

centration of compound required to inhibit 50% of specific neurotoxin binding) were determined from a dose-response curve generated by plotting the log of anticonvulsant concentration (over a range of 10–800  $\mu\text{M}$ ) versus percent of specifically bound [ $^3\text{H}$ ]BTX-B.

**Anticonvulsant Assays.** All anticonvulsant and neurotoxicity assays were conducted by the Anticonvulsant Drug Development Program of the Epilepsy Branch, National Institute of Neurological and Communicative Disorders and Stroke, National Institutes of Health. Compounds were injected intraperitoneally into mice as suspensions in either methylcellulose or 30% polyethylene glycol 400. After the time indicated in Table II, the animal was subjected to either a subcutaneous Metrazol (scMet) challenge (85 mg/kg), a maximal electroshock (MES) challenge

(produced with 60 cycle AC at 50 mA for 0.2 s via corneal electrodes), or a rotorod toxicity test. The details of these procedures have been published.<sup>12</sup>

**Acknowledgment.** We thank Gill Gladding and James Stables of the Epilepsy Branch, National Institute of Neurological and Communicative Disorders and Stroke, NIH, for the anticonvulsant assays. We also thank the NIH, NINCDS, for generous support of this work (Grant NS23866).

**Registry No.** 1, 93350-08-4; 2, 93350-09-5; 3, 92288-54-5; 4, 68475-20-7; 5, 65379-06-8; 6, 87532-76-1; 7, 87532-77-2; 8, 87532-78-3; 9, 51129-01-2; 10, 93350-14-2; 11, 93350-13-1.

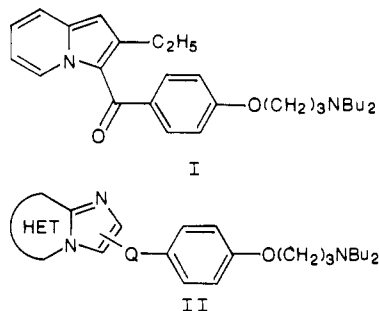
## Synthesis of (Aryloxy)alkylamines. 2. Novel Imidazo-fused Heterocycles with Calcium Channel Blocking and Local Anesthetic Activity<sup>1</sup>

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A series of imidazo-fused heterocycles substituted with an (aryloxy)alkylamine side chain were prepared as modifications to butopropazine (I) and found to possess calcium channel blocking activity similar in potency to that of bepridil in trachea smooth muscle and similar to that of verapamil in nitrendipine binding affinity in rabbit cardiac muscle. Of the various imidazo-fused heterocycles prepared, the imidazo[1,2-*a*]pyridines were also found to be potent local anesthetic agents. While most compounds in this series were equipotent to lidocaine in our initial screen, compounds 2 and 35 showed local anesthetic activity approximately 100 times more potent than lidocaine in our preliminary assays. These compounds represent a novel structural class of local anesthetic agents, and compound 2 is under further investigation.

Calcium channel blockers are utilized as antianginal agents<sup>2</sup> due to their peripheral vasodilating<sup>3</sup> and smooth muscle relaxing properties.<sup>4</sup> We became interested in preparing analogues of butopropazine<sup>5</sup> (I), an antianginal agent with antiadrenergic and calcium antagonist activities,<sup>6</sup> and developed a program to synthesize various heterocyclic (aryloxy)alkylamines of general structure II.



In particular, the 4-[3-(dibutylamino)propoxy]phenyl group specific to butopropazine (I) was utilized as a pharmacophore to explore the effects of altering the heterocyclic ring (HET) and the spacer Q (i.e. carbonyl, direct

bond) on biological activity as well as substituent effects on these various heterocyclic moieties. For expediency, the initial plan was confined to readily synthesized derivatives of available 2-amino heterocycles.

In addition to examining the compounds for potential calcium channel blocking activity, these imidazo-fused heterocyclic (aryloxy)alkylamines were evaluated in a wide variety of pharmacological and biochemical assays in order to determine any other potential pharmacological utility. We have previously reported<sup>1</sup> on compounds related to target II wherein a substituted thiazole, benzoxazole, or benzothiazole moiety (instead of the imidazo-fused heterocycle) was found to be a potent inhibitor of the  $\text{H}^+\text{K}^+$ -sensitive ATPase enzyme. As a result of broad screening, a series of imidazo[1,2-*a*]pyridines, a subset of II, were discovered to possess very interesting local anesthetic activity.

### Chemistry

Condensation of a variety of 2-amino heterocycles (III) with 4-hydroxy- $\alpha$ -bromoacetophenone<sup>7</sup> (IV) and subsequent alkylation of the phenol with (dibutylamino)propyl chloride produced the desired imidazo-fused heterocycles (II) but in unacceptably low yields (Scheme I). As noted previously,<sup>1</sup> protection of the phenol as a chloropropoxy ether as in VIa greatly improved the yields of the 2-amino heterocycle condensations. Subsequent displacement of the alkyl chloride with dibutylamine produced the desired product IIa as outlined in Scheme II. The various 2-aryl imidazo-fused heterocycles thus prepared are summarized in Table I.

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- (5) Charlier, R. H.; Richard, J. C.; Bauthier, J. A. *Arzneim-Forsch.* 1977, 7, 1455. Labaz, Belgium Patent 851,463.
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**Table I.** Various 2- and 3-Substituted Imidazo-Fused Heterocycles with [<sup>3</sup>H]Nitrendipine Binding, Inhibition of Calcium Dependent Smooth Muscle Contractions, and Local Anesthetic Activity

