

was added dropwise a solution of CAN (5.0 g, 9.1 mmol) in H<sub>2</sub>O (5 mL) and the resulting solution was stirred at this temperature for 2 h. The mixture was diluted with H<sub>2</sub>O (20 mL) and the aqueous layer was extracted with ether (3 × 100 mL). The extracts were combined, washed (brine, 3 × 100 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated. The brown residue was chromatographed using a flash column (silica gel, 250 g). Elution by 5% ether in *n*-hexane gave **49** (850 mg, 92%) as yellow needles; mp 37–38 °C; MS *m/e* 214 (M<sup>+</sup>), 199, 172; IR (Nujol) 1654, 1520, 1400 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.20–8.00 (2 H, m, C<sub>5</sub>-H, C<sub>8</sub>-H), 7.80–7.50 (2 H, m, C<sub>6</sub>-H, C<sub>7</sub>-H), 6.65 (1 H, s, C<sub>3</sub>-H), 3.00–2.80 (2 H, m, ArCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 2.00–1.30 (4 H, m, ArCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>), 1.20–0.95 (3 H, m, ArCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>). Anal. (C<sub>14</sub>H<sub>14</sub>O<sub>2</sub>) C, H. Quinones **50** and **51** were prepared in a similar fashion from **42** and **48**, respectively.

**Registry No.** **1a**, 27436-93-7; **1b**, 27436-99-3; **1c**, 27437-03-2; **1d**, 123332-48-9; **1e**, 123332-49-0; **1f**, 123332-50-3; **1g**, 123332-51-4; **1h**, 123357-80-2; **1i**, 84153-34-4; **1j**, 34741-93-0; **1k**, 62589-23-5;

**2**, 99107-53-6; **3**, 107536-17-4; **4**, 107536-14-1; **5**, 107536-22-1; **6**, 107536-20-9; **7**, 123332-22-9; **8**, 123332-23-0; **9**, 123332-24-1; **10**, 107536-19-6; **11**, 99107-52-5; **12**, 123332-25-2; **13**, 123332-26-3; **14**, 107536-21-0; **15**, 99120-56-6; **16**, 99107-70-7; **17**, 123332-27-4; **18**, 121444-82-4; **19**, 121444-83-5; **20**, 123332-28-5; **21**, 123332-29-6; **22**, 123332-30-9; **23**, 123332-31-0; **24**, 123332-32-1; **25**, 123332-33-2; **26**, 123332-34-3; **27**, 123332-35-4; **28**, 123332-36-5; **29**, 123332-37-6; **30**, 123332-38-7; **31**, 123332-39-8; **32**, 123332-40-1; **33**, 123332-41-2; **34**, 123332-42-3; **35**, 99107-56-9; **36**, 99497-21-9; **37**, 99497-22-0; **38**, 99107-54-7; **39**, 99107-55-8; **40**, 99497-23-1; **41**, 99107-57-0; **42**, 99107-50-3; **43**, 123332-43-4; **44**, 120255-00-7; **45**, 123332-44-5; **46**, 123332-45-6; **47**, 99107-58-1; **48**, 99107-51-4; **49**, 34491-88-8; **50**, 123332-46-7; **51**, 123332-47-8; *o*-MeC<sub>6</sub>H<sub>4</sub>Br, 95-46-5; *m*-BuC<sub>6</sub>H<sub>4</sub>Br, 54887-20-6; Cr(CO)<sub>6</sub>, 13007-92-6; BuC≡CBu, 1942-46-7; CH<sub>3</sub>-(CH<sub>2</sub>)<sub>4</sub>C≡CCO<sub>2</sub>Et, 10519-20-7; BuC≡CH, 693-02-7; EtC≡CEt, 928-49-4; PhC≡CPh, 501-65-5; HC≡C(CH<sub>2</sub>)<sub>7</sub>CH<sub>3</sub>, 764-93-2; 5-lipoxygenase, 80619-02-9; 2,5-dimethylbromobenzene, 553-94-6; 2,3,5-trimethylbromobenzene, 31053-99-3; 2,3,4,5-tetramethylbromobenzene, 40101-36-8; *N*-methylpyrrole, 96-54-8.

## Some Benzyl-Substituted Imidazoles, Triazoles, Tetrazoles, Pyridinethiones, and Structural Relatives as Multisubstrate Inhibitors of Dopamine β-Hydroxylase. 4.<sup>1</sup> Structure-Activity Relationships at the Copper Binding Site

Lawrence I. Kruse,\*† Carl Kaiser,† Walter E. DeWolf, Joseph A. Finkelstein,† James S. Frazee,† Eileen L. Hilbert,† Stephen T. Ross,† Kathryn E. Flaim,† and John L. Sawyer†‡

Research and Development Division, Smith Kline & French Laboratories, P.O. Box 1539, King of Prussia, Pennsylvania 19406-0939. Received January 26, 1989

Structure-activity relationships (SAR) were determined for novel multisubstrate inhibitors of dopamine β-hydroxylase (DBH; EC 1.14.17.1) by examining the effects upon in vitro inhibitory potencies resulting from structural changes at the copper-binding region of inhibitor. Attempts were made to determine replacement groups for the thione sulfur atom of the prototypical inhibitor 1-(4-hydroxybenzyl)imidazole-2-thione described previously. The synthesis and evaluation of oxygen and nitrogen analogues of the soft thione group demonstrated the sulfur atom to be necessary for optimal activity. An additional series of imidazole-2-thione relatives was prepared in an effort to probe the relationship between the pK<sub>a</sub> of the ligand group and inhibitor potency. In vitro inhibitory potency was shown not to correlate with ligand pK<sub>a</sub> over a range of approximately 10 pK<sub>a</sub> units, and a rationale for this is advanced. Additional ligand modifications were prepared in order to explore bulk tolerance at the enzyme oxygen binding site and to determine the effects of substituting a six-membered ligand group for the five-membered imidazole-2-thione ligand.

Recently we reported some multisubstrate inhibitors of dopamine β-hydroxylase (DBH; EC 1.14.17.1), the mixed-function oxidase that catalyzes the hydroxylation of dopamine to norepinephrine.<sup>1-5</sup> Kinetic characterization of these inhibitors has led to structural insights to the active site of DBH<sup>3</sup> while the pharmacological activity of certain DBH inhibitors lends support to the notion that inhibiting DBH might offer a novel approach to the treatment of cardiovascular disorders such as hypertension.<sup>1,2,5</sup> Previous structure-activity relationship (SAR) studies of these DBH inhibitors demonstrated a striking dependence of potency upon substitution patterns at the portion of inhibitor that mimics the phenethylamine substrate,<sup>5</sup> as well as the dependence upon the length and substitution patterns of the bridging chain.<sup>4</sup> The prototype of this class of inhibitor, 1-(4-hydroxybenzyl)imidazole-2-thione, was designed on the basis of a capacity to bind a hypothesized binuclear active site as illustrated in Figure 1. Evidence in support of a direct binding of inhibitor to one copper atom has already been presented,<sup>3,6</sup> but

further evidence to support the hypothesized binuclear copper site shown in Figure 1 is lacking. Indeed, EXAFS (extended X-ray absorption fine structure) studies have failed to detect a Cu...Cu interaction in either the resting Cu<sup>2+</sup> or reduced, catalytically competent Cu<sup>1+</sup> oxidation state of DBH.<sup>6</sup> For this reason and because of the stringent SAR shown at the bridging chain and phenethylamine mimic portions of inhibitor, it became of interest to explore inhibitory potency as a function of modifications of the copper-binding portion of inhibitor. In this paper we re-

\* Address correspondence to this author at: Sterlind Drug, Inc., 9 Great Valley Parkway, Malvern, PA 19355.

† Department of Medicinal Chemistry.

‡ Department of Molecular Pharmacology.

§ Deceased.

(1) For part 3 see: Ross, S. T.; Kruse, L. I.; Ohlstein, E. H.; Erickson, R. W.; Ezekiel, M.; Flaim, K. E.; Sawyer, J. L.; Berkowitz, B. A. *J. Med. Chem.* **1987**, *30*, 1987.

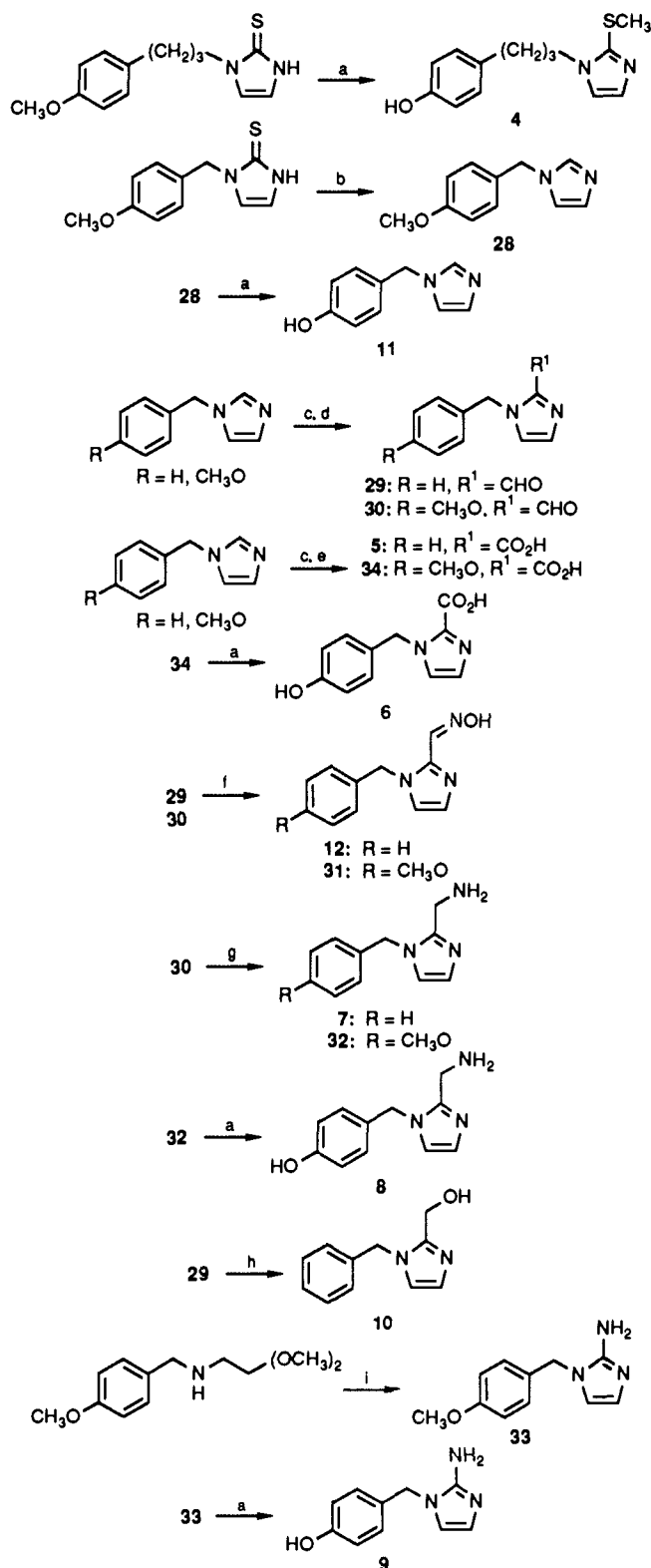
(2) Kruse, L. I.; Kaiser, C.; DeWolf, W. E., Jr.; Frazee, J. S.; Erickson, R. W.; Ezekiel, M.; Ohlstein, E. H.; Ruffolo, R. R., Jr.; Berkowitz, B. A. *J. Med. Chem.* **1986**, *29*, 887.

