	82	$C_9H_9N_3S$	56.51	4.74	21.97
								56.60	4.63	21.82
7b	H	Cl	C	114-117	Ether-hexane	79	$C_9H_8ClN_3S$	47.89	3.57	18.62
								47.47	3.63	18.44
7c	H	F	B	130-132	Ether	84	$C_9H_8FN_3S$	51.65	3.85	20.08
								51.74	3.84	20.01
7d	H	CF_3	C	90-93	Dichloromethane-hexane	84.3	$C_{10}H_8F_3N_3S$	46.33	3.10	16.20
								45.99	3.24	16.16
7e	H	OCH_3	C	122-125	Dichloromethane	92	$C_{10}H_{11}N_3OS$	54.27	5.01	18.97
								54.09	5.14	19.37
7f	CH_3	H	B	oil		89	$C_{10}H_{11}N_3S$	58.50	5.40	20.46
								58.24	5.21	20.08

Table III [a]

1-[2-(2-Imidazolyl)thiophenylimino(or thio)carbonyl]piperazines



	R_1	R_2	x	n	Mp °C	Crystallization Solvent	% Yield	Empirical Formula	Analyses % Calcd./Found C	H	N
12	H	H	S	2	212-214	Tetrahydrofuran	90	$C_{15}H_{19}N_5S_2$	54.02	5.74	21.00
									54.21	6.03	20.76
13a	H	H	O	2	197-200	Dichloromethane	97.8	$C_{15}H_{19}N_5OS$	56.76	6.03	22.06
									56.43	5.90	21.77
13b	H	H	O	3	135-139	Methanol-ether	100	$C_{16}H_{21}N_5OS$	57.98	6.39	21.13
									57.73	6.73	20.66
13c	H	CF_3	O	2	212-214	Dichloromethane	100	$C_{16}H_{18}F_3N_5OS$	49.86	4.71	18.17
									49.59	4.70	18.10
13d	CH_3	H	O	2	102-104	Dichloromethane-ether	88	$C_{16}H_{21}N_5OS$	57.98	6.39	21.13
									57.60	6.14	21.07

[a] These compounds were prepared as directed in Methods K or L.

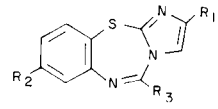
reaction. Satisfactory results were achieved only with hexamethyl phosphoramide (HMPA). With this solvent, compound **3a** was obtained in 80% yield, while only a trace of thiourea **8a** was detected in the reaction mixture. In principle, this reaction could be adapted to the cyclization of thiourea **12** to give **3a** *via* the intermediate **14**. Treatment of **12** with cyanogen bromide in dimethylformamide in the presence of potassium carbonate gave **3a** in 39% yield. The presumed intermediate **14**, however, could not be detected at any time during the course of the reaction.

The usefulness of the cyanothio group was further demonstrated in the preparation of imidazole derivative **3i** (Table IV). This compound was otherwise inaccessible from **10a** due to the weak nucleophilicity of the imidazole nitrogen.

Finally, the most efficient and general method for the synthesis of **3** turned out to be the cyclization of the ureas **13**. Treatment of **13a-d** with phosphorus oxychloride and phosphorus pentachloride at room temperature, removal of the reagents under reduced pressure, and cyclization of the amidine intermediates with triethylamine in methylene chloride gave the analogs **3a, c, f,** and **h**, respectively,