HET-Q——O(CH<sub>2</sub>)<sub>3</sub>NBu<sub>2</sub>

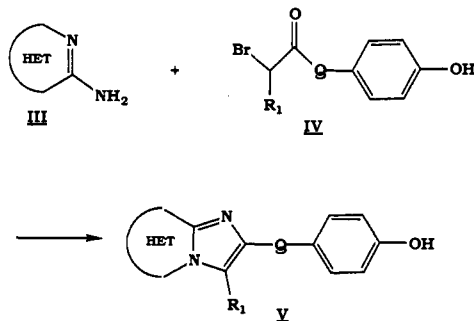
HET-Q	compd	formula <sup>a</sup>	mp, <sup>b</sup> °C	yield, %	[ <sup>3</sup> H]nitrendipine binding, μM <sup>g</sup>	inhibition of smooth muscle contraction (10 μM), <sup>h</sup> %	concentration causing local anesthetic activity, <sup>i</sup> %
	1	C <sub>24</sub> H <sub>33</sub> N <sub>3</sub> O·3HCl	179–183	93 <sup>c</sup>	2.7	54	0.1
	2	C <sub>25</sub> H <sub>35</sub> N <sub>3</sub> O·3HCl	214–7	32 <sup>c</sup>	0.6	61	0.01
	3	C <sub>25</sub> H <sub>35</sub> N <sub>3</sub> O·3HCl	134–6	29 <sup>c</sup>	6.0	46	0.1
	4	C <sub>31</sub> H <sub>39</sub> N <sub>3</sub> O <sub>2</sub> ·HCl· <sub>3/2</sub> H <sub>2</sub> O	153–6	73 <sup>c</sup>	45% (10 μM)	35	0.1
	5	C <sub>24</sub> H <sub>32</sub> BrN <sub>3</sub> O·2HCl· H <sub>2</sub> O	193–5	74 <sup>c</sup>	2.5	32	1.0
	6	C <sub>26</sub> H <sub>35</sub> N <sub>3</sub> O <sub>2</sub> ·3HCl· H <sub>2</sub> O	159–161	99 <sup>d</sup>	6.0	58	1.0
	7	C <sub>26</sub> H <sub>35</sub> N <sub>3</sub> O <sub>2</sub> ·3HCl	210–2	75 <sup>d</sup>	1.6	42	1.0
	8	C <sub>26</sub> H <sub>32</sub> BrN <sub>3</sub> O <sub>2</sub> ·2HCl	214–6	60 <sup>d</sup>	3.0	50	1.0
	9	C <sub>26</sub> H <sub>35</sub> N <sub>3</sub> O <sub>2</sub> ·3HCl	105–7	31 <sup>e</sup>	0.5	56	0.1
	10	C <sub>26</sub> H <sub>32</sub> BrN <sub>3</sub> O <sub>2</sub> ·3HCl· 2H <sub>2</sub> O <sup>f</sup>	162–5	8.8 <sup>e</sup>	0.2	62	0.1
	11	C <sub>22</sub> H <sub>31</sub> N <sub>3</sub> OS·2HCl· H <sub>2</sub> O	215–8	82 <sup>c</sup>	1.5	55	>1.0
	12	C <sub>23</sub> H <sub>33</sub> N <sub>3</sub> OS·2HCl· <sub>3/2</sub> H <sub>2</sub> O	210–3	30 <sup>c</sup>	1.3	75	0.1
	13	C <sub>22</sub> H <sub>32</sub> N <sub>4</sub> OS·2HCl· H <sub>2</sub> O	163–6	39 <sup>c</sup>	1.1	82	IA <sup>j</sup>
	14	C <sub>26</sub> H <sub>33</sub> N <sub>3</sub> OS·2HCl· H <sub>2</sub> O	215–7	69 <sup>c</sup>	3.1	15	1.0
	15	C <sub>22</sub> H <sub>31</sub> N <sub>5</sub> O·HCl	174–7	58 <sup>c</sup>	0.6	46	IA <sup>j</sup>
	16	C <sub>23</sub> H <sub>32</sub> N <sub>4</sub> O·2HCl· H <sub>2</sub> O	154–7	37 <sup>c</sup>	43% (68 μM)	46	>1.0
	17	C <sub>24</sub> H <sub>34</sub> N <sub>4</sub> O·3HCl· H <sub>2</sub> O	154–4	81 <sup>c</sup>	0	39	IA <sup>j</sup>
	18	C <sub>24</sub> H <sub>32</sub> N <sub>4</sub> O <sub>2</sub> ·2HCl	174–7	74 <sup>e</sup>	7.0	44	IA <sup>j</sup>
	19	C <sub>25</sub> H <sub>34</sub> N <sub>4</sub> O <sub>2</sub> ·2HCl· <sub>3/2</sub> H <sub>2</sub> O	168–171	26 <sup>e</sup>	6.1	19	IA <sup>j</sup>

Table I (Continued)

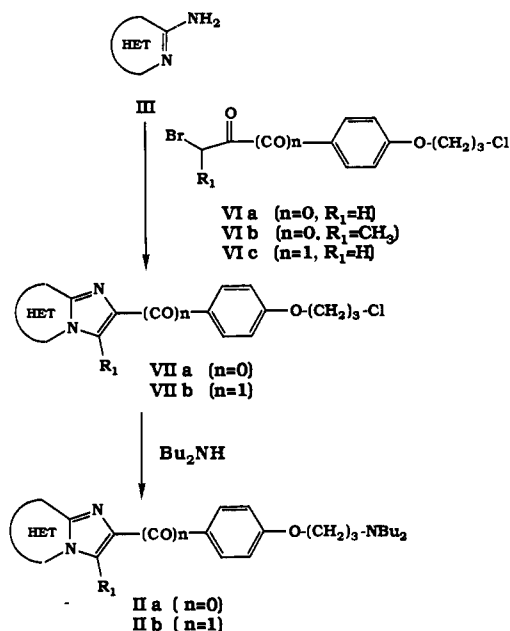
HET-Q	compd	formula <sup>a</sup>	mp, <sup>b</sup> °C	yield, %	[ <sup>3</sup> H]nitrendipine binding, $\mu\text{M}$ <sup>g</sup>	inhibition of smooth muscle contraction (10 $\mu\text{M}$ ), <sup>h</sup> %	concentration causing local anesthetic activity, <sup>i</sup> %
	bepidil				22	81	NT <sup>k</sup>
	diltiazem				30	96	NT <sup>k</sup>
	verapamil				1.0	93	1.0
	nifedipine				0.001 $\mu\text{M}$	95 (2 $\mu\text{M}$ )	>1.0
	lidocaine				>1000	>10000	1.0

<sup>a</sup> All compounds exhibited satisfactory ( $\pm 0.4\%$ ) elemental analysis as salts except where noted. <sup>b</sup> Recrystallized from methanol-acetone. <sup>c</sup> Procedure A. <sup>d</sup> Procedure B. <sup>e</sup> Procedure C. <sup>f</sup> Analyzed for Cl: calcd 17.85, found 17.94. <sup>g</sup> Inhibition of [<sup>3</sup>H]nitrendipine binding as IC<sub>50</sub> values in micromolar concentration as determined in rabbit cardiac muscle. All values are the mean  $\pm 15\%$  ( $N = 4$ ). <sup>h</sup> Inhibition of calcium-dependent potassium-polarized smooth muscle contractions as determined in canine trachea at 10  $\mu\text{M}$  except where noted. All values are the mean  $\pm 15\%$  ( $N = 4$ ). <sup>i</sup> Concentration causing local anesthetic activity in mice. All values reported are the lowest concentration of observed activity in the majority of three mice. <sup>j</sup> Inactive at screening dose. <sup>k</sup> Not tested.