(3) Kruse, L. I.; DeWolf, W. E., Jr.; Chambers, P. A.; Goodhart, P. J. *Biochemistry* **1986**, *25*, 7271.

(4) Kruse, L. I.; Kaiser, C.; DeWolf, W. E., Jr.; Frazee, J. S.; Garvey, E.; Hilbert, E. L.; Faulkner, W. A.; Flaim, K. E.; Sawyer, J. L.; Berkowitz, B. A. *J. Med. Chem.* **1986**, *29*, 2465.

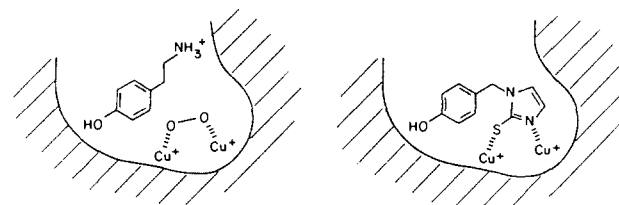
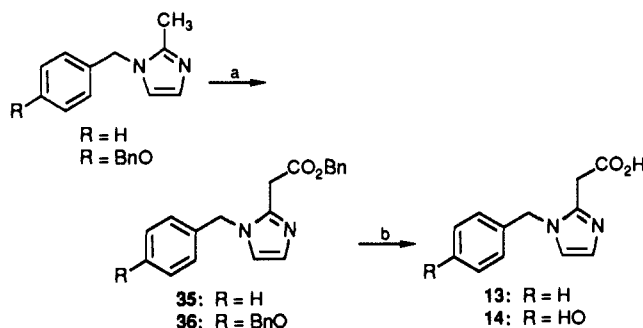
(5) Kruse, L. I.; Kaiser, C.; DeWolf, W. E., Jr.; Frazee, J. S.; Ross, S. T.; Wawro, J.; Wise, M.; Flaim, K. E.; Sawyer, J. L.; Erickson, R. W.; Ezekiel, M.; Ohlstein, E. H.; Berkowitz, B. A. *J. Med. Chem.* **1987**, *30*, 486.

(6) Scott, R. A.; Sullivan, J.; DeWolf, W. E., Jr.; Dolle, R. E.; Kruse, L. I. *Biochemistry* **1988**, *27*, 5411.

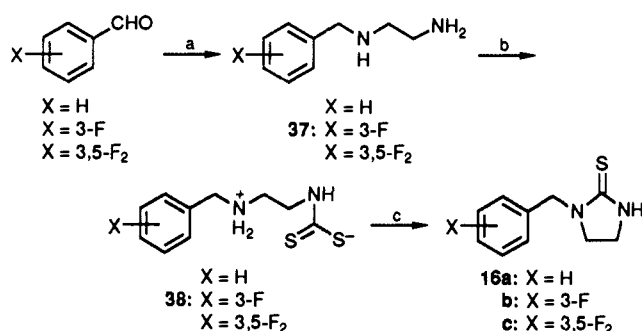
**Scheme I.** Synthesis of 2-Substituted 1-Aralkylimidazoles<sup>a</sup>

port the synthesis and *in vitro* DBH-inhibitory potency of some new multisubstrate inhibitors that resulted from a systematic exploration of ligand replacements.

**Chemistry.** Synthesis of compounds 4–12 (Table I) was accomplished from the corresponding 1-benzylimidazole-2-thiones by the sequences outlined in Scheme I. It was found that prolonged reaction of 1-[3-(4-methoxy-

**Figure 1.****Scheme II.** Synthesis of 1-Benzylimidazole-2-acetic Acids<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a)  $\text{BnOCOC}$ ,  $\text{NEt}_3$ , MeCN; (b)  $\text{H}_2$ , 10% Pd/C.

**Scheme III.** Synthesis of 1-Benzylimidazolone-2-thiones (16a–c)<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a)  $\text{NH}_2\text{CH}_2\text{CH}_2\text{NH}_2$ ,  $\text{CH}_3\text{OH}$ , NaBH<sub>4</sub>; (b)  $\text{CS}_2$ , EtOAc; (c)  $\Delta$ , *N*-methylpyrrolidinone.

phenyl)propyl]imidazole-2-thione with  $\text{BBr}_3$  produced the *S*-methyl inhibitor 4 via the  $\text{CH}_3\text{Br}$  produced *in situ*. Desulfurization of the imidazole-2-thiones with Raney nickel afforded the parent imidazoles which, upon lithiation and reaction with the appropriate electrophile, yielded the inhibitors 5–12.

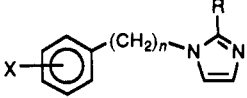
The imidazole-2-acetic acids 13 and 14 were prepared<sup>7</sup> by carboxylation of the corresponding 1-benzyl-2-methylimidazole<sup>8</sup> followed by catalytic debenzoylation (Scheme II).

The 1-benzylimidazolone-2-thiones 16a–c were prepared by the procedure outlined in Scheme III. Condensation of a substituted benzaldehyde with ethylenediamine followed by sodium borohydride reduction yielded the intermediate *N*-benzylethylenediamines which upon reaction with  $\text{CS}_2$  and pyrolysis provided 16a–c.

The 1-benzyl-1,2,3,4-tetrazole-5-thiols (20a,c) and the 4-benzyl-1,2,4-triazole-3-thiones (17a–d) were prepared from the appropriate benzyl isothiocyanates as depicted in Scheme IV. The reaction of the intermediate isothiocyanate with sodium azide yielded the tetrazoles 20a,c whereas reaction with *N*-formylhydrazine followed by cy-

(7) Macco, A. A.; Godefroi, E. F.; Drouen, J. J. M. *J. Org. Chem.* 1975, 40, 252.

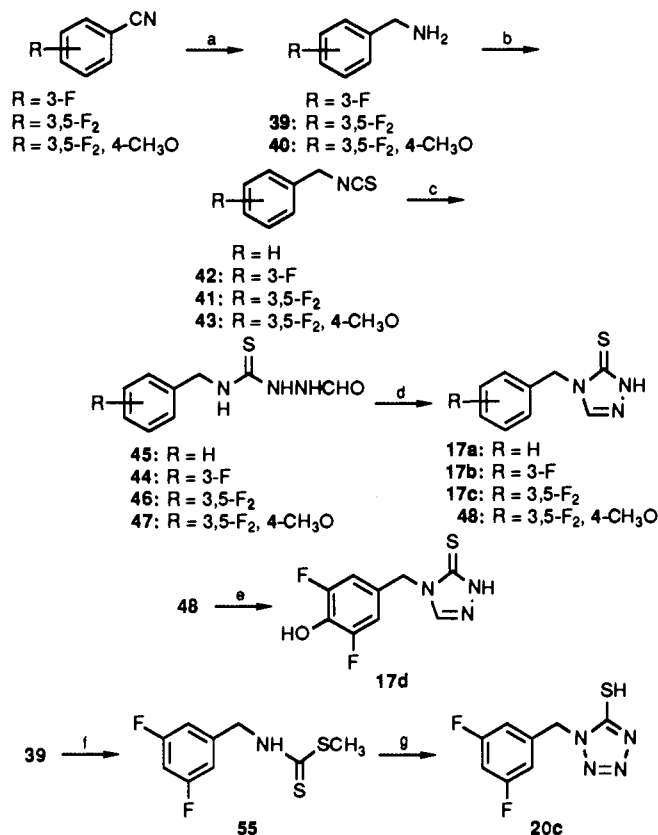
(8) Guida, W. C.; Mathre, D. J. *J. Org. Chem.* 1980, 45, 3172.

