gel chromatography column (2 × 25 cm) using ammonium acetate buffer (0.01 M, pH 5.5)/methanol (30:70, v/v, for I and 40:60 for II) as eluents. The purity of metabolites was checked by analytical HPLC.

Characterization of I and II (from in vitro and in vivo materials) was made by comparison with UV-visible, EI mass, proton NMR spectra of authentics **3** and **4**. Physicochemical data of I: MS, m/z 262 ($M^{+\cdot}$); NMR (CD_3OD, I was recorded as acetate salt; see Figure 5) δ 2.80 (s, 3p, Me_1 or Me_5), 3.09 (s, 3p, Me_5 or Me_1), 7.05 (dd, J = 8.8 and 2.2. Hz, 1p, H_9), 7.37 (d, J = 8.8 Hz, 1p, H_7), 7.66 (d, J = 2.2 Hz, 1p, H_{10}), 7.92 (d, J = 6.6 Hz, 1p, H_4), 8.12 (d, J = 6.6. Hz, 1p, H_3), 8.75 (s, 1p, H_{11}); UV-visible (methanol) λ_{max} 230, 239, 272, 293, 329, 399. Physicochemical data of II: MS, m/z 262 ($M^{+\cdot}$); NMR (CD_3OD, II was recorded as acetate salt; see Figure 5) δ 2.87 (s, 3p, Me_1 or Me_5), 3.08 (s, 3p, Me_5 or Me_1), 6.96 (d, J = 7.3 Hz, 1p, H_{10}), 7.09 (m, 1p, H_9), 7.79 (d, J = 8.1 Hz, 1p, H_8), 7.91 (d, J = 5.1 Hz, 1p, H_4), 8.16 (d, J = 5.1 Hz, 1p, H_3), 8.84 (s, 1p, H_{11}); UV-visible (methanol) λ_{max} 229, 241, 283, 328, 384.

Cytotoxic and Antitumor Activities. The inhibitory efficiency of cell growth was determined with L1210 leukemia cells in vitro as previously described[18] and expressed in terms of ID_{50} (inhibition dose 50), the drug concentration that reduces the number of cells by 50% as compared to the control, after 48 h to drug exposure. The antitumoral efficiency is expressed in terms of ILS (increase of life span), defined as [(median survival time in treated animals) − (median survival time in controls)/median survival time in controls] × 100. DBA/2 mice were treated with drug 24 h after intraperitoneal inoculation of 10^5 L1210 cells.

Acknowledgment. Dr. S. Cros and J. François are gratefully acknowledged for the determination of cytotoxic and antitumor data and J. Bonnefoux for technical assistance. We express our gratitude for invaluable comments from the three referees.

Registry No. **3**, 70173-18-1; **4**, 83201-13-2; **8a**, 1006-94-6; **8b**, 3189-22-8; **9**, 60553-32-4; **10a**, 79853-92-2; **10b**, 95589-85-8; **11a**, 93841-60-2; **11b**, 95589-86-9; **12a**, 94200-72-3; **13a**, 95589-87-0; **13b**, 95589-88-1; **14a**, 16101-08-9; **14b**, 95589-89-2; 4-acetylpyridine ethylene, 60553-33-5; 4-acetylpyridine ethylene ketal methyl iodide, 60553-34-6; olivacine, 484-49-1.

New Antiarrhythmic Agents. *N*-Aryl-8-pyrrolizidinealkanamides[1]

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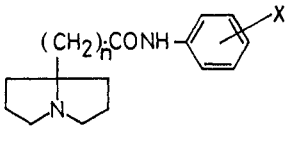
The synthesis and antiarrhythmic activity of *N*-aryl-8-pyrrolizidinealkanamides are described. The target compounds were evaluated for their ability to protect against chloroform-induced fibrillation in mice. Many of them were found to have antifibrillatory activity comparable to that of lidocaine; several are more potent than lidocaine. *N*-(2,6-Dimethylphenyl)-8-pyrrolizidineacetamide (**6n**), which was found to be more potent and less toxic (LD_{50}) than lidocaine, also showed a long duration of action in dogs with ventricular arrhythmias after oral administration.