## Scheme I



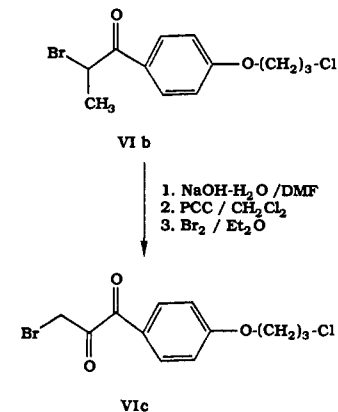
## Scheme II



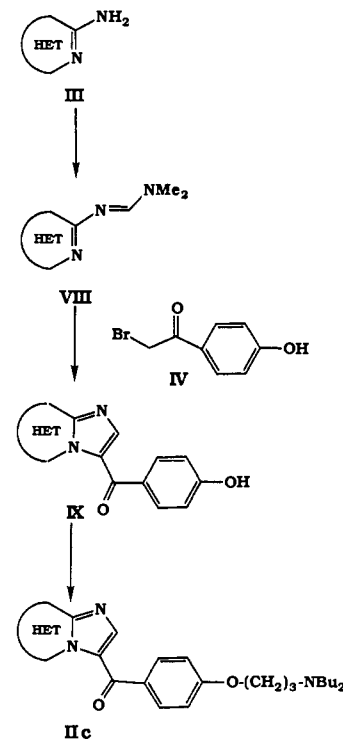
The substituted 2-benzoyl imidazo-fused heterocycles IIb were prepared from the  $\alpha$ -bromo diketone VIc, which was synthesized in three steps from the monobromo ketone VIb (Scheme III). Displacement of the bromide of VIb by hydroxide followed by PCC oxidation and subsequent bromination gave VIc in 70% overall yield. The 2-benzoyl-substituted imidazo-fused heterocycles prepared are also summarized in Table I.

The 3-benzoyl substituted imidazo-fused heterocycles IIc were prepared by condensing amidine VIII with 4-hydroxy- $\alpha$ -bromoacetophenone (IV) (Scheme IV).<sup>8</sup> Noteworthy were the reactions between amidines VIII and the protected  $\alpha$ -bromo ketone VIa in which the 2-aryl

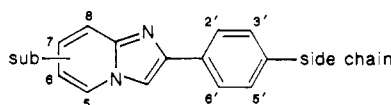
## Scheme III



## Scheme IV



imidazo-fused heterocycles VIIa were obtained as the major products with only a trace amount of the desired 3-benzoyl analogue isolated. Compounds VIIa most likely arise from cleavage of the amidine (by hydrogen bromide generated during the course of the condensation reaction) to produce precursor 2-amino heterocycle III, which then reacts as outlined in Scheme II. This cleavage could be circumvented by reacting the amidine with 4-hydroxy- $\alpha$ -bromoacetophenone (IV). In this case the free phenol,

Table II. Various Substituted Imidazo[1,2-*a*]pyridines and Their Local Anesthetic Activity

compd	sub	side chain	formula <sup>a</sup>	mp, <sup>b</sup> °C	yield, %	concentration causing local anesthetic activity, %
20	3,8-Me	O(CH <sub>2</sub> ) <sub>3</sub> NBu <sub>2</sub>	C <sub>26</sub> H <sub>37</sub> N <sub>3</sub> O·3HCl·H <sub>2</sub> O	202-4	62	0.1
21	8-OH	O(CH <sub>2</sub> ) <sub>3</sub> NBu <sub>2</sub>	C <sub>24</sub> H <sub>33</sub> N <sub>3</sub> O <sub>2</sub> ·3HCl·1/2H <sub>2</sub> O	174-7	69	0.1
22	8-NO <sub>2</sub>	O(CH <sub>2</sub> ) <sub>3</sub> NBu <sub>2</sub>	C <sub>24</sub> H <sub>32</sub> N <sub>4</sub> O <sub>3</sub> ·3HCl	242-4	27	>1.0
23	6-Me	O(CH <sub>2</sub> ) <sub>3</sub> NBu <sub>2</sub>	C <sub>25</sub> H <sub>35</sub> N <sub>3</sub> O·3HCl	188-91	57	0.1
24	5-Me	O(CH <sub>2</sub> ) <sub>3</sub> NBu <sub>2</sub>	C <sub>25</sub> H <sub>35</sub> N <sub>3</sub> O·3HCl	221-3	55	0.1
25	8-Me	O(CH <sub>2</sub> ) <sub>3</sub> NPr <sub>2</sub>	C <sub>23</sub> H <sub>31</sub> N <sub>3</sub> O·3HCl	188-90	62	0.1
26	8-Me	O(CH <sub>2</sub> ) <sub>3</sub> NMe <sub>2</sub>	C <sub>19</sub> H <sub>23</sub> N <sub>3</sub> O·3HCl·H <sub>2</sub> O	251-3	41	1.0
27	8-Me	O(CH <sub>2</sub> ) <sub>3</sub> NPen <sub>2</sub>	C <sub>27</sub> H <sub>39</sub> N <sub>3</sub> O·3HCl·1/2H <sub>2</sub> O	157-60	38	0.1
28	8-Me	O(CH <sub>2</sub> ) <sub>3</sub> piperidine	C <sub>22</sub> H <sub>27</sub> N <sub>3</sub> O·3HCl·H <sub>2</sub> O	189-92	52	1.0
29	8-Me	O(CH <sub>2</sub> ) <sub>3</sub> morpholine	C <sub>21</sub> H <sub>25</sub> N <sub>3</sub> O <sub>2</sub> ·3HCl·H <sub>2</sub> O	157-60	38	>1.0
30	8-Me	O(CH <sub>2</sub> ) <sub>3</sub> imidazole	C <sub>20</sub> H <sub>20</sub> N <sub>4</sub> O·3HCl	185-8	42	>1.0
31	8-Me	O(CH <sub>2</sub> ) <sub>4</sub> NBu <sub>2</sub>	C <sub>26</sub> H <sub>37</sub> N <sub>3</sub> O·3HCl·H <sub>2</sub> O	160-3	35	1.0
32	3',8-Me	O(CH <sub>2</sub> ) <sub>3</sub> NBu <sub>2</sub>	C <sub>26</sub> H <sub>37</sub> N <sub>3</sub> O·3HCl·1/2H <sub>2</sub> O	240-2	62	0.1
33	2',8-Me	O(CH <sub>2</sub> ) <sub>3</sub> NBu <sub>2</sub>	C <sub>26</sub> H <sub>37</sub> N <sub>3</sub> O·3HCl·H <sub>2</sub> O	178-81	65	0.1
34	8-Me, 3',5'-MeO	O(CH <sub>2</sub> ) <sub>3</sub> NBu <sub>2</sub>	C <sub>27</sub> H <sub>39</sub> N <sub>3</sub> O <sub>3</sub> ·3HCl	178-80	57	0.1
35	8-Me, 3'-MeO	O(CH <sub>2</sub> ) <sub>3</sub> NBu <sub>2</sub>	C <sub>26</sub> H <sub>37</sub> N <sub>3</sub> O <sub>2</sub> ·3HCl	167-70	61	0.01
	lidocaine					1.0
	nifedipine					>1.0
	verapamil					1.0

<sup>a</sup> All compounds exhibited satisfactory ( $\pm 0.4\%$ ) elemental analysis as salts except where noted. <sup>b</sup> Recrystallized from methanol-acetone.