**Table I.** Structure, Physical Properties, and DBH-Inhibitory Activity of Some 2-Substituted 1-Aralkylimidazoles


compd	X	n	R	mp, °C	recryst solvent	yield, <sup>a</sup> %	formula <sup>b</sup>	IC <sub>50</sub> , <sup>c</sup> $\mu$ M
1	H	1	SH					32 (20–46) <sup>d</sup>
2	4-OH	1	SH					2.6 (1.3–4.6) <sup>d</sup>
3	4-OH	3	SH					2.2 (1.8–2.8) <sup>d</sup>
4	4-OH	3	SCH <sub>3</sub>	140–142	EtOH	8	C <sub>13</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub> ·HCl	79 (36–117)
5	H	1	CO <sub>2</sub> H	128	MeOH–Et <sub>2</sub> O	60	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> ·HCl	57 (46–71)
6	4-OH	1	CO <sub>2</sub> H	135 dec	MeOH–Et <sub>2</sub> O	20	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> O <sub>3</sub> ·HCl	112 (54–220)
7	H	1	CH <sub>2</sub> NH <sub>2</sub>	185–187	EtOH	29	C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> ·2HCl	240 (120–390)
8	4-OH	1	CH <sub>2</sub> NH <sub>2</sub>	252–254	MeOH	10	C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> O·2HCl	165 (83–260)
9	4-OH	1	NH <sub>2</sub>	203–210	MeOH–Et <sub>2</sub> O	16	C <sub>10</sub> H <sub>11</sub> N <sub>3</sub> O·HCl	4% <sup>e</sup>
10	H	1	CH <sub>2</sub> OH	158	EtOH–Et <sub>2</sub> O	70	C <sub>11</sub> H <sub>12</sub> N <sub>2</sub> O	0% <sup>e</sup>
11	4-OH	1	H	212–213	EtOH	35	C <sub>10</sub> H <sub>10</sub> N <sub>2</sub> O	17% <sup>e</sup>
12	H	1	CH=NOH	170–172	EtOH	58	C <sub>11</sub> H <sub>11</sub> N <sub>3</sub> O	10% <sup>e</sup>
13	H	1	CH <sub>2</sub> CO <sub>2</sub> H	115–116	EtOH	6	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>2</sub>	0% <sup>e</sup>
14	4-OH	1	CH <sub>2</sub> CO <sub>2</sub> H	172	H <sub>2</sub> O	4	C <sub>12</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub>	0% <sup>e</sup>

<sup>a</sup>The overall yield is given. <sup>b</sup>All new compounds had C, H, N microanalyses within  $\pm 0.4\%$  of the calculated values. <sup>c</sup>Values are given as IC<sub>50</sub> in  $\mu$ M with upper and lower 95% confidence limits (mean  $\pm$ SEM) shown in parentheses. <sup>d</sup>Data from ref 4. <sup>e</sup>Activity expressed as percent inhibition at a compound concentration of  $10^{-4}$  M.

**Scheme IV.** Synthesis of 4-Benzyl-1,2,4-triazole-3-thiones (17a–d) and 1-(3,5-Difluorobenzyl)-1,2,3,4-tetrazole-5-thiol (20c)<sup>a</sup>

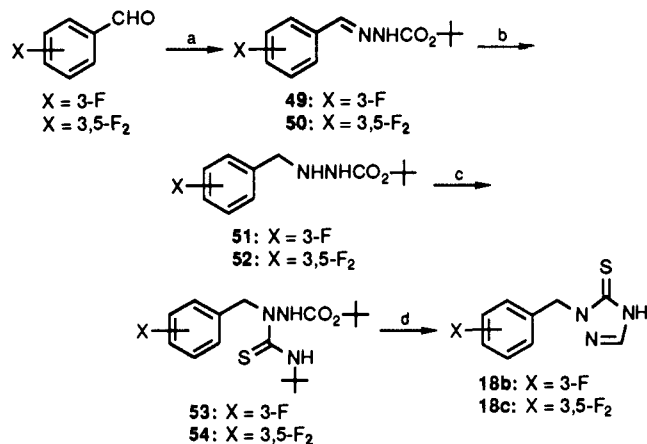


<sup>a</sup>Reagents and conditions: (a) H<sub>2</sub>, Raney Ni, NH<sub>3</sub>; (b) CS<sub>2</sub>, DCC, Et<sub>2</sub>O; (c) NH<sub>2</sub>NHCHO, EtOH; (d) NaOEt, EtOH; (e) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>; (f) KOH, CS<sub>2</sub>, CH<sub>3</sub>I; (g) NaN<sub>3</sub>, H<sub>2</sub>O.

clization under basic conditions provided the corresponding triazoles 17a–d.

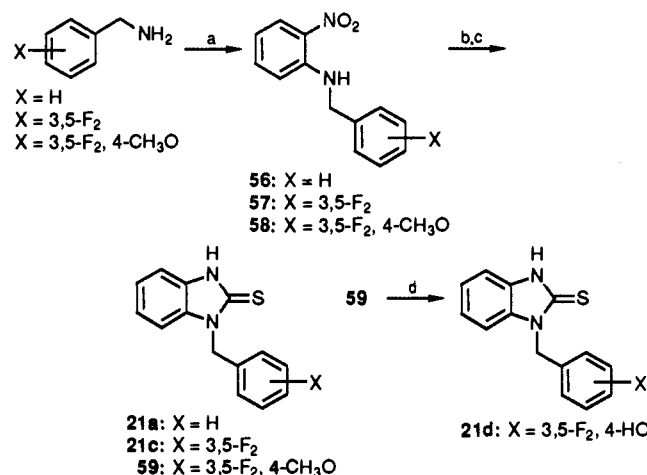
The 1-benzyl-1,2,4-triazole-5-thiones 18b,c were prepared by the condensation of *tert*-butyl carbazate with the appropriate benzaldehyde followed by hydrogenation as shown in Scheme V. The resulting *tert*-butyl *N*-benzylcarbazates were reacted with *tert*-butyl isothiocyanate to give the protected thiosemicarbazates which upon heating with formic acid gave low yields of the triazoles 18b,c (Scheme V).

**Scheme V.** Synthesis of 1-Benzyl-1,2,4-triazole-5-thiones (18b,c)<sup>a</sup>



<sup>a</sup>Reagents and conditions: (a) *t*-BuOCONHNH<sub>2</sub>, *n*-hexane; (b) H<sub>2</sub>, 10% Pd/C, MeOH; (c) *t*-BuNCS, EtOAc; (d) HCO<sub>2</sub>H,  $\Delta$ .

**Scheme VI.** Synthesis of 1-Benzylbenzimidazole-2-thiones (21a,c,d)<sup>a</sup>



<sup>a</sup>Reagents and conditions: (a) 2-chloronitrobenzene, NH<sub>4</sub>OAc,  $\Delta$ ; (b) H<sub>2</sub>, PtO<sub>2</sub>, EtOH; (c) CS<sub>2</sub>, KOH, H<sub>2</sub>O; (d) BBr<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>.

Synthesis of compound 19a was accomplished via the known procedure.<sup>9</sup> The 1-benzylbenzimidazole-2-thiones

Table II. Structure, Physical Properties, and DBH-Inhibitory Activity of Some Aralkyl-Substituted Heterocycles

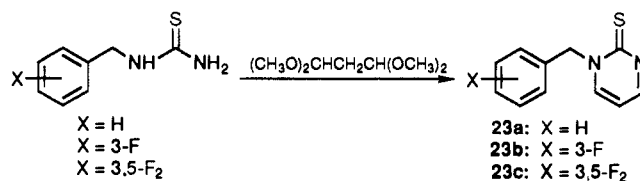
compd	ligand	side chain <sup>a</sup>	mp, °C	recryst solvent	yield, <sup>b</sup> %	formula <sup>c</sup>	IC <sub>50</sub> , <sup>d</sup> μM
1		A					32 (20-46) <sup>e</sup>
15b		B					5.6 (4.9-6.5) <sup>e</sup>
15c		C					1.2 (1.0-1.9) <sup>e</sup>
15d		D					0.074 (0.06-0.087) <sup>e</sup>
16a		A	177-182	MeOH-EtOAc	18	C <sub>10</sub> H <sub>12</sub> N <sub>2</sub> S	5% <sup>f</sup>
16b		B	187-188	MeOH-CHCl <sub>3</sub>	38	C <sub>10</sub> H <sub>11</sub> FN <sub>2</sub> S	3.7 (2.4-5.2)
16c		C	186-187	MeOH-CHCl <sub>3</sub>	32	C <sub>10</sub> H <sub>10</sub> F <sub>2</sub> N <sub>2</sub> S	1.4 (1.3-1.6)
17a		A	122-123	EtOH	21	C <sub>9</sub> H <sub>9</sub> N <sub>3</sub> S	24 (19-29)
17b		B	125-126	EtOH-H <sub>2</sub> O	4.6	C <sub>9</sub> H <sub>8</sub> FN <sub>3</sub> S	1.9 (1.7-3.2)
17c		C	129-130	EtOH-H <sub>2</sub> O	8.9	C <sub>9</sub> H <sub>7</sub> F <sub>2</sub> N <sub>3</sub> S	1.0 (0.93-1.1)
17d		D	184-185	EtOH-hexane	7.2	C <sub>9</sub> H <sub>7</sub> F <sub>2</sub> N <sub>3</sub> OS	0.035 (0.023-0.061)
18a		A			<i>g</i>		75 (70-80)
18b		B	155-156	Et <sub>2</sub> O-hexane	6	C <sub>9</sub> H <sub>8</sub> FN <sub>3</sub> S	15 (12.8-17.4)
18c		C	188-189	Et <sub>2</sub> O-hexane	8	C <sub>9</sub> H <sub>7</sub> F <sub>2</sub> N <sub>3</sub> S	6.2 (5.0-7.8)
19a		A	85-87	Et <sub>2</sub> O	21	C <sub>9</sub> H <sub>9</sub> N <sub>3</sub> S	0% <sup>f</sup>
20a		A			<i>h</i>		16 (14-19)
20c		C	155-156	hexane-EtOAc	18	C <sub>8</sub> H <sub>6</sub> F <sub>2</sub> N <sub>4</sub> S	1.54 (1.2-2.0)
21a		A	185	EtOH	61	C <sub>14</sub> H <sub>12</sub> N <sub>2</sub> S	61 (48-84)
21c		C	179-180	EtOH	42	C <sub>14</sub> H <sub>10</sub> F <sub>2</sub> N <sub>2</sub> S	6.2 (5.6-6.8)
21d		D	200	EtOAc-hexane	15	C <sub>14</sub> H <sub>10</sub> F <sub>2</sub> N <sub>2</sub> OS	0.66 (0.52-0.83)
22a		A	129-130	Et <sub>2</sub> O-CH <sub>2</sub> Cl <sub>2</sub>	4.2	C <sub>12</sub> H <sub>11</sub> NS	26% <sup>f</sup>
22b		B	159-160	CH <sub>2</sub> Cl <sub>2</sub> -Et <sub>2</sub> O-hexane	1.3	C <sub>12</sub> H <sub>10</sub> FNS	34% <sup>f</sup>
22c		C	195-197	CH <sub>2</sub> Cl <sub>2</sub>	3.9	C <sub>12</sub> H <sub>9</sub> F <sub>2</sub> NS	13.4 (11.1-16.4)
23a		A	139.5-140.5	EtOH	32	C <sub>11</sub> H <sub>10</sub> N <sub>2</sub> S	5% <sup>f</sup>
23b		B	182-183.5	MeOH	13	C <sub>11</sub> H <sub>9</sub> FN <sub>2</sub> S·HCl	15% <sup>f</sup>
23c		C	183-184	CH <sub>2</sub> Cl <sub>2</sub> -Et <sub>2</sub> O	10	C <sub>11</sub> H <sub>8</sub> F <sub>2</sub> N <sub>2</sub> S·HCl	2.8 (2.3-3.4)

<sup>a</sup> A = benzyl, B = 3-fluorobenzyl, C = 3,5-difluorobenzyl, D = 3,5-difluoro-4-hydroxybenzyl. <sup>b</sup> The overall yield is given. <sup>c</sup> All new compounds had C, H, N microanalyses within ±0.4% of the calculated values. <sup>d</sup> Values given are IC<sub>50</sub> in μM with upper and lower 95% confidence limits (mean ± SEM) shown in parentheses. <sup>e</sup> Data from ref 5. <sup>f</sup> Activity expressed as percent inhibition at a compound concentration of 10<sup>-5</sup> M. <sup>g</sup> Prepared according to ref 16. <sup>h</sup> Prepared according to ref 17.