Much research[2] has been done on the relationships between local anesthetics and their chemically related antiarrhythmic agents, and structural modifications of local anesthetics including amide groups, i.e., lidocaine and procainamide, as well as a large number of compounds[3] are attracting considerable attention.[4] The study of quantitative structure–activity relationships (QSAR)[4b] of the antiarrhythmic activity of aminoxylides has suggested that the pK_a value has an important effect on the biological properties of the molecule.[5] Consequently we have chosen pyrrolizidine as the prospective moiety[6] to be included in the molecule. Our recent synthetic accomplishments[7] that made available a number of bicyclic amines with a bridgehead nitrogen[8] led us to attempt an introduction of these amines as a moiety of lidocaine-type antiarrhythmic agents.

We report here the results of pharmacological screening tests in mice on the antiarrhythmic activity of a new "amide-type" pyrrolizidine series, which is represented by the general formula **1**.



1

n = 1 or 2

Chemistry. The synthetic routes to the target compounds are outlined in Scheme I. Compounds **4** and **5**,

[†] Fukuoka University.
[‡] Suntory Institute for Biomedical Research.

(1) Part 7 in the series of studies on pyrrolizidines and related compounds. For part 6, see: Miyano, S.; Mibu, N.; Fujii, S.; Yamashita, O.; Annoura, H.; Sumoto, K. *Heterocycles* **1983**, *20*, 2197.
(2) (a) Ye, J. E.; Narahashi, T. *J. Pharmacol. Exp. Ther.* **1976**, *196*, 62. (b) Baines, M. W.; Davies, J. E.; Kellett, D. N.; Munt, P. L. *J. Int. Med. Res.* **1976**, *4* (Suppl 1), 5. (c) Bassett, A. L.; Wit, A. L. *Prog. Drug. Res.* **1973**, *17*, 33. (c) Singh, B. N.; Williams, E. M. V. *Br. J. Pharmacol.* **1972**, *44*, 1. (e) Fasola, A. F.; Carmichael, R. *Acta Cardiol.* **1974**, *18*, 317. (f) Papp, J. G.; Williams, E. M. V. *Br. J. Pharmacol.* **1969**, *37*, 380. (g) Lanzoni, V.; Clark, B. B. *Circ. Res.* **1955**, *3*, 335.
(3) For example: (a) Morgan, P. H.; Mathison, I. W. *J. Pharm. Sci.* **1976**, *65*, 635. (b) Banitt, E. H.; Bronn, W. R.; Coyne, W. E.; Schmid, J. R. *J. Med. Chem.* **1977**, *20*, 821. (c) Kesteloot, H.; Stroobandt, R. *Arch. Int. Pharmacodyn. Ther.* **1977**, *230*, 225. (d) Ruenitz, P. C.; Mokler, C. M. *J. Med. Chem.* **1979**, *22*, 1142.
(4) (a) Tenthorey, P. A.; Adams, H. J.; Kronberg, G. H.; Takman, B. H. *J. Med. Chem.* **1981**, *24*, 1059. (b) Tenthorey, P. A.; Block, A. J.; Ronfeld, R. A.; McMaster, P. D.; Byrnes, E. W. *J. Med. Chem.* **1981**, *24*, 798. (c) McMaster, P. D.; Byrnes, E. W.; Block, A. J.; Tenthorey, P. A. *J. Med. Chem.* **1981**, *24*, 53. (d) Tenthorey, P. A.; Ronfeld, R. A.; Feldman, H. S.; Sandberg, R. V.; McMaster, P. D.; Smith, E. R. *J. Med. Chem.* **1981**, *24*, 47. (e) Tenthorey, P. A.; DiRubio, R. L.; Feldman, H. S.; Takman, B. H.; Byrnes, E. W.; McMaster, P. D. *J. Med. Chem.* **1979**, *22*, 1182. (f) McMaster, P. D.; Byrnes, E. W.; Feldman, H. S.; Takman, B. H.; Tenthorey, P. A. *J. Med. Chem.* **1979**, *22*, 1177. (g) Byrnes, E. W.; McMaster, P. D.; Smith, E. R.; Blair, M. R.; Boyes, R. N.; Duce, B. R.; Feldman, H. S.; Kronberg, G. H.; Takman, B. H.; Tenthorey, P. A. *J. Med. Chem.* **1979**, *22*, 1171.