Table IV

Imidazo[2,1-*b*][1,3,5]benzothiadiazepines



	R_1	R_2	R_3	Method	Mp °C	Crystallization Solvent	% Yield	Empirical Formula	Analyses % Calcd./Found C	H	N
8a	H	H	SH	D	152-154	THF-ether	78	$C_{10}H_7N_3S_2$	51.48	3.02	18.01
									51.64	3.15	17.87
8b	H	Cl	SH	D	171-173	Acetone	55.3	$C_{10}H_6ClN_3S_2$	44.85	2.26	15.69
									45.18	2.30	15.46
8c	H	F	SH	D	154-155	Dichloromethane	37.7	$C_{10}H_6FN_3S_2$	47.40	2.41	16.72
									47.44	2.59	16.49
8d	H	OCH_3	SH	D	142-145	Acetone	63.6	$C_{11}H_9N_3OS_2$	50.18	3.45	15.96
									49.98	3.38	15.76
9a	H	H	OH	E	257-259 [a]	THF	81	$C_{10}H_7N_3OS$	55.28	3.24	19.34
									55.58	3.61	18.97
9b	H	Cl	OH	F	261-263 [a]	THF	85	$C_{10}H_6ClN_3OS$	47.72	2.40	16.70
									47.67	2.69	16.64
9c	H	CF_3	OH	F	257-260	Ethyl acetate	72	$C_{11}H_6F_3N_3OS$	46.33	2.11	14.72
									46.24	2.40	14.36
9d	CH_3 [c]	H	OH	F	225-229	Dichloromethane	33	$C_{11}H_9N_3OS$	57.13	3.92	18.17
									56.79	4.02	18.28
10a	H	H	SCH_3	G	119-121	Dichloromethane-ether	93.4	$C_{11}H_9N_3S_2$	53.42	3.67	16.99
									53.15	3.64	16.79
10b	H	Cl	SCH_3	G	149-151	Dichloromethane-ether	78.6	$C_{11}H_8ClN_3S_2$	46.88	2.86	14.91
									46.98	2.89	14.87
10c	H	F	SCH_3	G	175-176	Dichloromethane-ether	82.8	$C_{11}H_8FN_3S_2$	49.80	3.04	15.84
									49.42	3.04	15.82
10d	H	OCH_3	SCH_3	G	143-146	Dichloromethane-ether	99	$C_{12}H_{11}N_3OS_2$	51.96	4.00	15.15
									51.91	4.03	15.20
11	H	H	SCN	H	131-134	Methanol-ether	83	$C_{11}H_6N_4S_2$	51.14	2.34	21.69
									51.27	2.54	21.46
3a	H	H	4-Methyl-piperazino	I	141-144	2-Propanol	57	$C_{15}H_{17}N_5S$	60.18	5.72	23.39
									59.93	5.60	23.30
				J	[b]		80				
				K			39				
				L			55				
3b	H	H	Piperazino	I	249 [a]	Methanol-ether	37	$C_{14}H_{15}N_5S\cdot 2HCl$	46.93	4.78	19.55
									46.81	4.95	19.19
3c	H	H	4-Methyl-perhydro-[1,4]diaz-epino	L	216-218 [a]	Acetone-methanol	80	$C_{16}H_{19}N_5S\cdot C_4H_4O_4$	55.93	5.40	16.31
									55.72	5.39	16.28
3d	H	Cl	4-Methyl-piperazino	I	190-192 [a]	Methanol-ether	29	$C_{15}H_{16}ClN_5S\cdot C_4H_4O_4$	50.72	4.48	15.57
									50.51	4.67	15.21
3e	H	F	4-Methyl-piperazino	I	204-206 [a]	Methanol-ethyl acetate	31	$C_{15}H_{16}FN_5S\cdot C_4H_4O_4$	52.64	4.65	16.16
									52.48	4.58	15.94
3f	H	CF_3	4-Methyl-piperazino	L	Foam		82	$C_{16}H_{16}F_3N_5S$	52.31	4.39	19.06
									51.94	4.17	18.83
3g	H	OCH_3	4-Methyl-piperazino	I	167-170 [a]	Ethanol-ether	39	$C_{16}H_{19}N_5OS\cdot C_4H_4O_4$	53.92	5.20	15.72
									53.83	5.14	15.50
3h	CH_3	H	4-Methyl-piperazino	L	191-193	Methanol-ether	51	$C_{16}H_{19}N_5S\cdot C_4H_4O_4$	55.93	5.40	16.31
									55.67	5.34	15.98
3i	H	H	1-Imid-azolyl	J	154-156	Acetone	68	$C_{13}H_9N_5S\cdot C_4H_4O_4$	53.27	3.42	18.27
									53.10	3.64	18.09

[a] Melts with decomposition. [b] Melting point of dihydrochloride, 216-219° and 1:1 maleate, 194-196°. [c] This product was isolated as 6:1 mixture with the corresponding C_3-methyl isomeric compound.

in moderate to excellent yields (Table IV). Interestingly, in contrast to the case of the **9d** formation, only compound **3h** of the two possible isomers expected from the cyclization of **13d** was isolated. The structural assignment of **3h** was once again based solely on steric considerations.

Compound **3a** displays neuroleptic properties, for instance in the rat avoidance test at an oral dose of 10 mg/Kg.