<sup>c</sup> Concentration causing local anesthetic activity in mice. All values reported are the lowest concentration of observed activity in the majority of three mice.

which had caused problems in the earlier condensations, might facilitate the desired reaction by acting as a hydrogen bromide scavenger and thereby preventing cleavage of the amidine. The desired 3-ketoaryl-substituted imidazo-fused heterocycles IIc were obtained by alkylating the phenol IX with (dibutylamino)propyl chloride in good yield. The various 3-ketoaryl-substituted imidazo-fused heterocycles prepared in this manner are also summarized in Table I.

## Results and Discussion

A variety of 2- and 3-aryl-substituted imidazo-fused heterocycles (1-19) were prepared and found to possess moderate calcium channel blocking activity in two primary *in vitro* assays (Table I). The nitrendipine binding assay measures the ability of a test compound to inhibit the binding of radiolabeled [<sup>3</sup>H]nitrendipine to plasma membrane receptors in rabbit cardiac muscle. The second *in vitro* assay (inhibition of smooth muscle contraction) measures the inhibition by a test compound of calcium-dependent potassium-polarized smooth muscle contractions in canine trachea. Both assays detect the activity of dihydropyridines such as nifedipine,<sup>9</sup> as well as other calcium channel blockers such as bepridil,<sup>10</sup> verapamil,<sup>11</sup> and diltiazem.<sup>12</sup>

The (aryloxy)alkylamines inhibited potential-dependent Ca<sup>2+</sup> channel influx with potency comparable to bepridil, which demonstrated 81% inhibition of the Ca<sup>2+</sup> dependent contraction at 10  $\mu$ M. The most interesting heterocyclic compounds prepared were the imidazo[2,1-*b*]thiazoles and imidazo[2,1-*b*]thiadiazoles (11-13), which demonstrated 55-82% inhibition of the Ca<sup>2+</sup> dependent contraction at 10  $\mu$ M. The imidazo[1,2-*a*]pyridine series also exhibited

good activity in this assay with potency similar to bepridil. A brief study of the structure-activity relationships (SAR) in the imidazo[1,2-*a*]pyridine series indicated that inhibition of smooth muscle contractions appears to be independent of substituent effects on the pyridine ring (1-8).

With the exception of the imidazo[1,2-*a*]pyrimidines 16-19, the various imidazo-fused heterocyclic compounds inhibited nitrendipine binding with a potency comparable to verapamil. In contrast to the smooth muscle contraction assay, potency in this assay was sensitive to substituent effects in the imidazo[1,2-*a*]pyridine series (1-10). Interestingly, the most potent compounds as calcium channel blocking agents in both smooth muscle contraction and nitrendipine binding assays were the imidazo[1,2-*a*]pyridines 2, 9, and 10, with 9 and 10 having structural similarities to butopropazine (I). Unfortunately, these compounds had little *in vivo* activity in the anesthetized dog, and further work directed at this goal is not planned.

Broad pharmacological screening of these compounds resulted in the discovery that the imidazo[1,2-*a*]pyridine series (1-10) also possessed potent local anesthetic activity in mice (Table I). This was determined by measurement of the inability of dosed mice to grip an inverted screen with the toes of the injected leg. This effect has been proposed to result from infiltration of the test compound into the sciatic nerve causing blockade of motor and, presumably, sensory fibers. This type of assay<sup>13</sup> is predictive of the clinical local anesthetic activity of lidocaine as well as other clinical agents. Additional substituted imidazo[1,2-*a*]pyridines were prepared to study the SAR and are summarized in Table II.

In contrast to the lack of substituent effects for calcium channel blocking activity in smooth muscle, local anesthetic potency was very sensitive to substituent effects on the pyridine ring in the imidazo[1,2-*a*]pyridine series. Compound 2, with a methyl substituent in the 8-position, was found to be 100-fold more potent than lidocaine. Compounds with hydrogen (1), benzyloxy (4), or hydroxy

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(21) substituents in the 8-position were less potent than compound 2 but still 10-fold more potent than lidocaine. A nitro group (22) at the 8-position greatly reduced local anesthetic potency. Altering the methyl substitution to the 7-position (3), 6-position (23), or 5-position (24) or introducing a methyl group onto the imidazole ring (20) reduced potency to that of lidocaine. Compound 2 was chosen for further SAR studies.

The effects of varying the (dialkylamino)alkoxy side chain were explored while maintaining the methyl substituent at the 8-position. A variety of dialkylamines (25–27), cycloalkylamines (28, 29), and heterocyclic amines (30) were prepared and all were 10–100-fold less potent than compound 2. Lengthening the side chain to a four methylene unit separation (31) also decreased potency by 100-fold. These results indicate that local anesthetic activity is sensitive to both the amino moiety and the length of alkoxy side chain.

The effects of substitution on the aryloxy ring were also studied. Compounds substituted with a methyl group either ortho or meta to the alkoxy side chain (32, 33), as well as the dimethoxy substituted compound 34 were 10-fold less potent than compound 2. Interestingly, the monomethoxy-substituted compound 35 was the only compound in this study found equipotent with compound 2 in our preliminary assay.

In conclusion, a series of imidazo-fused heterocycles were prepared as analogues of butopropazine (I) and found to possess *in vitro* potencies similar to those of bepridil as calcium channel blocking agents in smooth muscle contractions and similar to those of verapamil in the nitrendipine binding assay. However, these compounds possessed little *in vivo* activity and are no longer being pursued as potential antianginal agents. Most interestingly, a subset of these compounds, the imidazo[1,2-*a*]pyridines, were found to be potent local anesthetic agents.

Certain calcium channel blockers (such as verapamil) have local anesthetic activity similar in potency to that of lidocaine (Tables I and II). The most potent imidazo[1,2-*a*]pyridines in both the smooth muscle and nitrendipine binding assays (2, 9, and 10) were also potent local anesthetic agents with the best compound (2) having potency 100-fold greater than lidocaine. However, a strong correlation between local anesthetic activity and calcium channel blocking activity obviously does not exist. Lidocaine, a standard for local anesthetic activity, is inactive as a calcium channel blocking agent, whereas nifedipine, the most potent calcium channel blocking agent used as a standard in our assays, is devoid of local anesthetic activity.