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Scheme I

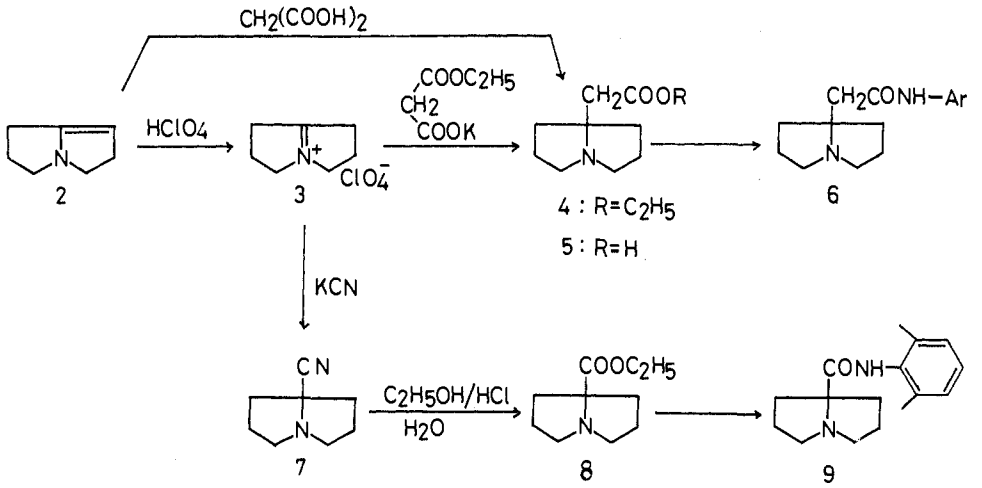
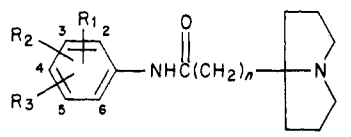


Table I. Structures, Physical Properties, and Yields of Target Compounds



compd	R_1	R_2	R_3	n	method	yield, %	formula[a]	mp,[b] °C	anal.
6a	H	H	H	1	A	26	$C_{15}H_{20}N_2O\cdot HCl$	206–207	C, H, N
6b	2-Br	H	H	1	A	64	$C_{15}H_{19}N_2OBr\cdot HCl$	237–239	C, H, N
6c	2-Cl	H	H	1	A	79	$C_{15}H_{19}N_2OCl\cdot HCl$	222–224	C, H, N
6d	2-Cl	6-Cl	H	1	A	56	$C_{15}H_{18}N_2OCl_2\cdot HCl$	229–231	C, H, N
6e	2-Me	H	H	1	A	63	$C_{16}H_{22}N_2O\cdot HCl$	179–181	C, H, N
6f	4-Me	H	H	1	A	74	$C_{16}H_{22}N_2O\cdot HCl$	222–227	C, H, N
6g	2-NH_2	H	H	1	A	44	$C_{15}H_{21}N_3O\cdot 2C_6H_3N_3O_7$[c]	191.5–196	C, H, N
6h	4-NH_2	H	H	1	A	49	$C_{15}H_{21}N_3O\cdot 2HCl\cdot xH_2O$[d]	207–212	*d*
6i	2-OMe	H	H	1	A	51	$C_{16}H_{22}N_2O_2\cdot HCl$	189–196	C, H, N
6j	3-OMe	H	H	1	A	79	$C_{16}H_{22}N_2O_2\cdot HCl$	143.5–145	C, H, N
6k	4-OMe	H	H	1	A	72	$C_{16}H_{22}N_2O_2\cdot HCl$	201–204	C, H, N
6l	2-Me	3-Me	H	1	A	39	$C_{17}H_{24}N_2O\cdot HCl$	210–215	C, H, N
6m	2-Me	5-Me	H	1	A	57	$C_{17}H_{24}N_2O\cdot HCl$	211–212	C, H, N
6n	2-Me	6-Me	H	1	A (B)	80 (83)	$C_{17}H_{24}N_2O\cdot HCl\cdot {}^1/_2H_2O$	212–214	C, H, N
6o	3-Me	4-Me	H	1	A	48	$C_{17}H_{24}N_2O\cdot HCl$	207–209.5	C, H, N
6p	3-Me	5-Me	H	1	A	40	$C_{17}H_{24}N_2O\cdot HCl$	214–216	C, H, N
6q	2-Et	6-Et	H	1	A	61	$C_{19}H_{28}N_2O\cdot HCl$	217–218	C, H, N
6r	2-OMe	5-OMe	H	1	A	42	$C_{17}H_{24}N_2O_3\cdot HCl\cdot H_2O$	73–77	C, H, N
6s	2-Me	4-Me	6-Me	1	A	49	$C_{19}H_{28}N_2O\cdot HCl$	226–228	C, H, N
9	2-Me	6-Me	H	0	C	74	$C_{16}H_{22}N_2O\cdot HCl\cdot xH_2O$[d]	127–130	*d*