EXPERIMENTAL

Physical constants, yields and analytical values for the compounds below are reported in Tables I-IV. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ultraviolet and infrared spectra were obtained respectively with a Carry 14 spectrophotometer and a Perkin-Elmer 281 B spectrograph. Unless otherwise stated, the former were determined as solutions in methanol and the latter as Nujol mulls. The pmr spectra were recorded on a Hitachi Perkin-Elmer R-600 and Varian CFT 20 spectrometer.

The proton magnetic resonance spectra (pmr) for aromatic and heteroaromatic protons were included only in those instances where their assignment was needed for structure elucidation.

2-(2-Nitrophenylthio)imidazole (**6a**).

Method A.

To a stirred 1.28 *M* solution (500 ml) of ethanolic sodium ethoxide was added at once 64 g (0.64 mole) of 2-mercaptoimidazole [7]. The mixture was stirred until all solids went into solution. To the resulting solution was added 125.5 g (0.64 mole) of 2-nitro-1-bromobenzene; the mixture was refluxed for 4 hours and filtered while hot. The filtrates were cooled to room temperature and the yellow precipitate which was formed was filtered and washed with ethanol. Recrystallization from ethanol gave 116 g (83%) of 2-(2-nitrophenylthio)imidazole (**6a**), mp 179-181°; ir: 1591, 1570, 1508, 1335, 1305, 1010 (split band), 965 cm^{-1}.

Similarly, the following compounds were prepared.

2-(4-Chloro-2-nitrophenylthio)imidazole (**6b**).

This compound was prepared from 2-nitro-1,4-dichlorobenzene and 2-mercaptoimidazole in a yield of 81%, mp 184-186° (ethanol); ir: 3070, 1545, 1512, 1330, 1099 cm^{-1}.

2-(4-Fluoro-2-nitrophenylthio)imidazole (**6c**).

This compound was prepared from 2-nitro-1,4-difluorobenzene and 2-mercaptoimidazole in a yield of 85%, mp 167-169° (ether); ir: 3070, 1592, 1570, 1365, 1320, 1200, 1090 cm^{-1}.

2-(2-Nitro-4-trifluoromethylphenylthio)imidazole (**6d**).

This compound was prepared from 2-nitro-4-trifluoromethyl-1-chlorobenzene and 2-mercaptoimidazole in a yield of 91%, mp 158-161° (ether); ir: 1619, 1560, 1526, 1321, 1292, 1180, 1160, 1130, 970 cm^{-1}.

2-(4-Methoxy-2-nitrophenylthio)imidazole (**6e**).

This compound was prepared from 4-methoxy-2-nitro-1-chlorobenzene and 2-mercaptoimidazole in a yield of 68%, mp 187-190° (ethanol); ir 1609, 1520, 1330, 1280, 1230, 1094, 960 cm^{-1}; pmr (DMSO-d_6): δ 3.86 (3H, s, OCH_3).

4-Methyl-2-(2-nitrophenylthio)imidazole (**6f**).

This compound was prepared from 2-chloronitrobenzene and 2-mercapto-4-methylimidazole [8] in a yield of 81%, mp 149-152° (dichloromethane-ether); ir: 1584, 1562, 1508, 1320, 1330, 1005, 845 cm^{-1}; pmr (DMSO-d_6): δ 2.25 (3H, s, CH_3).

2-(2-Aminophenylthio)imidazole (**7a**).

Method B.

To a solution of 5.52 g (0.025 mole) of 2-(2-nitrophenylthio)imidazole (**6a**) in 10 ml of 50% aqueous ethanol was added 8.5 g (100 mesh, 0.15 mole) of iron powder and the mixture was heated to reflux with vigorous stirring. To the refluxing mixture was carefully added dropwise a solution of 0.52 ml (0.006 mole) of concentrated hydrochloric acid in 2.5 ml of 50% aqueous ethanol over a period of 10 minutes. The mixture was further refluxed for 2 hours, cooled and basified with 15% ethanolic potassium hydroxide. The precipitated iron hydroxides were filtered and washed with ethanol. The combined filtrate and washings were evaporated *in vacuo*, the residue was triturated with water and extracted 4 times with methylene chloride. The combined extracts were washed with water, dried over magnesium sulfate and evaporated *in vacuo*. The crystalline residue was recrystallized from ethanol to give 3.9 g (82%) of 2-(2-aminophenylthio)imidazole (**7a**), mp 135-137°; ir: 3775, 3380 (NH, NH_2), 1611, 1320, 1250, 1090, 960 cm^{-1}.