Of the various substituted imidazo[1,2-*a*]pyridines prepared, compounds 2 and 35 have the best local anesthetic activity in our initial assay. Interestingly, all of the compounds in this series, with the exception of compounds 22, 29, and 30, were at least as potent as lidocaine in our initial screen. This imidazo[1,2-*a*]pyridine series represents a novel structural class of local anesthetic agents. Compound 2 is currently undergoing further evaluation as a local anesthetic agent in rabbit cornea and guinea pig intradermal wheal tests. Results from these tests will be the subject of a future report.<sup>14</sup>

## Experimental Section

Melting point determinations were done on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared

Table III. Reaction Times for Preparing Imidazo-Fused Heterocycles (VIIa)

$\omega$ -amino heterocycle	reflux, h	yield, %
2-amino-3-picoline	1	86
2-amino-4-picoline	8	29
2-amino-3-(benzyloxy)pyridine	24	48
2-amino-5-bromopyridine	8	43
2-amino-1,3-thiazole	6	69
2-amino-5-methyl-1,3,4-thiadiazole	5	86
2-amino-1,3-benzothiazole	8	70
3-amino-1,2,4-triazine	16	49
2-amino-1,3-pyrimidine	8	79
2-amino-6-methyl-1,3-pyrimidine	3	77

(IR) spectra were obtained on a Perkin-Elmer IR8 and are reported in wavenumbers ( $\text{cm}^{-1}$ ). Nuclear magnetic resonance ( $^1\text{H}$  NMR) spectra were recorded on a Bruker WH-100 (100MHz) spectrometer. Chemical shifts are reported in parts per million ( $\delta$ ) downfield relative to tetramethylsilane as standard. Mass spectra (MS) were obtained on a Finnigan-MAT Model 8230. Combustion analyses were within  $\pm 0.4\%$  of theory unless otherwise noted. Compounds in the tables were prepared according to the general procedures described. Physical properties of the compounds are summarized in Tables I and II.

**Procedure A. 4-(3-Chloropropoxy)acetophenone.** To a mixture of 4-hydroxyacetophenone (50.7 g, 0.37 mol) and 1-bromo-3-chloropropane (160 mL, 1.5 mol) in methanol (250 mL) was added portionwise potassium hydroxide (63 g, 1.12 mol). The mixture was stirred at reflux for 24 h, cooled to room temperature, filtered through Celite, and evaporated *in vacuo*. The residual semisolid was dissolved in diethyl ether (500 mL) and washed with water ( $2 \times 300$  mL). The ether solution was dried over  $\text{MgSO}_4$ , filtered, and evaporated to give the title compound as a liquid in 68% yield (53.4 g):  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  7.98–7.89 (d,  $J = 8.9$  Hz, 2 H), 7.02–6.92 (d,  $J = 8.9$  Hz, 2 H), 4.16 (t,  $J = 5.9$  Hz, 2 H), 3.75 (t,  $J = 6.4$  Hz, 2 H), 2.52 (s, 3 H), 2.34–2.16 (m, 2 H).

**$\alpha$ -Bromo-4-(3-chloropropoxy)acetophenone (VIa).** To a stirred solution of 4-(3-chloropropoxy)acetophenone (53.3 g, 0.25 mol) in diethyl ether (250 mL) was slowly added bromine (13 mL, 0.25 mol), and the mixture was stirred at room temperature for 16 h. The dark mixture was poured into an aqueous saturated sodium bicarbonate solution (300 mL), and the organic layer was separated. The ether layer was washed with an aqueous saturated sodium bicarbonate solution (300 mL) and water (300 mL) and was dried over  $\text{MgSO}_4$ . The solution was filtered and evaporated *in vacuo* to yield VIa (64.4 g, 88%) as a dark oil.

**2-[4-[3-(Dibutylamino)propoxy]phenyl]-8-methylimidazo[1,2-*a*]pyridine (2).** A mixture of VIa (5.0 g, 17.4 mmol) and 2-amino-3-picoline (1.9 g, 17.4 mmol) in ethanol (20 mL) was stirred at reflux for 1 h, cooled to room temperature, and filtered to give 2-[4-(chloropropoxy)phenyl]-8-methylimidazo[1,2-*a*]pyridine (4.5 g, 86%) as a white solid:  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.25 (d,  $J = 8$  Hz, 1 H), 8.08 (s, 1 H), 7.97–7.01 (m, 6 H), 4.19 (t,  $J = 5.9$  Hz, 2 H), 3.79 (t,  $J = 6.3$  Hz, 2 H), 2.59 (s, 3 H), 2.25 (m, 2 H).

A suspension of 2-[4-(3-chloropropoxy)phenyl]-8-methylimidazo[1,2-*a*]pyridine (4.5 g, 14.3 mmol) in dibutylamine (30 mL) was stirred at reflux for 5 h. The excess dibutylamine was removed by distillation, and the resulting oil was flash chromatographed (silica gel, 9:1  $\text{CH}_2\text{Cl}_2$ -acetone) to give the free base of the title compound (2.1 g, 37%) as an oil. Dropwise addition of concentrated HCl to a solution of the free base in methanol, concentration of the solution, and recrystallization of the isolated product from methanol-acetone yielded 2 as the HCl salt as a white crystalline solid: mp 214–7 °C; IR (KBr) 3420, 2960, 1650, 1615  $\text{cm}^{-1}$ ; mass spectrum,  $m/z$  393 ( $\text{M}^+$ );  $^1\text{H}$  NMR ( $\text{CD}_3\text{OD}$ )  $\delta$  8.25 (d,  $J = 8$  Hz, 1 H), 8.06 (s, 1 H), 7.92–7.49 (m, 5 H), 7.18 (d,  $J = 8$  Hz, 1 H), 4.13 (t,  $J = 4.6$  Hz, 2 H), 3.00–2.81 (m, 6 H), 2.59 (s, 3 H), 2.25 (m, 2 H), 1.82–1.34 (m, 8 H), 1.01 (m, 6 H). Anal. ( $\text{C}_{25}\text{H}_{35}\text{N}_3\text{O}\cdot 3\text{HCl}$ ) C, H, N.

**Procedure B.  $\beta$ -Bromo- $\alpha$ -keto-4-(3-chloropropoxy)propiofenone (VIc).** To a solution of  $\alpha$ -bromo-4-(3-chloropropoxy)propiofenone (60 g, 0.20 mol) in dimethylformamide (120 mL) was slowly added an aqueous solution of sodium hy-

(14) Dubinsky, B.; Shriver, D. A.; Sanfilippo, P. J.; Press, J. B.; Schupsky, J.; Tobia, A. J. *Drug Dev. Res.*, in press.

dioxide (8.6 g, 0.20 mol, in 50 mL of water). The mixture was stirred at room temperature for 30 min, diluted with diethyl ether (500 mL), and washed with water (1 × 500 mL). The ether layer was dried over MgSO<sub>4</sub>, filtered, and concentrated to give the  $\alpha$ -hydroxy ketone (30.5 g, 65%) as a yellow oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  7.93 (d,  $J$  = 8.9 Hz, 2 H), 6.98 (d,  $J$  = 8.9 Hz, 2 H), 5.12 (m, 1 H), 4.21 (t,  $J$  = 5.9 Hz, 2 H), 3.77 (t,  $J$  = 6.2 Hz, 2 H), 2.28 (m, 2 H), 1.46 (d,  $J$  = 6.9 Hz, 3 H).