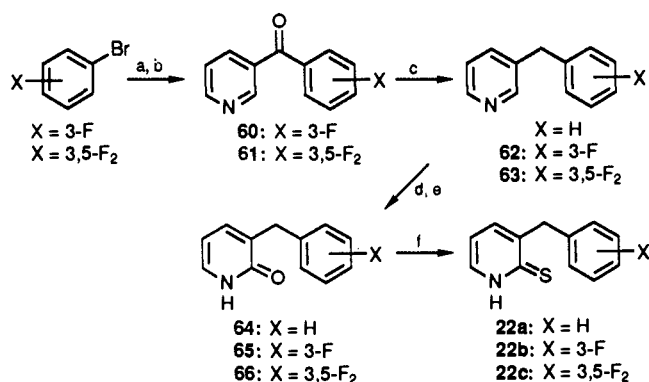
were prepared by the route outlined in Scheme VI. Alkylation of the appropriate benzylamine with 2-chloronitrobenzene, followed by hydrogenation and cyclization with CS<sub>2</sub>, yielded the target compounds 21a,c,d.

Preparation of the 3-benzylpyridine-2-thiones 22a-c was accomplished as shown in Scheme VII. The requisite 3-benzylpyridines were prepared from 3-cyanopyridine, and these were converted to the corresponding 2-pyridone by oxidation and rearrangement of the pyridine *N*-oxide. The desired regioisomer was isolated and reacted with Lawesson's reagent to yield the corresponding pyridine-2-thiones.

The final class of inhibitors, the 1-benzyl-1,2-dihydroimidazole-2-thiones 23a-c, was prepared by cyclizing the appropriate *N*-benzylthiourea with propane-1,3-dial bis(dimethyl acetal).



**Enzymology.** The compounds in Tables I and II were screened for DBH-inhibitory activity with use of commercially available bovine enzyme. Enzymatic assays and data analyses were performed by the methods previously

Scheme VII. Synthesis of 3-Benzylpyridine-2-thiones **22a-c**<sup>a</sup>

<sup>a</sup> Reagents and conditions: (a) *t*-BuLi; (b) 3-cyanopyridine; (c) Zn/Hg, HCl,  $\Delta$ ; (d) *m*-CPBA,  $\text{CHCl}_3$ ; (e)  $\text{Ac}_2\text{O}$ ,  $\Delta$ , base; (f) [4- $\text{C}_6\text{H}_4\text{P}(\text{S})_2$ ], PhMe,  $\Delta$ .

described<sup>4,5</sup> to yield the indicated  $\text{IC}_{50}$  values and confidence limits.

## Results and Discussion

One objective of the present study was to explore the dependence of DBH-inhibitory activity upon the thione group of the multisubstrate inhibitor **2**. The design of **2** was based upon the hypothesis that the ligand portion of inhibitor binds the "soft"  $\text{Cu}^{1+}$  oxidation state of enzyme in a fashion that mimics the binding of oxygen substrate during normal catalysis.<sup>4</sup> Detailed kinetic<sup>3</sup> and X-ray fluorescence studies<sup>6</sup> have subsequently supported this hypothesis. In light of these results, the compounds in Table I were prepared to evaluate the potential of nitrogen or oxygen ligands to substitute for the sulfur-containing thione. In the most interesting cases, the relative activities of 1-benzyl- and 1-(4-hydroxybenzyl)-substituted inhibitors were compared since in the case of the imidazole-2-thione inhibitors, an increase in potency results from the 4-hydroxyl group (cf. **1** vs **2**). This has been demonstrated to result from a greater resemblance of inhibitor to phenethylamine substrate. The results in Table I indicate the soft sulfur atom is required for optimal activity. Methylation of the sulfur as in **4** significantly decreases activity relative to **2** or **3**, inhibitors of identical potency.<sup>4</sup> Replacement of the sulfur by an oxygen ligand as in **5**, **6**, **10**, **12**, **13** and **14** greatly diminishes activity. The alcohol **10**, the aldoxime **12**, and the imidazole-2-acetic acids **13** and **14** are much less active, whereas the carboxylic acids **5** and **6** retain significant activity. Interestingly, the 4-hydroxyl group slightly *decreases* the potency of **6** relative to **5** to suggest inhibition of enzyme by these inhibitors occurs in a fashion different from the parent inhibitor **2**, perhaps via chelation of solution copper ions, as is known to be the case with fusaric acid.<sup>10</sup> The aminomethyl compounds **7** and **8** are significantly less potent than **1** and **2**, but in this case the presence of the 4-hydroxyl group does marginally improve inhibitory potency. The amine **9** is of greatly reduced potency, as is the simple imidazole **11**. The various heteroatoms that were explored as potential replacements for the sulfur ligand in inhibitor **2** appear to be inferior to the parent inhibitor. Perhaps this is not surprising in view of the direct binding of the ligand portion of **2** to the very "soft"  $\text{Cu}^{1+}$  from of DBH.<sup>3,6</sup>

Having established the necessity of the soft thione functional group, it was of interest to explore structural

variations of this ligand. The collection of inhibitors found in Table II represents an attempt to vary the following structural parameters: (1) ligand  $\text{pK}_a$ , (2) ring size, (3) bulk, and (4) an acidic proton at N-3. The previously determined, optimal<sup>5</sup> fluorinated benzyl substituents were used to calibrate activity trends for the ligand substitutions reported in Table II.

The inhibitor thiol/thione  $\text{pK}_a$  was varied by increasing the number of nitrogens present in the heterocyclic ring. It was anticipated that the family of azoles (**2**, **17a-d**, **18a-c**, **19a**, **20a,c**) resulting from this study would be nearly isosteric. With the exception of **19a**, which was of greatly diminished activity, the other inhibitors were essentially identical in potency, a striking observation in light of the range of  $\text{pK}_a$  (ca. 10 units) for these ligands. The apparent independence of inhibitor potency upon ligand  $\text{pK}_a$  is of interest with respect to the binding mode hypothesized in Figure 1. If, as illustrated, the binding *does* involve the electron pair on N-3, then the deprotonated, anionic form of inhibitor must be that which binds enzyme. There appear to be two explanations for the lack of correlation between inhibitor  $\text{pK}_a$  and potency. Firstly, the hypothesized interaction between the lone-pair electrons on N-3 and the second copper atom or another enzymatic group might not occur, making deprotonation at N-3 unnecessary. Alternatively, an initial ligation of the thione sulfur to a copper atom could labilize the N-3 hydrogen toward removal, thereby rendering irrelevant the  $\text{pK}_a$  of these inhibitors in solution.<sup>11</sup> The available data do not allow a distinction between these possibilities at present. Compound **19a**, which lacks the lone-pair electrons at position 4 (corresponding to position 3 in **1** and **2**) and which should therefore be a critical test compound, undergoes a facile air-oxidation of the thiol to a disulfide under the DBH assay conditions. The "dihydro" analogues **16a-c**, which also have a labile N-3 hydrogen, were found to be comparable in potency to the parent imidazole-2-thiones.

The six-membered ligand groups in **22a-c** and **23a-c** were prepared in an attempt to explore the effects of ligand ring size upon DBH inhibitory potency. However, the ligands present in **22a-c** and **23a-c** do not afford an ideal comparison since several structural changes are present relative to **2** in addition to the desired ring expansion. Thus, **22a-c** lack the N-1 heteroatom while **23a-c** lack the labile N-3 hydrogen present in **2**. Other, more analogous six-membered ring counterparts to **2** were not immediately obvious. Whereas **22a-c** have reduced inhibitory potency relative to **2**, **23a-c** are of comparable potency although the effects that cause this are unclear due to the multiple structural changes present in these inhibitors. It is worth noting, however, that both classes of inhibitors have a lone pair of electrons at the position corresponding to N-3 in **2**: compounds **22a-c** by deprotonation and compounds **23a-c** in the neutral molecule.

The extremely large inhibitors **21a-c** appear to define a location of considerable bulk tolerance at the DBH active site. Whereas earlier studies demonstrated a lack of bulk

(10) Brenner, M.; Krueger, M.; Klinman, J. P. *Fed. Proc., Fed. Am. Soc. Exp. Biol.* 1983, 42, 2059.

(11) An alternative explanation would have enzyme binding that fraction of inhibitor which is present in solution in the deprotonated, anionic form. The fraction of inhibitor in this form at pH 5.5 will vary from >90% for **20a,c** ( $\text{pK}_a$  ca. 3.3) to 1/10<sup>7</sup> for **2** ( $\text{pK}_a$  ca. 12.5). Since the  $K_i$  for **2** has been determined at pH 5.5 to be  $6 \times 10^{-8}$  M, if the true inhibitory species were the small fraction of **2** present as the anion under these conditions, then this must bind enzyme with an implausibly low  $K_i$  of ca.  $10^{-15}$  M. An inhibitor of this potency would exhibit essentially irreversible inhibition or at minimum, tight binding behavior. Neither has been observed (see ref 3).

tolerance at the phenethylamine binding site and the intersite bridging methylene chain, the enzyme appears to tolerate considerable steric bulk at the "backside" of the oxygen mimic. This may become particularly relevant to the design of DBH inhibitors bearing additional or more complex pharmacophores.