According to Method B, the following compounds were prepared from the corresponding 2-(2-nitrophenylthio)imidazoles **6**.

2-(2-Amino-4-fluorophenylthio)imidazole (**7c**).

This compound was prepared in a yield of 84%, mp 130-132° (ether); ir: 3450, 3340 (NH, NH_2), 1620, 1578, 1289, 1170, 1101, 965 cm^{-1}.

4-Methyl-2-(2-aminophenylthio)imidazole (**7f**).

This compound was prepared as an oil; pmr (deuteriochloroform): δ 2.2 (3H, s, CH_3), 6.4 (2H, br s, NH_2, deuterium oxide exchangeable).

2-(2-Amino-4-chlorophenylthio)imidazole (**7b**).

Method C.

To a stirred suspension of 4 g (0.016 mole) of 2-(4-chloro-2-nitrophenylthio)imidazole (**6b**) and 3.8 g (0.032 mole) of tin in 20 ml of ethanol was added dropwise 13.8 ml (0.16 mole) of concentrated hydrochloric acid while maintaining the reaction temperature at 40-50° using an ice-water cooling bath. After the addition was completed, the reaction mixture was heated on a steam bath for 30 minutes, then cooled to room temperature, neutralized with 2*N* sodium hydroxide and extracted 3 times with methylene chloride. The combined extracts were washed with water, dried over magnesium sulfate and evaporated *in vacuo*. The crystalline residue was recrystallized from ether-hexane to give 2.85 g (79%) of 2-(2-amino-4-chlorophenylthio)imidazole (**7b**), mp 114-117°; ir: 3450, 3350 (NH, NH_2), 1605, 1370, 1320, 1250, 1088 cm^{-1}.

According to Method C, the following compounds were prepared from the corresponding 2-(2-nitrophenylthio)imidazoles **6**.

2-(2-Amino-4-trifluoromethylphenylthio)imidazole (**7d**).

This compound was prepared in a yield of 84%, mp 90-93° (methylene chloride-hexane); ir: 3475, 3360 (NH, NH_2), 1622, 1574, 1552, 1534, 1290, 1260, 1130, 970 cm^{-1}.

2-(2-Amino-4-methoxyphenylthio)imidazole (**7e**).

This compound was prepared in a yield of 92%, mp 122-125° (methylene chloride); ir: 3450, 3350 (NH, NH_2), 1617, 1588, 1570, 1318, 1290, 1260, 1220, 1090, 951 cm^{-1}; pmr (DMSO-d_6): δ 3.65 (3H, s, OCH_3).

Imidazo[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-thione (**8a**).

Method D.

To a stirred solution of 1.9 g (0.01 mole) of 2-(2-aminophenylthio)imidazole (**7a**) and 2.02 g (0.02 mole) of triethylamine in 150 ml of methylene chloride was added dropwise a solution of 1.15 g (0.01 mole) of thiophosgene in 50 ml of methylene chloride over a period of 30 minutes at −5°. Stirring continued at room temperature overnight. The white precipitate which was formed was filtered, washed with methylene chloride and water, and dried under vacuum to give 1.42 g (61%) of imidazo-[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-thione (**8a**). Recrystallization from tetrahydrofuran gave analytically pure material, mp 152-154°; uv: λ max nm (ϵ) 304 sh (1590), 294 sh (1840), 278 (11590), 241 (22090), 218 (46080); ir: 3120 (NH), 1590, 1535, 1370, 1340, 1240, 1085, 970 cm^{-1}.

According to Method D, the following compounds were prepared from the corresponding 2-(2-aminophenylthio)imidazoles **7**.

8-Chloroimidazo[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-thione (**8b**).

This compound was prepared in a yield of 55%, mp 171-173° (acetone); ir: 1583, 1534, 1234, 1195, 1087 cm^{-1}.

8-Fluoroimidazo[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-thione (**8c**).

This compound was prepared in a yield of 38%, mp 154-155° (methylene chloride); ir: 1595, 1550, 1260, 1222, 1140, 1095 cm^{-1}.