To a solution of the  $\alpha$ -hydroxy ketone (30.5 g, 0.13 mol) in methylene chloride (250 mL) was added pyridinium chlorochromate (41 g, 0.19 mol) portionwise. The mixture was stirred at room temperature for 24 h, filtered through Celite, and concentrated. The dark oil was taken up in diethyl ether (500 mL), and the resulting solution was filtered through Celite and concentrated to give the diketone (18.7 g, 62%) as an amber oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.03 (d,  $J$  = 8.9 Hz, 2 H), 6.96 (d,  $J$  = 8.9 Hz, 2 H), 4.21 (t,  $J$  = 5.9 Hz, 2 H), 3.76 (t,  $J$  = 6.2 Hz, 2 H), 2.51 (s, 3 H), 2.27 (m, 2 H).

To a solution of the diketone (18.7 g, 77.9 mmol) in diethyl ether (300 mL) was added bromine (4.0 mL, 77.9 mmol) dropwise. The solution was stirred at room temperature for 24 h and then poured into an aqueous saturated sodium bicarbonate solution (500 mL). The organic layer was separated, washed with an aqueous sodium bicarbonate solution (500 mL), dried over MgSO<sub>4</sub>, filtered, and concentrated to give VIc (24.4 g, 98%) as an amber oil: <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.02 (d,  $J$  = 8.9 Hz, 2 H), 6.99 (d,  $J$  = 8.9 Hz, 2 H), 4.40 (s, 2 H), 4.23 (t,  $J$  = 7.5 Hz, 2 H), 3.76 (t,  $J$  = 7.5 Hz, 2 H), 2.70 (m, 2 H).

**2-[4-(Chloropropoxy)benzoyl]-8-methylimidazo[1,2-*a*]pyridine (VIIb).** A solution of 2-amino-3-picoline (1.6 g, 14.7 mmol) and VIc (4.7 g, 14.7 mmol) in ethanol (50 mL) was stirred at reflux for 3 h. The mixture was concentrated, and the resulting semisolid was collected and recrystallized from methanol-acetone to give VIIb as an off-white solid (2.4 g, 41%): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  9.94 (s, 1 H), 9.59 (d,  $J$  = 7.4 Hz, 1 H), 8.21 (d,  $J$  = 8.8 Hz, 2 H), 7.73 (m, 1 H), 7.10 (d,  $J$  = 8.8 Hz, 2 H), 6.74 (t,  $J$  = 6.9 Hz, 1 H), 4.25 (t,  $J$  = 5.7 Hz, 2 H), 3.77 (t,  $J$  = 6.2 Hz, 2 H), 2.76 (s, 3 H), 2.30 (m, 2 H).

**2-[4-[(Dibutylamino)propoxy]benzoyl]-8-methylimidazo[1,2-*a*]pyridine (6).** Reaction of VIIb with dibutylamine and workup as described in procedure A yielded compound 6 in 99% yield: mp 159–161 °C; IR (KBr) 3420, 1650 cm<sup>-1</sup>; mass spectrum,  $m/z$  421 (M<sup>+</sup>); <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  8.89 (s, 1 H), 8.72 (d,  $J$  = 6.6 Hz, 1 H), 8.15 (d,  $J$  = 8.9 Hz, 2 H), 7.89 (d,  $J$  = 7.3 Hz, 1 H), 7.48 (t,  $J$  = 6.9 Hz, 1 H), 7.21 (d,  $J$  = 8.9 Hz, 2 H), 4.29 (t,  $J$  = 7 Hz, 2 H), 3.26 (m, 6 H), 2.73 (s, 3 H), 2.33 (m, 2 H), 1.79–1.35 (m, 8 H), 1.02 (m, 6 H). Anal. (C<sub>26</sub>H<sub>35</sub>N<sub>3</sub>O<sub>2</sub>·3HCl·H<sub>2</sub>O) C, H, N.

**Procedure C. *N,N*-Dimethyl-*N'*-(3-methylpyridyl)formamide (VIII).** To a solution of 2-amino-3-picoline (5.0 g, 46 mmol) in toluene (60 mL) was added the dimethylformamide dimethyl acetal (7.9 g, 66.2 mmol) dropwise, and the mixture was stirred at reflux for 6 h. The mixture was concentrated to give VIII as an oil (7.0 g, 94%): <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  8.33 (s, 1 H), 8.12–8.05 (m, 1 H), 7.42–7.33 (m, 1 H), 6.79 (dd,  $J$  = 4.9 Hz, 1 H), 3.08 (s, 6 H), 2.30 (s, 3 H).

In a similar manner *N,N*-dimethyl-*N'*-pyrimidylformamide (VIII) was prepared from 2-aminopyrimidine (5.0 g, 52 mmol) and dimethylformamide dimethyl acetal (12.5 g, 0.11 mol) to give 8.0 g (100%) of the amidine VIII as a white solid: <sup>1</sup>H NMR (DMSO)  $\delta$  8.64 (s, 1 H), 8.48 (d,  $J$  = 4.8 Hz, 2 H), 6.95 (t,  $J$  = 4.8 Hz, 1 H), 3.16 (s, 3 H) 3.12 (s, 3 H).

**3-(4-Hydroxybenzoyl)-8-methylimidazo[1,2-*a*]pyridine (IX).** A mixture of *N,N*-dimethyl-*N'*-(3-methylpyridyl)formamide (VIII) (2.8 g, 17 mmol) and  $\alpha$ -bromo-4-hydroxyacetophenone (3.6 g, 17 mmol) in ethanol (10 mL) was stirred at reflux for 2 h. The mixture was cooled to room temperature, and the resulting precipitate was collected by filtration and washed with cold ethanol to give IX (2.6 g, 63%): <sup>1</sup>H NMR (DMSO)  $\delta$  9.68 (d,  $J$  = 8 Hz, 1 H), 8.74 (s, 1 H), 8.00–7.61 (m, 4 H), 7.21 (d,  $J$  = 7.2 Hz, 2 H), 2.74 (s, 3 H).

In a similar manner 3-(4-hydroxybenzoyl)imidazo[1,2-*a*]pyrimidine (IX) was prepared from *N,N*-dimethyl-*N'*-pyrimidylformamide (VIII) (3.5 g, 23 mmol) and  $\alpha$ -bromo-4-hydroxyacetophenone (5.0 g, 23 mmol) to give 3-(4-hydroxybenzoyl)imidazo[1,2-*a*]pyrimidine (IX) (3.4 g, 76%): <sup>1</sup>H NMR (DMSO)  $\delta$  9.73–8.76 (m, 2 H), 8.19 (s, 1 H), 7.62 (d,  $J$  = 8.0 Hz, 2 H), 7.26 (m, 1 H), 6.16 (d,  $J$  = 8.0 Hz, 2 H).