In summary, this study has afforded several insights to the structural requirements for the inhibitor group that binds the DBH copper atom. Firstly, the presence of a "soft" ligand atom, such as sulfur, confers maximal inhibitory potency. Other atoms or functional groups have proved decidedly inferior. Secondly, the ligand  $pK_a$  is of little importance as convincingly shown by the data for nitrogen-containing isosteres of 2. Lastly, the enzymatic site near the copper atom shows considerable bulk tolerance, such that even very large "oxygen mimics" bind tightly.

### Experimental Section

Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. When appropriate, all solvents used in reaction mixtures were dried and/or purified by standard procedures.<sup>12</sup> IR spectra were recorded on a Perkin-Elmer 727 spectrophotometer as neat oils or Nujol mulls calibrated with the 1601  $\text{cm}^{-1}$  absorption of polystyrene film. NMR spectra were obtained as  $\text{CDCl}_3$  solutions on a Hitachi Perkin-Elmer R-24 spectrometer and/or a Varian EM 390 spectrometer using  $\text{Me}_4\text{Si}$  as an internal reference; IR and NMR spectra were obtained for all new compounds and were judged to be consistent with the assigned structure.

**1-[3-(4-Hydroxyphenyl)propyl]-2-(methylthio)imidazole Hydrochloride (4).** A solution of 1-[3-(4-methoxyphenyl)propyl]imidazole-2-thione<sup>4</sup> (1.2 g, 0.0046 mol) in  $\text{CH}_2\text{Cl}_2$  (40 mL) was stirred at 22 °C as a solution of  $\text{BBr}_3$  (3.5 g, 0.014 mol) in  $\text{CH}_2\text{Cl}_2$  (10 mL) was added. After 4 h, excess  $\text{BBr}_3$  was destroyed by the careful addition of MeOH, and the reaction mixture was stirred for an additional 16 h. The solution was concentrated and the residue was dissolved in  $\text{H}_2\text{O}$  and washed with EtOAc. The aqueous phase was basified with  $\text{NaHCO}_3$  and extracted with EtOAc. The extracts were washed with  $\text{H}_2\text{O}$  and dried, and the solvent was evaporated. The residue was dissolved in 5 mL of EtOH, and the solution was treated with ethereal HCl. The crystalline product was filtered and recrystallized from EtOH to give 0.61 g (45%) of 4 (Table I).

**1-(4-Methoxybenzyl)imidazole (28).** A mixture of 1-(4-methoxybenzyl)imidazole-2-thione<sup>4</sup> (15.0 g, 0.068 mol) and Raney Ni (80 g) in EtOH (400 mL) was heated at reflux for 4 h. The mixture was cooled and filtered, and the filtrate was concentrated. The residue was dissolved in 1 N HCl (100 mL) and washed with Et<sub>2</sub>O. The aqueous phase was basified and extracted with Et<sub>2</sub>O. The extracts were combined, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated to yield 28 as an oil: 8.7 g (63%).

**1-Benzylimidazole-2-carboxaldehyde (29).** A solution of 1-benzylimidazole (7.9 g, 0.05 mol) in Et<sub>2</sub>O (150 mL) was stirred at -45 °C while a solution of *n*-BuLi in hexanes (44.5 mL, 1.6 M, 0.071 mol) was added. After stirring for 30 min, the yellow solution was cooled to -75 °C and DMF (4.38 g, 0.06 mol) was added. The cooling bath was replaced with an ice- $\text{H}_2\text{O}$  bath, and after 10 min the reaction mixture was poured into saturated  $\text{NH}_4\text{Cl}$ . The mixture was extracted with Et<sub>2</sub>O, the extracts were washed with  $\text{H}_2\text{O}$  and dried ( $\text{Na}_2\text{SO}_4$ ), and the solvent was concentrated to give 29 as an oil: 7.2 g (77%).

**1-(4-Methoxybenzyl)imidazole-2-carboxaldehyde (30).** The reaction of 28 as in the preparation of 29 yielded 30 (68%) as an oil.

**1-Benzylimidazole-2-carboxaldehyde Oxime (12).** A solution of 29 (1.80 g, 0.0097 mol) in  $\text{H}_2\text{O}$  (50 mL) was stirred vigorously during the addition of  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (2.0 g, 0.029 mol) and NaOAc (5.0 g). After 10 min the solution became cloudy, and an oil separated and then solidified. The solid was filtered, washed with  $\text{H}_2\text{O}$ , and recrystallized from EtOH to give 1.72 g (75%) of 12 (Table I).

**1-(4-Methoxybenzyl)imidazole-2-carboxaldehyde Oxime (31).** The reaction of 30 as in the preparation of 12 yielded (68%) 31: mp 201–204 °C.

**2-(Aminomethyl)-1-benzylimidazole Dihydrochloride (7).** Oxime 12 (1.25 g, 0.0053 mol) was dissolved in warm EtOH (125 mL), Raney Ni (2 mL of an aqueous slurry) was added, and the mixture was hydrogenated at 50 psi  $\text{H}_2$  for 4.5 h. The mixture was filtered, the filtrate was treated with an ethereal HCl solution, and the solvents were concentrated until crystallization commenced. The crystalline precipitate was filtered and recrystallized from EtOH to give 0.76 g (49%) of 7 (Table I).

**2-(Aminomethyl)-1-(4-methoxybenzyl)imidazole Dihydrochloride (32).** The reduction of 31 as in the preparation of 7 yielded (22%) 32: mp 147–157 °C.

**1-Benzyl-2-(hydroxymethyl)imidazole (10).** A solution of 29 (1.86 g, 0.01 mol) in MeOH (20 mL) was stirred at 0 °C while  $\text{NaBH}_4$  (1.0 g) was added. After stirring at 0 °C for 2.5 h the solution was concentrated. The residue was taken up in Et<sub>2</sub>O, washed with  $\text{H}_2\text{O}$ , dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated. The residue was dissolved in EtOH and treated with ethereal HCl. Crystallization was induced by the addition of Et<sub>2</sub>O and cooling to give 1.7 g (91%) of 1-benzyl-2-(hydroxymethyl)imidazole hydrochloride (Table I).

**2-Amino-1-(4-methoxybenzyl)imidazole Hydrochloride (33).** A mixture of *N*-(4-methoxybenzyl)aminoacetaldehyde dimethyl acetal<sup>4</sup> (4.5 g, 0.02 mol) and cyanamide (3.36 g, 0.08 mol) in glacial AcOH (1.13 mL, 0.02 mol) and  $\text{H}_2\text{O}$  (4 mL) was heated at 40 °C for 16 h and then at 60 °C for 2 h. The solution was concentrated and the residue was triturated with a mixture of  $\text{Me}_2\text{CO}$  and Et<sub>2</sub>O and filtered. The solid was dissolved in concentrated HCl (5 mL), heated to 50 °C for 20 min, and then concentrated. The solid was recrystallized from a mixture of MeOH and Et<sub>2</sub>O to give 1.6 g (33%) of 33: mp 216–218 °C.

**1-Benzylimidazole-2-carboxylic Acid Hydrochloride (5).** A solution of 1-benzylimidazole (3.16 g, 0.02 mol) in Et<sub>2</sub>O (100 mL) was cooled to -50 °C and treated with a solution of *n*-BuLi in *n*-hexane (12.5 mL, 1.6 M, 0.02 mol). After stirring at -50 °C for 30 min, a stream of dry  $\text{CO}_2$  was passed into the reaction. After 10 min, the color of the reaction mixture had changed from yellow to clear and a white precipitate formed. The mixture was warmed to ambient temperature and filtered and the precipitate was washed with Et<sub>2</sub>O. This white powder was dissolved in  $\text{H}_2\text{O}$  (10 mL), the pH was adjusted to 3, and the mixture was cooled to induce crystallization. The resulting 1-benzylimidazole-2-carboxylic acid was filtered and dried. The hydrochloride salt was formed by treating a methanolic solution of the imidazole with ethereal HCl and inducing crystallization by the addition of Et<sub>2</sub>O (Table I).

**1-(4-Methoxybenzyl)imidazole-2-carboxylic Acid Hydrochloride (34).** The reaction of 28 as in the preparation of 5 yielded (78%) 34: mp 115 °C dec.

**General Method A. Cleavage of *O*-Methyl Ethers.** A solution of the appropriate *O*-methyl ether (0.05 mol) in  $\text{CH}_2\text{Cl}_2$  (150 mL) was cooled to -20 °C and a solution of  $\text{BBr}_3$  (0.10 mol) in  $\text{CH}_2\text{Cl}_2$  (50 mL) was added. The cooling bath was replaced with an ice-water bath, and the reaction was followed by TLC until completion (generally 2–4 h). When completed, the reaction was cooled to -20 °C, and MeOH was cautiously added to decompose excess  $\text{BBr}_3$ . The solvents were evaporated under reduced pressure, and the residue was recrystallized from the appropriate solvent.

**1-(4-Hydroxybenzyl)imidazole-2-carboxylic Acid Hydrochloride (6).** The demethylation of 34 by general procedure A yielded (41%) 6 (Table I).

**2-(Aminomethyl)-1-(4-hydroxybenzyl)imidazole Dihydrochloride (8).** The demethylation of 32 by general procedure A yielded (27%) 8 (Table I).

**2-Amino-1-(4-hydroxybenzyl)imidazole Hydrochloride (9).** The demethylation of 33 by general procedure A yielded (47%) 9 (Table I).

**1-(4-Hydroxybenzyl)imidazole (11).** The demethylation of 28 by general procedure A yielded (56%) 11.

**Benzyl 1-Benzylimidazole-2-acetate (35).**<sup>7</sup> A solution of 1-benzyl-2-methylimidazole<sup>8</sup> (2.8 g, 16.3 mmol) and triethylamine (23.0 mL, 0.163 mol) in MeCN (15 mL) was stirred at 0 °C during the dropwise addition of benzyl chloroformate (23 mL, 0.163 mol)

(12) Perrin, D. D.; Armarego, W. F. L. *Purification of Laboratory Chemicals*; Pergamon: Oxford, 1966.

and then heated at reflux for 18 h. The resulting mixture was partitioned between Et<sub>2</sub>O (50 mL) and H<sub>2</sub>O (150 mL) and the aqueous phase was washed with Et<sub>2</sub>O. The combined Et<sub>2</sub>O washes were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated, and the residue was purified by silica gel chromatography using CH<sub>2</sub>Cl<sub>2</sub> and then 1% MeOH-CH<sub>2</sub>Cl<sub>2</sub> as eluent to yield 1.2 g (24%) of 35 as an oil, which solidified.