8-Methoxyimidazo[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-thione (**8d**).

This compound was prepared in a yield of 64%, mp 142-145° (acetone); ir: 1595, 1542, 1347, 1320, 1280, 1260, 1229 cm^{-1}; pmr (DMSO-d_6): δ 3.77 (3H, s, OCH_3).

Imidazo[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-one (**9a**).

Method E.

To a stirred solution of 2.3 g (0.012 mole) of 2-(2-aminophenylthio)imidazole (**7a**) and 2.5 g (0.025 mole) of triethylamine in 200 ml of methylene chloride was added dropwise a solution of 1.2 g (0.012 mole) of phosgene in 35 ml of methylene chloride at −5° over a period of 1 hour. Stirring continued at room temperature overnight, the reaction mixture was evaporated *in vacuo*, and the residue was triturated with water and ethyl acetate. The insoluble material was filtered, washed with ethyl acetate and dried under vacuum to give 2.2 g (81%) of imidazo[2,1-*b*][1,3,5]-benzothiadiazepine-5(6*H*)-one (**9a**), mp 249-251° dec. Recrystallization from tetrahydrofuran gave analytically pure white crystals, mp 257-259° dec; uv: λ max nm (ε) 282 sh (2060), 234 (20530), 206 (28800); ir: 3190 (NH), 1691 (CO), 1270, 1245, 1120 cm^{-1}.

8-Chloroimidazo[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-one (**9b**).

Method F.

To a stirred solution of 8 g (0.035 mole) of 2-(4-chloro-2-aminophenylthio)imidazole (**7b**) in 400 ml of methylene chloride was added 5.75 g (0.035 mole) of 1,1'-carbonyl diimidazole and the mixture was stirred at room temperature for 3 hours. The solids were filtered, washed with methylene chloride, and recrystallized from tetrahydrofuran to give 7.5 g (85%) of white crystals of 8-chloroimidazo[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-one (**9b**), mp 261-263° dec; ir: 1713 (CO), 1566, 1510, 1280, 1228, 1089 cm^{-1}.

According to Method F, the following compounds were prepared from the corresponding 2-(2-aminophenylthio)imidazoles (**7**).

8-Trifluoromethylimidazo[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-one (**9c**).

This compound was prepared in a yield of 72%, mp 257-260° (ethyl acetate); ir: 3135 (NH), 1734 (CO), 1600, 1580, 1512, 1332 (split band), 1288, 1232, 1170, 1100 cm^{-1}.

2-Methylimidazo[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-one (**9d**).

This compound was isolated as a 6:1 mixture with the corresponding C_3-methyl isomer in a yield of 33%, mp 225-229°; ir: 3200 (NH), 1710 (CO), 1579, 1370, 1330, 1280, 1130 cm^{-1}; pmr (DMSO-d_6): δ 2.02 (3H, d, J = 0.02 Hz, CH_3 for **9d**), δ 2.28 (3H, d, J = 0.02 Hz, CH_3 for C_3-methyl isomer).

5-Methylthioimidazo[2,1-*b*][1,3,5]benzothiadiazepine (**10a**).

Method G.

To a stirred suspension of 2.25 g (0.094 mole) of sodium hydride in 220 ml of tetrahydrofuran was added in portions 22 g (0.094 mole) of imidazo[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-thione (**8a**) and the mixture was stirred for 2 hours at room temperature. To the resulting solution was added 13.4 g (0.094 mole) of methyl iodide, the mixture was stirred for 1 hour at room temperature, evaporated *in vacuo* and the residue was triturated with a mixture of methylene chloride and water. The organic layer was dried over magnesium sulfate, decolorized with charcoal, evaporated to a small volume and diluted with ether to give 21.7 g (93%) of 5-methylthioimidazo[2,1-*b*][1,3,5]benzothiadiazepine (**10a**), mp 119-121°; uv: λ max nm (ε) 262 sh (1193), 244 (14750), 232 (15250), 206 (36270); ir: 1633, 1455, 1262, 923 cm^{-1}; pmr (deuteriochloroform): δ 2.65 (3H, s, SCH_3).

A monohydrochloride of **10a** was prepared in acetone with ethereal hydrochloric acid, mp 169-171°.

According to Method G, the following compounds were prepared from the corresponding imidazo[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-thiones **8**.