**3-[4-[(Dibutylamino)propoxy]benzoyl]-8-methylimidazo[1,2-*a*]pyridine (9).** A mixture of 3-(4-hydroxybenzoyl)-8-methylimidazo[1,2-*a*]pyridine (2.3 g, 9.6 mmol), 3-(dibutylamino)propyl 1-chloride (6.8 g, 33 mmol), and potassium hydroxide (1.3 g, 23 mmol) in methanol (60 mL) was stirred at reflux for 96 h. The mixture was concentrated, and the resulting oil was flash chromatographed (silica gel, 2.5% MeOH in Et<sub>2</sub>O) to give the free base of the title compound (1.3 g, 31%). Dropwise addition of concentrated HCl to a solution of the free base in methanol, concentration of the solution, and recrystallization of the isolated product from acetone-ether gave the HCl salt of 9 as an off-white solid: mp 105–107 °C; IR (KBr) 3440, 2640, 1645, 1605 cm<sup>-1</sup>; mass spectrum,  $m/z$  421 (M<sup>+</sup>); <sup>1</sup>H NMR (CD<sub>3</sub>OD)  $\delta$  9.66 (d,  $J$  = 8 Hz, 1 H), 8.74 (s, 1 H) 8.00–7.61 (m, 4 H), 7.20 (d,  $J$  = 7.2 Hz, 2 H), 4.29 (t,  $J$  = 5 Hz, 2 H), 3.41–3.15 (m, 6 H), 2.75 (s, 3 H), 2.31 (m, 2 H), 1.80–1.42 (m, 8 H), 1.02 (m, 6 H). Anal. (C<sub>26</sub>H<sub>35</sub>N<sub>3</sub>O<sub>3</sub>·2HCl) C, H, N.

**Calcium Channel Blocking Activity.** The nitrendipine binding assay was performed on female, New Zealand white rabbits (1–2 kg), which were sacrificed by cervical dislocation.<sup>15,16</sup> The heart was immediately removed, cleaned, and chopped into small pieces. The tissue was homogenized in 5X volume of 0.05 M Hepes buffer, pH 7.4. The homogenate was centrifuged at 4000g for 10 min; the supernatant was recentrifuged at 42000g for 90 min. The resulting membrane pellet was resuspended (0.7 mL/g weight in 0.05 M Hepes, pH 7.4) and stored at -70 °C until used. Each tube of the binding assay contained [<sup>3</sup>H]nitrendipine (0.05–0.50 nM), buffer, membranes (0.10 mL), and test compound in a total volume of 1.0 mL. After 90 min at 4 °C, the bound nitrendipine was separated from the unbound by filtration on Whatman GF/C fibers. After rinsing, the filters were dried and counted in a liquid scintillation counter. Nonspecific binding of [<sup>3</sup>H]nitrendipine (that amount bound in the presence of excess unlabeled nitrendipine) is subtracted from the total bound to obtain specifically bound radiolabeled nitrendipine. The amount of specifically bound nitrendipine in the presence of a test compound is compared to that amount bound in the absence of a compound. A percent displacement (or inhibition) can then be obtained.

The inhibition of calcium dependent smooth muscle contraction was measured with the trachea from dogs sacrificed by excess KCl injection and stored overnight at 4 °C in oxygenated Krebs-Henseleit buffer.<sup>17,18</sup> Tracheal rings, one cartilage segment wide (5–10 mm), were cut, starting from the bronchial end. After cutting the cartilage, the trachealis muscle tissue was suspended in oxygenated Krebs-Henseleit buffer at 37 °C in a 25-mL tissue bath. After a 60-min equilibration period, the tissues were challenged with 10  $\mu$ M carbachol. After 5 min the tissues were rinsed and allowed to rest for 50 min. The tissues were then challenged with 50 mM KCl, and after 30 min, the contractions were quantitated. The tissues were then rinsed and reequilibrated for 50 min. Test compounds were then added for 10 min, and the tissue was rechallenged with 50 mM KCl. After 30 min, the contraction was recorded and used to determine the percent inhibition of control.

The percent inhibition of smooth muscle contraction is calculated from response data before and after drug treatment.

$$\% \text{ inhibition} = 100 - 100(\text{peak response after drug treatment}) / (\text{peak response before drug treatment})$$

**Local Anesthetic Activity in the Mouse Horizontal Screen Test.** Local anesthetic activity was determined in groups of three male CD-1 mice (18–29 g), which were deprived of food but not water for 18 h before use. Water was withheld during the experiment. The ability of the animals to grasp an inverted wire-mesh screen (0.8-mm diameter wire; 0.25-in. mesh) was evaluated, and mice that were capable of grasping the wire screen with the

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- (16) Gould, R.; Murphy, K. M. M.; Snyder, S. *Mol. Pharmacol.* 1984, 25, 235.
- (17) Creese, B. R.; Denborough, M. A. *Clin. Exp. Pharmacol. Physiol.* 1981, 8, 175.
- (18) Weiss, G. B.; Pang, I. H.; Goodman, F. R. *J. Pharmacol. Exp. Ther.* 1985, 233, 289.

toes of all four legs were used for drug evaluation. A test compound was injected intramuscularly (0.05 mL, dose volume) into the thigh in one hind leg, in the region of the sciatic nerve. The vehicle (aqueous 0.5%, w/v, methylcellulose solution, containing 0.4% w/v, Tween-80) was administered to a separate group of mice. Mice were individually placed on the wire-mesh screen after being treated with test substances. Animals were tested at several time periods after drug administration, and the number of animals that were not able to grasp the screen with the toes of the injected leg (the local anesthetic response) was recorded. Each compound was administered as the HCl salt, and doses were calculated as the active moieties.

**Registry No.** 1, 114604-40-9; 1·3HCl, 114604-54-5; 2, 114604-41-0; 2·3HCl, 114604-55-6; 3, 114604-43-2; 3·3HCl, 114604-57-8; 4, 114604-59-0; 4·HCl, 115406-99-0; 5, 114604-42-1; 5·2HCl, 114604-56-7; 6, 114604-47-6; 6·3HCl, 114604-62-5; 7, 114604-49-8; 7·3HCl, 114604-64-7; 8, 114604-51-2; 8·2HCl, 114604-66-9; 9, 114604-52-3; 9·3HCl, 114621-58-8; 10, 114604-53-4; 10·3HCl, 114604-67-0; 11, 115407-33-5; 11·2HCl, 115407-47-1; 12, 115407-34-6; 12·2HCl, 115407-48-2; 13, 115407-35-7; 13·2HCl, 115407-49-3; 14, 115407-36-8; 14·2HCl, 115407-50-6; 15, 115407-37-9; 15·HCl, 115407-51-7; 16, 115407-38-0; 16·2HCl, 115407-52-8; 17, 115407-39-1; 17·3HCl, 115407-53-9; 18, 115407-42-6; 18·2HCl, 115407-54-0; 19, 115407-43-7; 19·3HCl, 115407-55-1; 20, 114604-44-3; 20·3HCl, 114604-61-4; 21, 114604-45-4; 21·3HCl, 114604-58-9; 22, 115407-17-5; 22·3HCl, 115407-00-6; 23, 115407-18-6; 23·3HCl, 115407-01-7; 24, 115419-73-3; 24·3HCl, 115407-02-8; 25, 115407-19-7; 25·3HCl, 115407-03-9; 26, 115407-20-0; 26·3HCl, 115407-04-0; 27, 115407-21-1; 27·3HCl, 115407-05-1; 28, 115407-22-2; 28·3HCl, 115407-06-2; 29, 115407-23-3; 29·3HCl, 115407-07-3; 30, 115407-24-4; 30·3HCl, 115407-08-4; 31, 115407-25-5; 31·3HCl, 115407-09-5; 32, 115407-26-6; 32·3HCl, 115407-10-8; 33, 115407-27-7; 33·3HCl, 115407-11-9; 34, 115407-28-8; 34·3HCl, 115407-12-0; 35, 115407-29-9; 35·3HCl, 115407-13-1; VIa, 114604-68-1; VIb, 114604-75-0;