**Benzyl 1-[4-(benzyloxy)benzyl]imidazole-2-acetate (36)**<sup>7</sup> was prepared in 39% yield as an oil, which solidified from 1-[4-(benzyloxy)benzyl]-2-methylimidazole<sup>8</sup> by the method used to prepare 35.

**1-Benzylimidazole-2-acetic Acid (13).** A solution of 35 (1.1 g, 3.6 mmol) in EtOH (50 mL) was hydrogenated (50 psi) over 10% palladium on carbon (0.2 g) for 2 h and then filtered and concentrated. The residue was recrystallized from EtOH to yield 0.18 g (23%) of 13 (Table I).

**1-(4-Hydroxybenzyl)imidazole-2-acetic acid (14)** was prepared in 10% yield by hydrogenation of 36 by the procedure used to prepare 13 (Table I).

**N-(3-Fluorobenzyl)ethylenediamine (37).** A solution of ethylenediamine (45.3 g, 0.754 mol) in MeOH (500 mL) was stirred at 0 °C during the dropwise addition of 3-fluorobenzaldehyde (23.4 g, 0.189 mol). After the addition was completed, the solution was stirred and maintained at 0 °C while NaBH<sub>4</sub> (7.13 g, 0.189 mol) was added *cautiously* in small portions. The reaction mixture was allowed to warm to ambient temperature and was stirred overnight. The resulting cloudy solution was filtered, the filtrate was concentrated and the residual oil was partitioned between EtOAc and H<sub>2</sub>O. The EtOAc layer was dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give a viscous oil, which was distilled to yield 37 (21.6 g, 68%): bp 89–91 °C (0.7 mmHg).

**N-(3-Fluorobenzyl)ethylenediaminecarbodithioic Acid (38).** A solution of 37 (5.0 g, 0.03 mol) in EtOAc (50 mL) was cooled to 0 °C and stirred during the dropwise addition of a solution of CS<sub>2</sub> (2.26 g, 0.03 mol) in EtOAc (10 mL). The reaction mixture was diluted with MeOH and filtered and the filtrate was concentrated to yield 6.28 g (87%) of 38 as an amorphous white solid. Trituration with hot MeOH yielded a white solid: mp 178–182 °C.

**1-(3-Fluorobenzyl)imidazoline-2-thione (16b).** A 5.73 g (0.024 mol) quantity of 38 was heated as a neat melt to 165 °C in an oil bath for several minutes. *N*-Methyl-2-pyrrolidinone (5 mL) was added followed by heating to 185 °C for 15 min. The resulting semisolid mass was cooled, triturated with EtOAc, and filtered to yield 2.3 g of solid. The filtrate was concentrated and the residue was triturated with H<sub>2</sub>O and filtered to yield an additional 2.1 g of product. The combined crops were recrystallized from MeOH-CHCl<sub>3</sub> to yield 3.15 g (64%) of 16b (Table II).

**1-Benzylimidazoline-2-thione (16a)** was prepared (18% yield) from benzaldehyde by the procedure described for the preparation of 16b.

**1-(3,5-Difluorobenzyl)imidazoline-2-thione (16c)** was prepared (32% yield) from 3,5-difluorobenzaldehyde<sup>5</sup> by the procedure described for the preparation of 16b.

**3,5-Difluorobenzylamine (39).** A solution of 3,5-difluorobenzonitrile<sup>5</sup> (13.9 g, 0.1 mol) in ammonia-saturated MeOH (140 mL) was hydrogenated (50 psi) over Raney Ni for 1.5 h. The resulting mixture was filtered and concentrated, and the residue was dissolved in EtOAc. The solution was extracted twice with 1 N HCl, and the aqueous extracts were washed with EtOAc. The aqueous solution was made basic with 2.5 N NaOH and extracted three times with EtOAc. The extracts were washed with H<sub>2</sub>O and brine and then dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to yield 39 as a colorless oil: 11.7 g (82%).

**3,5-Difluoro-4-methoxybenzylamine (40).** The hydrogenation of 3,5-difluoro-4-methoxybenzonitrile<sup>3</sup> as in the preparation of 39 yielded 40 (98%) as a colorless oil.

**3,5-Difluorobenzyl Isothiocyanate (41).** A solution of 39 (11.6 g, 0.081 mol) in Et<sub>2</sub>O (20 mL) was added dropwise to a cooled (-5 to -10 °C) solution of dicyclohexylcarbodiimide (16.7 g, 0.081 mol) and CS<sub>2</sub> (32.4 mL, 0.539 mol) in Et<sub>2</sub>O (100 mL), and the resulting mixture was stirred overnight at ambient temperature. The mixture was filtered, the filtrate was concentrated, and the residual oil was dissolved in 19:1 *n*-hexane-Et<sub>2</sub>O and filtered. The filtrate was concentrated and the residue was purified by flash

chromatography<sup>13</sup> using *n*-hexane as eluant to yield 5.40 g (36%) of 41 as a colorless oil.

**3-Fluorobenzyl isothiocyanate (42)** was prepared as a colorless oil in 51% yield from 3-fluorobenzylamine by the procedure used to prepare 41.

**3,5-Difluoro-4-methoxybenzyl isothiocyanate (43)** was prepared as a colorless oil in 79% yield from 3,5-difluoro-4-methoxybenzylamine by the procedure used to prepare 41.

**4-(3-Fluorobenzyl)-1-formyl-3-thiosemicarbazide (44).** A solution of 42 (4.27 g, 25.5 mmol) and formylhydrazine (1.69 g, 28.7 mmol) was heated at reflux in EtOH (30 mL) for 1 h. The resulting mixture was concentrated and the residue was triturated with 1:1 hexane-EtOAc and filtered. The crude product was recrystallized from EtOH-hexane to yield 1.29 g (22%) of 44: mp 124–125 °C.

**4-Benzyl-1-formyl-3-thiosemicarbazide (45)** was prepared in 38% yield from benzyl isothiocyanate by the procedure used to prepare 44. The crude product was recrystallized from EtOH: mp 162–165 °C.

**4-(3,5-Difluorobenzyl)-1-formyl-3-thiosemicarbazide (46)** was prepared in 35% yield from 41 by the procedure used to prepare 44. A sample was purified by flash chromatography using 9:1 CH<sub>2</sub>Cl<sub>2</sub>-EtOAc as eluant followed by recrystallization from CH<sub>2</sub>Cl<sub>2</sub>-hexane: mp 129–130 °C.

**4-(3,5-Difluoro-4-methoxybenzyl)-1-formyl-3-thiosemicarbazide (47)** was prepared in 62% yield from 43 by the procedure used to prepare 44. A sample was recrystallized from EtOH-hexane: mp 124–126 °C.

**4-(3-Fluorobenzyl)-1,2,4-triazole-3-thione (17b).** A solution of 44 (1.29 g, 5.68 mmol) in ethanolic sodium ethoxide [prepared from sodium (0.26 g, 11.0 g-atom) and EtOH (25 mL)] was heated at reflux for 24 h. The resulting mixture was filtered and concentrated and the residue was dissolved in H<sub>2</sub>O. The aqueous solution was acidified to pH 3 with 10% HCl and the precipitate was filtered and recrystallized from EtOH-H<sub>2</sub>O to yield 0.48 g (41%) of 17b (Table II).

**4-Benzyl-1,2,4-triazole-3-thione (17a).** The reaction of 45 as in the preparation of 17b yielded (56%) 17a (Table II).

**4-(3,5-Difluorobenzyl)-1,2,4-triazole-3-thione (17c).** The reaction of 46 as in the preparation of 17b yielded 17c (71%) (Table II).

**4-(3,5-Difluoro-4-methoxybenzyl)-1,2,4-triazole-3-thione (48).** The reaction of 47 using the same procedure as described for preparation of 17b yielded (65%) 48: mp 124–126 °C.

**4-(3,5-Difluoro-4-hydroxybenzyl)-1,2,4-triazole-3-thione (17d)** was prepared in 23% yield from 48 by demethylation according to general procedure A.

**3-Fluorobenzaldehyde (*tert*-Butoxycarbonyl)hydrazone (49).** A solution of 3-fluorobenzaldehyde (6.21 g, 0.05 mol) and *tert*-butyl carbazate (6.61 g, 0.05 mol) in *n*-hexane (50 mL) was heated at reflux for 30 min. The mixture was cooled to 0 °C and filtered. The product was recrystallized from ethanol to yield (8.79 g, 74%) 49: mp 165–168 °C.

**3,5-Difluorobenzaldehyde (*tert*-butoxycarbonyl)hydrazone (50)** was prepared in 58% yield from 3,5-difluorobenzaldehyde by the procedure used to prepare 49: mp 190–191 °C.

**1-(3-Fluorobenzyl)-2-(*tert*-butoxycarbonyl)hydrazine (51).** A suspension of 49 (1.02 g, 4.28 mmol) in MeOH (40 mL) was hydrogenated (40 psi) over 10% palladium on carbon (0.22 g) for 1 h. The mixture was filtered and concentrated to give 1.0 g (97%) of 51 as an oil.

**1-(3,5-Difluorobenzyl)-2-(*tert*-butoxycarbonyl)hydrazine (52).** The hydrogenation (4.5 h) of 50 as in the preparation of 51 yielded (95%) 52 as a colorless oil.

**1-(*tert*-Butoxycarbonyl)-2-(3-fluorobenzyl)-4-*tert*-butylthiosemicarbazide (53).** A solution of 51 (2.29 g, 9.53 mmol) and *tert*-butyl isothiocyanate (2.41 mL, 19.1 mmol) in EtOAc (15 mL) was heated at reflux for 7 h. The mixture was concentrated and the residue was triturated to yield 1.28 g (38%) of 53 as an amorphous solid.

**1-(*tert*-Butoxycarbonyl)-2-(3,5-difluorobenzyl)-4-*tert*-butylthiosemicarbazide (54).** The reaction of 52 as in the



preparation of **53** yielded (65%) **54** as an amorphous solid.

**1-(3-Fluorobenzyl)-1,2,4-triazole-5-thione (18b)**. A solution of **53** (1.28 g, 3.6 mmol) in 98% HCO<sub>2</sub>H (15 mL) was heated at reflux for 4 h and then concentrated. The residue was purified by flash chromatography using 4:1 CH<sub>2</sub>Cl<sub>2</sub>-EtOAc followed by trituration with Et<sub>2</sub>O-hexane to yield 0.165 g (22%) of **18b** (Table II).