[a] All compounds are hydrochloride salts with the exception of compound **6g**. [b] Compounds were recrystallized from EtOH/Et_2O. [c] Dipicrate salt. [d] Consistent and correct results could not be obtained because the compound is extremely hygroscopic.

both of which are easily available by the chemical transformation of $\Delta^{1(8)}$-dehydropyrrolizidine (**2**),[9] are the key intermediates for the target compounds with the exception of compound **9**. Treatment of compound **4** with various substituted anilines in the presence of sodium hydride in dioxane affords the target compounds **6** in moderate to good yields (method A).

The alternate route via compound **5** consists of acyl chloride formation with oxalyl chloride followed by treatment with anilines (method B). On the other hand, compound **9** could be obtained by the treatment of ethyl 8-pyrrolizidinecarboxylate (**8**), which is also derived from perchlorate **3**.[7]

The yields and physical properties of these target compounds are summarized in Table I. Details of the synthetic work are published elsewhere.[7,9,10] The Experimental Section describes the synthesis of new target compounds, as well as improvement in methodology.

Results and Discussion

The physical properties of the target compounds are listed in Table I. Antiarrhythmic effect (ED_{50}), acute toxicity (LD_{50}) (both determined in mice), and the LD_{50}/ED_{50} ratio are summarized in Table II. The results

(5) In ref 4b, Tenthorey et al. suggested that antiarrhythmic potency can be enhanced by increasing lipophilicity, while the therapeutic index can be improved by increasing the pK_a value.

(6) Regarding the properties including the basicity of pyrrolizidine and its homologues, see the following reviews: (a) Neuberger, A.; Tatum, E. L. *Front. Biol.* **1968**, *9*. (b) Skvortsov, I. M. *Russ. Chem. Rev.* **1979**, *48*(3), 262.

(7) Miyano, S.; Yamashita, O.; Fujii, S.; Somehara, T.; Sumoto, K.; Satoh, F.; Masuda, T. *Heterocycles* **1981**, *16*, 755.

(8) The pyrrolizidine skeleton exists mainly in the cis-fused ring conformation with pseudorotation occurring in each ring and usually shows high basicity: (a) Leonard, N. J.; Beck, K. M. *J. Am. Chem. Soc.* **1948**, *70*, 2504. (b) Skvortsov, I. M.; Antipova, I. V. *Khim. Geterotsikl. Soed.* **1976**, 1061.

(9) Miyano, S.; Somehara, T.; Nakao, M.; Sumoto, K. *Synthesis* **1978**, 701.