VIc, 115354-34-2; H<sub>3</sub>CCH(OH)CO-*p*-C<sub>6</sub>H<sub>4</sub>O(CH<sub>2</sub>)<sub>3</sub>Cl, 114604-77-2; H<sub>3</sub>CCOCO-*p*-C<sub>6</sub>H<sub>4</sub>O(CH<sub>2</sub>)<sub>3</sub>Cl, 115354-33-1; 4-hydroxyacetophenone, 99-93-4; 1-bromo-3-chloropropane, 109-70-6; 4-(3-chloropropoxy)acetophenone, 91427-23-5; 2-amino-3-picoline, 1603-40-3; 2-amino-4-picoline, 695-34-1; 2-amino-3-(benzyloxy)pyridine, 24016-03-3; 2-amino-5-bromopyridine, 1072-97-5; 2-amino-1,3-thiazole, 96-50-4; 2-amino-5-methyl-1,3,4-thiadiazole, 108-33-8; 2-amino-1,3-benzothiazole, 136-95-8; 3-amino-1,2,4-triazine, 1120-99-6; 2-amino-1,3-pyrimidine, 109-12-6; 2-amino-6-methyl-1,3-pyrimidine, 108-52-1; 2-[4-(chloropropoxy)phenyl]-8-methylimidazo[1,2-*a*]pyridine, 114604-70-5; 2-[4-(chloropropoxy)phenyl]-7-methylimidazo[1,2-*a*]pyridine, 114604-72-7; 2-[4-(chloropropoxy)phenyl]-7-(benzyloxy)imidazo[1,2-*a*]pyridine, 114604-74-9; 6-bromo-2-[4-(chloropropoxy)phenyl]imidazo[1,2-*a*]pyridine, 114604-71-6; 6-[4-(chloropropoxy)phenyl]imidazo[2,1-*b*]thiazole, 115407-44-8; 6-[4-(chloropropoxy)phenyl]-2-methylimidazo[2,1-*b*]-1,3,4-thiadiazole, 115407-45-9; 2-[4-(chloropropoxy)phenyl]imidazo[2,1-*b*]benzothiazole, 115407-46-0; 6-[4-(chloropropoxy)phenyl]imidazo[1,2-*b*]triazine, 115407-30-2; 2-[4-(chloropropoxy)phenyl]imidazo[1,2-*a*]pyrimidine, 115407-31-3; 2-[4-(chloropropoxy)phenyl]-7-methylimidazo[1,2-*a*]pyrimidine, 115407-32-4; 2-aminopyridine, 504-29-0; 2-[4-(chloropropoxy)phenyl]imidazo[1,2-*a*]pyridine, 114604-69-2; dibutylamine, 111-92-2; 2-[4-(chloropropoxy)benzoyl]-8-methylimidazo[1,2-*a*]pyridine, 114604-80-7; 2-[4-(chloropropoxy)benzoyl]-7-methylimidazo[1,2-*a*]pyridine, 115407-14-2; 6-bromo-2-[4-(chloropropoxy)benzoyl]imidazo[1,2-*a*]pyridine, 115407-15-3; *N,N*-dimethyl-*N'*-(3-methylpyridyl)-formamide, 36172-55-1; *N,N*-dimethyl-*N'*-pyrimidylformamide, 6578-34-3; *α*-bromo-4-hydroxyacetophenone, 2491-38-5; 3-(4-hydroxybenzoyl)-8-methylimidazo[1,2-*a*]pyridine, 114604-81-8; 3-(4-hydroxybenzoyl)imidazo[1,2-*a*]pyrimidine, 115407-40-4; 3-(dibutylamino)propyl chloride, 36421-15-5; 6-bromo-3-(4-hydroxybenzoyl)imidazo[1,2-*a*]pyridine, 115407-16-4; 3-(4-hydroxybenzoyl)-7-methylimidazo[1,2-*a*]pyrimidine, 115407-41-5.

## Additions and Corrections

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**David B. Kanne\*** and **Leo G. Abood**: Synthesis and Biological Characterization of Pyridohomotropans. Structure-Activity Relationships of Conformationally Restricted Nicotinoids.

Page 506. The tropane derived name for structure **3a** should read "pyrido[3,4-*b*]norhomotropane" (instead of "pyrido[3,4-*b*]homotropane"). The correct tropane derived names for **3b** and **3c** are "2'-methylpyrido[3,4-*b*]norhomotropane" and "pyrido[3,4-*b*]homotropane", respectively.

**Andre Rosowsky,\* Henry Bader, William Kohler, James H. Freisheim, and Richard G. Moran**: Methotrexate Analogues. 34. Replacement of the Glutamate Moiety in Methotrexate and Aminopterin by Long-Chain 2-Aminoalkanedioic Acids.

Page 1344. The registry numbers for compounds **21-24** should be as follows: **21**, 95485-01-1; **22**, 113976-36-6; **23**, 113976-37-7; **24**, 113976-38-8.

**James Burton,\* Stephen G. Wood, Mary Lynch, and Andrew G. Plaut**: Substrate Analogue Inhibitors of the IgA1 Proteinases from *Neisseria gonorrhoeae*.

Page 1651. Corrected registry numbers are as follows: HRP-18 (tritium labeled), 116099-30-0; HRP-19 (tritium labeled), 116099-31-1; HRP-20 (tritium labeled), 116099-32-2; HRP-21 (tritium labeled), 116099-33-3; HRP-25 (tritium labeled), 116099-29-7; HRP-59 (tritium labeled), 114819-68-0; HRP-61 (tritium labeled), 114819-70-4; HRP-62 (tritium labeled), 114791-18-3; HRP-63 (tritium labeled), 114791-19-4; HRP-64 (tritium labeled), 114791-20-7.