**1-(3,5-Difluorobenzyl)-1,2,4-triazole-5-thione (18c)**. The reaction of **54** using the identical conditions as described for the preparation of **18b** yielded (22%) **18c** (Table II).

**1-Benzyl-1,2,3-triazole-5-thione (19a)**. A solution of 1-benzyl-1,2,3-triazole<sup>9</sup> (3.2 g, 0.02 mol) in THF (40 mL) was cooled to -80 °C and stirred under nitrogen during the dropwise addition of a 2.6 M *n*-butyllithium solution in *n*-hexane (8.8 mL, 0.023 mol). After stirring for 15 min sublimed sulfur (0.64 g, 0.02 mol) was added in one portion. The reaction mixture was stirred for 45 min at -20 °C and then poured into Et<sub>2</sub>O and filtered. The hygroscopic solid product was dissolved in H<sub>2</sub>O, and the resulting solution was washed twice with EtOAc and acidified with 3 N HCl. The aqueous solution was extracted with EtOAc, and the EtOAc extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give a solid product which was recrystallized from Et<sub>2</sub>O to yield 0.8 g (21%) of **19a** (Table II).

**Methyl N-(3,5-Difluorobenzyl)dithiocarbamate (55)**. A solution of **39** (4.2 g, 29.7 mmol) and KOH (1.66 g, 29.7 mmol) in a mixture of H<sub>2</sub>O (20 mL) and EtOH (18 mL) was stirred during the addition of CS<sub>2</sub> (8.9 mL, 0.148 mol) and then heated at reflux for 1 h. Iodomethane (1.8 mL, 29.7 mmol) was added and the resulting mixture was stirred at ambient temperature for 48 h and then concentrated. The residue was dissolved in EtOAc and the solution was washed with H<sub>2</sub>O, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated. The residue was purified by flash chromatography using 6:1 hexane-EtOAc as eluant to yield 4.7 g (68%) of **55** as a yellow oil.

**1-(3,5-Difluorobenzyl)-1,2,3,4-tetrazole-5-thiol (20c)**. A solution of **55** (4.2 g, 0.018 mol) and NaN<sub>3</sub> (1.8 g, 0.027 mol) in H<sub>2</sub>O (35 mL) was heated at reflux overnight. The solution was cooled, extracted with EtOAc, acidified to pH 1 with 10% HCl, and extracted with EtOAc. The EtOAc extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated, and the residue was recrystallized from hexane-EtOAc to give 1.3 g (32%) of **20c** (Table II).

**N-Benzyl-2-nitroaniline (56)**. A mixture of 1-chloro-2-nitrobenzene (10.0 g, 0.063 mol), benzylamine (40 g, 0.37 mol), and ammonium acetate (4.6 g, 0.06 mol) was heated at 100 °C for 24 h. The reaction mixture was cooled and dissolved in EtOAc. The solution was washed three times with 3 N HCl and once with brine, then dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to yield 14.0 g (97%) of **56**: mp 65-67 °C.

**N-(3,5-Difluorobenzyl)-2-nitroaniline (57)** was prepared in 99% yield from 3,5-difluorobenzylamine by following the procedure used for **56**: mp 105-108 °C.

**N-(3,5-Difluoro-4-methoxybenzyl)-2-nitroaniline (58)** was prepared in 100% yield from 3,5-difluoro-4-methoxybenzylamine by following the procedure used for preparation of **56**: oil which solidified.

**1-Benzylbenzimidazole-2-thione (21a)**. Platinum oxide (0.38 g) was hydrogenated (50 psi) in EtOH (50 mL) for 30 min. Compound **56** (1.0 g, 4.4 mmol) was added and the solution was hydrogenated (50 psi) for 3 h. The solution was filtered directly into a 250-mL flask containing KOH (0.38 g) and CS<sub>2</sub> (1.1 mL, 18.3 mmol) in H<sub>2</sub>O (10 mL). The resulting mixture was heated at reflux for 2 h and then diluted with H<sub>2</sub>O and acidified with 3 N HCl. The product was filtered and recrystallized from EtOH to yield 0.65 g (63%) of **21a** (Table II).

**1-(3,5-Difluorobenzyl)benzimidazole-2-thione (21c)** was prepared from **57** in 42% yield by the procedure used in the preparation of **21a** (Table II).

**1-(3,5-Difluoro-4-methoxybenzyl)benzimidazole-2-thione (59)** was prepared from **58** in 32% yield by the procedure used in the preparation of **21a**. The crude product was purified by flash chromatography using CH<sub>2</sub>Cl<sub>2</sub> as eluant to give a yellow oil which solidified.

**1-(3,5-Difluoro-4-hydroxybenzyl)benzimidazole-2-thione (21d)** was prepared from **59** in 47% yield by general procedure A (Table II).

**3-(3-Fluorobenzyl)pyridine (60)**. A solution of 3-bromofluorobenzene (25.0, 0.143 mol) in ether (250 mL) was cooled to -78 °C and stirred during the dropwise addition of a 2.3 M solution of *t*-BuLi in pentane (62 mL, 0.143 mol). After the addition was completed, stirring was continued for 15 min and a solution of 3-cyanopyridine (14.9 g, 0.143 mol) in ether (125 mL) was added dropwise. The resulting mixture was allowed to warm to 15 °C and a solution of concentrated HCl (36 mL) in H<sub>2</sub>O (90 mL) was added dropwise. After the resulting light yellow solution had stirred for 30 min, 10% NaOH was added to give a pH of 10, and the Et<sub>2</sub>O layer was separated. The aqueous phase was extracted twice with Et<sub>2</sub>O, the combined Et<sub>2</sub>O extracts were concentrated, and the residue was distilled to yield 21.3 g (74%) of **60**: bp 112-128 °C (0.45 mmHg).

**3-(3,5-Difluorobenzyl)pyridine (61)**. The reaction of 1-bromo-3,5-difluorobenzene as in the preparation of **60** yielded (42%) of the ketone **61**: bp 110-137 °C (0.4 mmHg).

**3-(3-Fluorobenzyl)pyridine (62)**. Zn(Hg) amalgam was prepared by stirring zinc (41 g) and HgCl<sub>2</sub> (4.1 g) in a mixture of H<sub>2</sub>O (25 mL) and concentrated HCl (60 mL) and then ketone **60** (19.0 g, 0.095 mol) was added. The resulting mixture was stirred and heated at reflux for 30 h. Occasionally during the course of the reaction HCl gas was passed through the mixture, and after 20 h, additional zinc metal (41 g) was added. After 30 h, the reaction mixture was cooled, decanted, made strongly basic with 10% NaOH, and extracted three times with CH<sub>2</sub>Cl<sub>2</sub>. The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated, and the residue was distilled to yield 5.2 g (29%) of **62**: bp 100-110 °C (0.6 mmHg).

**3-(3,5-Difluorobenzyl)pyridine (63)**. The reaction of ketone **61** as in the preparation of **62** yielded (61%) **63**: bp 90-110 °C (0.6 mmHg).

**3-Benzyl-2-pyridone (64)**. A solution of 3-benzylpyridine (50 g, 0.3 mol) in CHCl<sub>3</sub> (500 mL) was stirred during the portionwise addition of 3-chloroperbenzoic acid (60 g, 0.325 mol). The reaction mixture was stirred for 2 h and then diluted with H<sub>2</sub>O (200 mL) and made basic to pH 8 with 10% NaOH. The CHCl<sub>3</sub> layer was separated, extracted twice with 5% NaHCO<sub>3</sub>, and concentrated to give 57.5 g of crude *N*-oxide which was used without purification. The crude *N*-oxide (19.5 g, 0.1 mol) was added *cautiously* to Ac<sub>2</sub>O (200 mL) which had been heated to 85 °C. After the addition was completed, the solution was heated at reflux for 45 min, then cooled, and concentrated. The residual oil was dissolved in Et<sub>2</sub>O and the resulting solution was stirred with EtOH and 40% NaOH until the precipitation of solid was completed. The product was filtered to yield 2.26 g (12% overall) of **64** as a white solid: mp 158.5-160 °C.

**3-(3-Fluorobenzyl)-2-pyridone (65)**. The reaction of **62** as in the preparation of **64** yielded (18%) **65**: mp 110 °C.

**3-(3,5-Difluorobenzyl)-2-pyridone (66)**. The reaction of **63** as in the preparation of **64** yielded (44%) **66**: amorphous solid; TLC *R<sub>f</sub>* 0.3 with 10% MeOH-CHCl<sub>3</sub>.

**3-Benzylpyridine-2-thione (22a)**. A mixture of **64** (777 mg, 4.2 mmol) and Lawesson's reagent<sup>14</sup> in toluene (10 mL) was heated at reflux for 1 h, then cooled, and decanted. The residue was washed with CH<sub>2</sub>Cl<sub>2</sub>, and the combined organic layers were concentrated. The resulting solid was purified by flash chromatography using 5% MeOH-CH<sub>2</sub>Cl<sub>2</sub> as eluant followed by recrystallization from CH<sub>2</sub>Cl<sub>2</sub>-Et<sub>2</sub>O-hexane to yield 320 mg (35%) of **22a** (Table II).

**3-(3-Fluorobenzyl)pyridine-2-thione (22b)**. The reaction of **65** as in the preparation of **22a** yielded (35%) **22b** (Table II).

**3-(3,5-Difluorobenzyl)pyridine-2-thione (22c)**. The reaction of **66** as in the preparation of **22a** yielded (35%) **22c** (Table II).

**1-Benzyl-1,2-dihydropyrimidine-2-thione (22a)**. A solution of *N*-benzylthiourea<sup>15</sup> (8.0 g, 0.0482 mol) and malondialdehyde tetramethyl acetal (7.91 g, 0.048 mol) in H<sub>2</sub>O (65 mL), concentrated HCl (16 mL), and EtOH (65 mL) was heated at reflux for 25 min. The solution was cooled, washed with Et<sub>2</sub>O, and then made basic with 10% NaOH. The resulting solution was extracted

(14) Shabana, R.; Scheibye, S.; Clausen, K.; Olesen, S. O.; Lawesson, S. O. *Nouv. J. Chim.* 1980, 4, 47.