8-Chloro-5-methylthioimidazo[2,1-*b*][1,3,5]benzothiadiazepine (**10b**).

This compound was obtained in a yield of 78%, mp 149-151° (methylene chloride-ether); ir (methylene chloride): 1620, 1570, 1380, 1350, 1084, 930 cm^{-1}; pmr (deuteriochloroform): δ 2.63 (3H, s, SCH_3).

8-Fluoro-5-methylthioimidazo[2,1-*b*][1,3,5]benzothiadiazepine (**10c**).

This compound was obtained in a yield of 83%, mp 175-176° (methylene chloride-ether); ir (methylene chloride): 1635, 1592, 1470, 1360, 1140, 1090, 930 cm^{-1}; pmr (deuteriochloroform): δ 2.67 (3H, s, SCH_3).

8-Methoxy-5-methylthioimidazo[2,1-*b*][1,3,5]benzothiadiazepine (**10d**).

This compound was obtained in a yield of 99%, mp 143-146° (methylene chloride-ether); ir: 1630, 1589, 1560, 1278, 1136, 930 cm^{-1}; pmr (DMSO-d_6): δ 2.7 (3H, s, SCH_3), 3.8 (3H, s, OCH_3).

5-Cyanothioimidazo[2,1-*b*][1,3,5]benzothiadiazepine (**11**).

Method H.

To a stirred suspension of 2.03 g (0.043 mole) of sodium hydride in 100 ml of tetrahydrofuran was added in portions 10 g (0.043 mole) of imidazo[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-thione (**8a**) and the mixture was stirred at room temperature for 2 hours. To the resulting solution was added dropwise a solution of 4.56 g (0.043 mole) of cyanogen bromide in 40 ml of dry tetrahydrofuran at 0°. The mixture was stirred at 0° for 30 minutes, poured into water and extracted with ethyl acetate. The organic extracts were washed with brine, dried over magnesium sulfate, and evaporated *in vacuo* to a small volume to give 10.8 g (83%) of 5-cyanothioimidazo[2,1-*b*][1,3,5]benzothiadiazepine (**11**) as white crystals. Recrystallization from methanol-ether gave analytically pure material, mp 131-134°; uv: λ max nm (ε) 281 (4560), 234 (17330), 206 (35600); ir: 2170 (CN), 1650, 1216, 905 cm^{-1}.

5-(4-Methyl-1-piperazinyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine (**3a**).

Method I.

From 5-Methylthioimidazo[2,1-*b*][1,3,5]benzothiadiazepine (**10a**).

A mixture of 61.8 g (0.25 mole) of 5-methylthioimidazo[2,1-*b*][1,3,5]-benzothiadiazepine (**10a**), 86.5 g (0.5 mole) of *N*-methylpiperazine dihydrochloride and 50.1 g (0.5 mole) of *N*-methylpiperazine in 600 ml of amyl alcohol was refluxed under nitrogen for 48 hours. The amyl alcohol was evaporated *in vacuo*, the residue was dissolved in methylene chloride, and the solution was washed 3 times with 100 ml of 3*N* sodium hydroxide. The organic phase was then extracted 4 times with 75 ml of 2*N* hydrochloric acid and the combined extracts were washed with methylene chloride. The aqueous layer was decolorized with charcoal, basified with concentrated ammonium hydroxide and extracted twice with methylene chloride. The combined extracts were dried over magnesium sulfate and evaporated *in vacuo* to give 58.2 g of crystalline residue, mp 121-134°. This material was dissolved in 2-propanol, decolorized with charcoal, and evaporated to a small volume to give 42.6 g (57%) of 5-(4-methyl-1-piperazinyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine (**3a**), mp 141-144°; uv: λ max nm (ε) 284 sh (7000), 258 (13610), 222 sh (20160), 210 (25530); ir (methylene chloride): 1637, 1580, 1150, 1002 cm^{-1}; pmr (deuteriochloroform): δ 2.4 (3H, s, NCH_3), 2.4-2.8 (4H, m, CH_2NCH_3), 3.3-3.7 (4H, m, N=C-NCH_2).

A dihydrochloride of **3a** was prepared in acetone, mp 216-219°. A monomaleate salt was prepared in acetone and recrystallized from ethyl acetate-ether, mp 194-196°.

Method J.

From 5-Cyanothioimidazo[2,1-*b*][1,3,5]benzothiadiazepine (**11**).