(10) Miyano, S.; Sumoto, K.; Morita, M.; Satoh, K. JP Patent Appl. 57-42297.

Table II. Antiarrhythmic Potencies and LD_{50} of Target Compounds

compd	ED_{50},[a-c] mg/kg	LD_{50},[c] mg/kg	potency[d]	LD_{50}/ED_{50}
6a	no effect	*i*	*i*	*i*
6b	59 (38.1–91.5)	445	0.76	7.54
6c	100[e,g]	347	*i*	*i*
6d	100[e,g]	200	*i*	*i*
6e	100[f,g]	385	*i*	*i*
6f	100[e,g]	413	*i*	*i*
6g	100	633	0.90	6.33
6h	*h*	12	*i*	*i*
6i	100[f,g]	381	*i*	*i*
6j	100[f,g]	417	*i*	*i*
6k	60 (21.7–100.2)	288	0.60	4.80
6l	64 (40.8–100.5)	469	0.56	7.33
6m	72 (41.1–126)	400	0.50	5.56
6n	24 (11.5–50.2)	410	1.51	17.08
6o	76 (59.4–97.8)	559	0.47	7.36
6p	52 (34.9–77.5)	355	0.69	6.83
6q	28 (20.1–38.9)	278	1.41	9.93
6r	90 (71.4–113.4)	203	0.44	2.26
6s	34 (19.4–59.5)	309	1.22	9.09
9	100[e,g]	603	*i*	*i*
lidocaine	29 (20–41)	238	1.00	8.21

[a] Details of the test method are described in the Experimental Section. [b] Figures in parentheses are 95% confidence limits. Subcutaneous administration. [c] Estimated in the mouse. [d] The data are expressed on a molar basis: potency = ED_{50} (mmol/kg) of lidocaine/ED_{50} (mmol/kg) of investigated compound. [e] Values are ED_{20}. [f] Values are ED_{40}. [g] ED_{50} not determined due to poor dose–response curve. [h] ED_{50} not obtainable due to deaths at doses required for high degree of protection. [i] Not determined.

obtained with the reference compound lidocaine are also presented for comparison. Many of the target compounds synthesized were active in suppressing chloroform-induced ventricular fibrillation, and several compounds showed good separation between antiarrhythmic effect and acute toxicity. On the basis of limited biological information, a tentative conclusion regarding structure–activity relationships could be drawn.

With the exception of 2,6-dichloro **6d**, compounds **6l–s**, having two substituents (R_1, R_2) on the aromatic ring, were found to have moderate to high abilities to inhibit chloroform-induced arrhythmias ($ED_{50} \leq 90$ mg/kg). Concerning the compounds with only one additional substituent on the aromatic ring, two specific exceptions were found to be potent antiarrhythmics; namely, the 2-bromo **6b** (but not the 2-chloro) and the 4-methoxy **6k** (but not the 2- and 3-methoxy) analogues. Considering the general trend of the structure–activity relationships in the anilide series reported previously, the reason for this anomaly is not explained.[11]

In the studies regarding antiarrhythmic activity of the anilide series, it has been observed that the substitution of alkyl or aryl groups in the ortho position generally enhances the antiarrhythmic (antifibrillatory) activity, suggesting that the steric influence of two ortho substituents prevents coplanarity of the amide function and aromatic ring.[4g] The results obtained from compounds **6n**, **6q**, and **6s**, in which both ortho positions of the aromatic ring are substituted by methyl or ethyl groups, are in good agreement with this conclusion.

Interestingly, compound **9** prepared for comparison, which is the close congener of the most active compound **6n** and structurally related to lidocaine, was almost inactive (ED_{20} = 100 mg/kg). This result could be attributed to one or more differences in such factors as pK_a value,[12] lipophilicity, and conformation reflecting upon its lipophilicity.

In the current series, active compounds, e.g., **6n**, having a high LD_{50}/ED_{50} ratio indicate that the introduction of a pyrrolizidine nucleus as an amine functional group may act well to provide desirable pharmacological activity.