(15) Prepared by the method of: Neville, R. G.; McGee, J. J. *Can. J. Chem.* 1963, 41, 2123.

(16) Blackman, A. J.; Polya, J. B. *J. Chem. Soc. C* 1971, 1016.

(17) Altland, H. W. *J. Org. Chem.* 1976, 41, 3395.



twice with  $\text{CHCl}_3$ , and the combined  $\text{CHCl}_3$  extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated. The residue was recrystallized from EtOH to give 3.2 g (32%) of **23a** (Table II).

1-(3-Fluorobenzyl)-1,2-dihydropyrimidine-2-thione hydrochloride (**23b**) was prepared from *N*-(3-fluorobenzyl)thiourea<sup>15</sup> in 13% yield by the method used to prepare **23a**.

1-(3,5-Difluorobenzyl)-1,2-dihydropyrimidine-2-thione hydrochloride (**23c**) was prepared from *N*-(3,5-difluorobenzyl)thiourea<sup>15</sup> in 10% yield by the same method used for the preparation of **23a**.

**pK<sub>a</sub> Determinations** were obtained by titration of the compounds in 2:1 MeOH-H<sub>2</sub>O (to overcome solubility constraints).

**Enzymology.** In vitro IC<sub>50</sub> determinations were made as previously reported.<sup>4</sup> The IC<sub>50</sub> is defined as the concentration of compound that produces 50% inhibition of product formation when compared to uninhibited control.

**Registry No.** 1, 23269-10-5; 2, 95333-64-5; 3, 95333-65-6; 4, 95333-56-5; 4-HCl, 95359-66-3; 5, 16042-26-5; 5-HCl, 123566-30-3; 6, 95460-25-6; 6-HCl, 123566-31-4; 7, 26163-58-6; 7·2HCl, 22600-75-5; 8, 95460-13-2; 8·2HCl, 123593-05-5; 9, 123593-06-6; 9-HCl, 123566-32-5; 10, 5376-10-3; 10-HCl, 5272-57-1; 11, 41833-17-4; 12, 10045-64-4; 13, 123566-33-6; 14, 123566-34-7; 15b, 95333-80-5; 15c, 95333-81-6; 15d, 95333-60-1; 16a, 123566-44-9; 16b, 123566-45-0; 16c, 123566-46-1; 17a, 23289-13-6; 17b, 107186-77-6; 17c, 107186-78-7; 17d, 107186-80-1; 18a, 29983-31-1; 18b, 112961-33-8; 18c, 112961-34-9; 19a, 68700-73-2; 20a, 33898-72-5; 20c, 105219-26-9; 21a, 31493-51-3; 21c, 105968-95-4; 21d, 105968-97-6; 22a, 123566-55-2; 22b, 123566-56-3; 22c, 123566-57-4; 23a, 123566-58-5; 23b, 123566-63-2; 23b-HCl, 123566-60-9; 23c, 123566-64-3; 23c-HCl,

123566-62-1; 28, 56643-95-9; 29, 10045-65-5; 30, 95460-12-1; 31, 95460-14-3; 32, 95460-15-4; 33, 123566-35-8; 34, 95460-23-4; 35, 123566-36-9; 36, 123566-37-0; 37, 123566-39-2; 38, 123566-42-7; 39, 90390-27-5; 40, 105969-16-2; 41, 107186-81-2; 42, 63351-94-0; 43, 107186-82-3; 44, 107186-83-4; 45, 93114-14-8; 46, 107186-84-5; 47, 107186-85-6; 48, 107186-79-8; 49, 112961-36-1; 50, 112961-39-4; 51, 112961-37-2; 52, 123566-47-2; 53, 123566-48-3; 54, 123566-49-4; 55, 105219-25-8; 56, 5729-06-6; 57, 105969-13-9; 58, 105969-11-7; 59, 105968-93-2; 60, 79568-07-3; 61, 123566-50-7; 62, 123566-51-8; 63, 123566-52-9; 64, 32967-14-9; 65, 123566-53-0; 66, 123566-54-1; *p*-MeOC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>NHCH<sub>2</sub>CH(OMe)<sub>2</sub>, 54879-77-5; NH<sub>2</sub>CN, 420-04-2; PhCHO, 100-52-7; *m*-FC<sub>6</sub>H<sub>4</sub>CHO, 456-48-4; 3,5-F<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CHO, 32085-88-4; NH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, 107-15-3; PhCH<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, 4152-09-4; 3,5-F<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>NH<sub>2</sub>, 123566-40-5; PhCH<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>NHC(=S)SH, 123566-41-6; 3,5-F<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>NHCH<sub>2</sub>CH<sub>2</sub>NHC(=S)SH, 123566-43-8; 3,5-F<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CN, 64248-63-1; *m*-FC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>NH<sub>2</sub>, 100-82-3; PhCH<sub>2</sub>NCS, 622-78-6; *t*-BuOCONHNH<sub>2</sub>, 870-46-2; *o*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>Cl, 88-73-3; PhCH<sub>2</sub>NH<sub>2</sub>, 100-46-9; *m*-BrC<sub>6</sub>H<sub>4</sub>F, 1073-06-9; 3,5-F<sub>2</sub>C<sub>6</sub>H<sub>3</sub>Br, 461-96-1; *m*-FC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>NHC(=S)NH<sub>2</sub>, 123566-59-6; 3,5-F<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CH<sub>2</sub>NHC(=S)NH<sub>2</sub>, 123566-61-0; 1-[3-(4-methoxyphenyl)propyl]imidazole-2-thione, 95333-89-4; 1-(4-methoxybenzyl)imidazole-2-thione, 95460-09-6; 1-benzylimidazole, 4238-71-5; 1-benzyl-2-methylimidazole, 13750-62-4; 1-[4-(benzyloxy)benzyl]-2-methylimidazole, 123566-38-1; 3,5-difluoro-4-methoxybenzotrile, 104197-15-1; 1-benzyl-1,2,3-triazole, 4368-68-7; 3-pyridinecarbonitrile, 100-54-9; 3-benzylpyridine, 620-95-1; *N*-benzylthiourea, 621-83-0; malonaldehyde tetramethyl acetal, 102-52-3; dopamine  $\beta$ -hydroxylase, 9013-38-1; 3-benzylpyridine *N*-oxide, 32361-74-3.

## Synthesis and Pharmacological Evaluation of a Series of Dibenzo[*a,d*]cycloalkenimines as *N*-Methyl-D-aspartate Antagonists

Wayne J. Thompson,\* Paul S. Anderson,\* Susan F. Britcher, Terry A. Lyle, J. Eric Thies, Catherine A. Magill, Sandor L. Varga, John E. Schwering, Paulette A. Lyle, Marcia E. Christy, Ben E. Evans, C. Dylon Colton, M. Katharine Holloway,<sup>†</sup> James P. Springer, Jordan M. Hirshfield, Richard G. Ball, Joseph S. Amato, Robert D. Larsen,<sup>‡</sup> Erik H. F. Wong, John A. Kemp, Mark D. Tricklebank, Lakhbir Singh, Ryszard Oles, Tony Priestly, George R. Marshall, Antony R. Knight, Derek N. Middlemiss, Geoffrey N. Woodruff, and Leslie L. Iversen

Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486, Merck Sharp & Dohme Research Laboratories, Rahway, New Jersey 07065, and Merck Sharp & Dohme Research Laboratories, Neuroscience Research Centre, Terlings Park, Harlow, Essex CM20 2QR, United Kingdom. Received April 10, 1989

A series of 73 dibenzo[*a,d*]cycloalkenimines were synthesized and evaluated for their ability to displace (+)-10,11-dihydro-5-methyl-5*H*-dibenzo[*a,d*]cyclohepten-5,10-imine ([<sup>3</sup>H]-(+)-10) from its specific binding site on rat cortical membranes. A number of the more active compounds (*K<sub>i</sub>* ranging from 0.006 to 0.21  $\mu\text{M}$ ) were evaluated for *N*-methyl-D-aspartate (NMDA) antagonist activity in the rat cortical slice (*K<sub>b</sub>* ranging from 0.08 to 0.9  $\mu\text{M}$ ) and anticonvulsant activity in the mouse against NMDA induced convulsions. The ED<sub>50</sub> values ranged from 0.22 to 7.76 mg/kg and correlated reasonably well with the *K<sub>b</sub>* determination. In the dibenzo[*a,d*]cyclohepten-5,10-imine series, the (+)-5*S*,10*R* enantiomer displayed consistently higher levels of biological activity. While substitution at the 3-position of (+)-10 with electronegative atoms generally increased in vitro activity, a loss of potency relative to (+)-10 (MK-801) was observed in vivo for all of the compounds tested.

Sometime ago a number of 1,4-dihydronaphthalen-1,4-imines were synthesized in our laboratory to explore the biologic properties of these molecules.<sup>1</sup> Interest in these rigid heterocycles had been stimulated by the observation that 9-methyl-5,6,7,8-tetrafluoro-1,4-dihydronaphthalen-1,4-imine (**1**) displayed modest antiseizure and apparent anxiolytic activity when orally administered to rodents. In the course of pursuing this study, the structurally related 9,10-dihydroanthracen-9,10-imines<sup>2</sup> were found to have similar biological properties. Placement of methyl groups on the bridgehead positions of this construction

gave rise to compounds which were surprisingly more potent than the lead structure **1**, and also exhibited a high level of central sympathomimetic activity.<sup>3</sup>

Sedation is a frequently encountered side effect of available anticonvulsant drugs. The spectrum of phar-

- (1) Anderson, P. S.; Christy, M. E.; Engelhardt, E. L.; Lundell, G. F.; Ponticello, G. S. *J. Heterocycl. Chem.* 1977, 14, 213.
- (2) Anderson, P. S.; Christy, M. E.; Colton, C. D.; Halczenko, W.; Ponticello, G. S.; Shepard, K. L. *J. Org. Chem.* 1979, 44, 1519.
- (3) Anderson, P. S.; Clineschmidt, B. v.; Christy, M. E.; Evans, B. E.; Yarbrough, G. C. In *Natural Products and Drug Development*; P. Krosggaard-Larsen, H. Kofod, and S. B. Christenen, Eds.; Munksgard: Copenhagen, 1984; pp 98-107.

<sup>†</sup>Rahway, NJ.

<sup>‡</sup>Harlow, Essex, U.K.