To a stirred solution of 1 g (0.0039 mole) of 5-cyanothioimidazo[2,1-*b*]-[1,3,5]benzothiadiazepine (**11**) in 2 ml of hexamethyl phosphoramide was

added dropwise and over a period of 5 minutes 0.78 g (0.0078 mole) of *N*-methylpiperazine at 0°. The mixture was stirred at 0° for 5 minutes, the cooling bath was removed and the stirring continued for another 5 minutes. The reaction mixture was diluted with 25 ml of ethyl acetate and washed 3 times with brine. The organic layer was dried over magnesium sulfate and evaporated to dryness. The residue was dissolved in 10 ml of acetone and 0.452 g (0.0039 mole) of maleic acid was added, the acetone was evaporated *in vacuo*, the residue was diluted with ethyl acetate and ether to give 1.3 g (80%) 5-(4-methyl-1-piperazinyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine monomaleate (**3a**), mp 194-196°.

Method K.

From 1-[2-(2-Imidazolyl)thiophenyliminothiocarbonyl]-4-methylpiperazine (**12**).

A mixture of 2.3 g (0.01 mole) of imidazo[2,1-*b*][1,3,5]benzothiadiazepine-5(6*H*)-thione (**8a**) and 1 g (0.01 mole) of *N*-methylpiperazine in 23 ml of methylene chloride was stirred at room temperature overnight. A precipitate was filtered and washed with methylene chloride to give 2.8 g (84%) of 1-[2-(2-imidazolyl)thiophenyliminothiocarbonyl]-4-methylpiperazine (**12**), mp 212-214° (tetrahydrofuran): ir 2640 (plateau), 1573, 1500, 1239, 967 cm^{-1}.

To a stirred solution of 0.33 g (0.001 mole) of **12** and 20 mg of 18-Crown-6- in 3.3 ml of dimethylformamide were added 0.276 g (0.002 mole) of potassium carbonate and 0.116 g (0.0011 mole) of cyanogen bromide and the mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, washed 3 times with brine and evaporated *in vacuo*. The residue was dissolved in acetone, the solution was treated with 0.116 g (0.001 mole) of maleic acid and evaporated *in vacuo* to a small volume to give 160 mg (39%) of 5-(4-methyl-1-piperazinyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine monomaleate (**3a**), mp 190-193°.

Method L.

From 1-[2-(2-Imidazolyl)thiophenyliminocarbonyl]-4-methylpiperazine (**13a**).

A mixture of 2.17 g (0.01 mole) of imidazo[2,1-*b*][1,3,5]benzothiadiazepine-5 (6*H*)-one (**9a**) and 1 g (0.01 mole) of *N*-methylpiperazine in 20 ml of methylene chloride was stirred at room temperature overnight. A precipitate was filtered and washed with methylene chloride to give 3.1 g (98%) of analytically pure 1-[2-(2-imidazolyl)thiophenyliminocarbonyl]-4-methylpiperazine (**13a**), mp 197-200°; ir (potassium bromide): 1617 (CO), 1588, 1577, 1525, 1285, 1095, 995 cm^{-1}.

A mixture of 3.1 g (0.0098 mole) of **13a**, 25 ml of phosphorus oxychloride and 2.04 g (0.0098 mole) of phosphorus pentachloride was stirred at room temperature for 4 hours and evaporated *in vacuo*. The residue was suspended in 50 ml of methylene chloride, the suspension was cooled to 0° and 2.02 g (0.02 mole) of triethylamine was added dropwise. The mixture was then stirred at room temperature for 30 minutes, washed once with water and extracted twice with 2*N* hydrochloric acid. The acidic extracts were basified with concentrated ammonium hydroxide and extracted twice with methylene chloride. The combined extracts were dried over magnesium sulfate and evaporated *in vacuo* to give 1.7 g of 5-(4-methyl-1-piperazinyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine (**3a**), which was treated with maleic acid to give 2.2 g (55%) of the monomaleate, mp 190-193°.

According to Method I, the following compounds were prepared from the corresponding 5-methylthioimidazo[2,1-*b*][1,3,5]benzothiadiazepines (**10**).

5-(4*H*-1-Piperazinyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine Dihydrochloride (**3b**).

This compound was obtained in a yield of 37%, mp 249° dec (methanol-ether); ir: 3060 (NH), 1673, 1585, 1566, 1270 (split band), 1153, 931 cm^{-1}.

8-Chloro-5-(4-methyl-1-piperazinyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine Monomaleate (**3d**).

This compound was obtained in a yield of 29%, mp 190-192° dec (methanol-ether); ir: 1700, 1630, 1290, 1090, 970 cm^{-1}.

8-Fluoro-5-(4-methyl-1-piperazinyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine 1:1 Maleate (**3e**).

This compound was obtained in a yield of 31%, mp 204-206° dec (methanol-acetone-ether); ir: 1700, 1630, 1573 (split band), 1891, 970 (split band) cm^{-1}.

8-Methoxy-5-(4-methyl-1-piperazinyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine Monomaleate (**3g**).

This compound was obtained in a yield of 39%, mp 167-170° dec (acetone-ether); ir: 1700, 1640, 1590, 1290, 1140, 980 cm^{-1}.

According to Method L, the following compounds were prepared from the corresponding 1-[2-(2-imidazolyl)thiophenyliminocarbonyl]-4-methylpiperazines **13**.

5-(4-Methyl-1-homopiperazinyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine 1:1 Fumarate (**3c**).

This compound was prepared *via* the intermediate 1-[2-(2-imidazolyl)-thiophenyliminocarbonyl]-4-methylhomopiperazine [**13b**, 100%, mp 135-139° (methanol-ether); ir: 1650 (CO), 1570, 1525, 1370, 1320, 1280, 1230, 1030, 930 cm^{-1}] in a yield of 80%, mp 216-218° dec (acetone-methanol); ir: 1688, 1629, 1594, 1524, 1288, 1243, 1195, 982 cm^{-1}; nmr (DMSO-d_6): δ 2.06 (2H, m, CCH_2C), 2.56 (3H, s, NCH_3), 2.8-4 (8H, m, NCH_2), 6.62 (2H, s, fumaric H).

8-Trifluoromethyl-5-(4-methyl-1-piperazinyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine (**3f**).

This compound was prepared *via* the intermediate 1-[2-(2-imidazolyl)thio-5-trifluoromethylphenyliminocarbonyl]-4-methylpiperazine [**13c**, 100%, mp 212-214° (methylene chloride)] in a yield of 82%, foam; ir: 1645, 1605, 1565, 1335, 1140, 1080, 1010 cm^{-1}; pmr (deuteriochloroform): δ 2.4 (3H, s, NCH_3), 2.45-2.8 (4H, m, CH_2NCH_3), 3.3-3.8 (4H, m, N=C-NCH_2).

2-Methyl-5-(4-methyl-1-piperazinyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine Monomaleate (**3h**).

This compound was prepared *via* the intermediate 1-[2-(4-methyl-2-imidazolyl)thiophenyliminocarbonyl]-4-methylpiperazine [**13d**, 88%, mp 102-104° (methylene chloride-ether)] in a yield of 51%, mp 191-193° (methanol-ether); ir: 1693, 1625, 1573, 1350, 970 cm^{-1}; pmr (DMSO-d_6): δ 2.19 (3H, s, CH_3), 2.79 (3H, s, NCH_3), 3-4 (8H, m, NCH_2), 6.08 (2H, s, maleic H).

5-(1-Imidazolyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine Monomaleate (**3i**).

A mixture of 6 g (0.023 mole) of 5-cyanothioimidazo[2,1-*b*][1,3,5]benzothiadiazepine (**11**) and 3.1 g (0.046 mole) of imidazole in 12 ml of hexamethylphosphoramide was stirred at room temperature for 24 hours. The reaction mixture was diluted with ethyl acetate and extracted 3 times with 1*N* hydrochloric acid. The combined acidic extracts were basified with 2*N* sodium hydroxide and extracted 3 times with ethyl acetate. The combined organic extracts were dried over magnesium sulfate, decolorized with charcoal, and evaporated *in vacuo*. The oily residue was crystallized from ether to give 3.4 g (68%) of 5-(1-imidazolyl)imidazo[2,1-*b*][1,3,5]benzothiadiazepine (**3i**), mp 114-117°. A monomaleate salt was prepared in acetone, mp 145-146° dec; ir: 1681, 1621, 1562, 1529, 1298, 1170, 1110, 1010 cm^{-1}.

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