Judging from the additional investigation of the antiarrhythmic activity after oral administration to conscious dogs with ventricular arrhythmias induced by the method of Harris,[13] compound **6n** emerges as the most promising compound in the current series. Among the compounds tested by this route by administration at 10 mg/kg, compound **6n** was found to have the most potent activity in abolishing the arrhythmias and restoring the normal sinus rhythm. At the lower dose of 1 mg/kg, compound **6n** still displayed antiarrhythmic activity (maximum reduction of ectopic beats = 80%) and its effect (over 20% reduction of ectopic beats) was maintained for 2–5 h.[14]

The results with compound **6n** in subsequent investigations will be published elsewhere in detail.

Experimental Section

Melting points were determined on a Yanako melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 240B elemental analyzer, and NMR and IR spectra were recorded on a Hitachi MH-100 or R-24B spectrometers using tetramethylsilane as an internal standard and on a Hitachi 260-10 or a Hitachi EPI-G-3 instrument, respectively. High-resolution mass spectra were obtained with a JEOL JMS-ISG instrument with a direct inlet system at 75 eV.

Ethyl 8-Pyrrolizidineacetate (4). To a solution of potassium ethyl malonate (6.64 g, 0.039 mol) in ethanol (50 mL) was added $\Delta^{4(8)}$-dehydropyrrolizidinium perchlorate (**3**;[9] 7.0 g, 0.0334 mol) at room temperature. The resulting mixture was refluxed for 8 h and then cooled in an ice bath. After filtration of the precipitated crystals, the solvent was evaporated to give the crude product. Distillation under reduced pressure afforded 5.01 g of a colorless oil (**4**): bp 122 °C (17 mmHg); NMR ($CDCl_3$) δ 1.24 (t, 3 H, J = 7 Hz, CH_3), 4.13 (q, 2 H, J = 7 Hz, $COOCH_2$), 2.43 (s, 2 H, CH_2CO), 1.50–3.20 (m, 12 H, other aliphatic protons on pyrrolizidine nucleus); mass spectrum, m/e 197.14218 (M^+, $C_{11}H_{19}NO_2$). Anal. ($C_{11}H_{19}NO_2$) C, H, N.

8-Pyrrolizidineacetic Acid (5). To a stirred solution $\Delta^{1(8)}$-dehydropyrrolizidine[7,9] (8.8 g, 0.081 mol) in 1,4-dioxane (50 mL) was added malonic acid (8.4 g, 0.081 mol) at room temperature. The mixture was heated under reflux for 14 h and then cooled with ice, and the resulting crystals were collected by filtration. The crystals were recrystallized from acetone to afford 9.9 g of needles (66%): mp 192–194 °C; NMR ($CDCl_3$) δ 2.50 (s, 2 H, CH_2CO), 13.73 (s, 1 H, COOH), 1.3–3.9 (m, 12 H, other aliphatic protons on pyrrolizidine nucleus). The picrate of this compound melted at 159 °C. Anal. ($C_{21}H_{24}N_8O_4$) C, H, N.

Ethyl 8-Pyrrolizidinecarboxylate (8). To 100 mL of ethanol saturated with hydrogen chloride was added dropwise a solution of 8-cyanopyrrolizidine[7,9] (13.49 g, 0.099 mol) and water (1.78 mL, 0.099 mol) in ethanol (400 mL). The mixture was heated under reflux for 18 h and then cooled with an ice bath. The resulting crystals were removed by filtration, and the filtrate was evaporated to leave an oil, which was dissolved in 20% aqueous NaOH (80 mL) and extracted with chloroform. The chloroform layer was washed with saturated sodium chloride solution, dried over magnesium sulfate, and evaporated to give 14.9 g of oily material (82%). This was subjected to distillation under reduced pressure to afford a colorless oil: bp 80–81 °C (4 mmHg); NMR ($CDCl_3$) δ 1.26 (t, 3 H, J = 7 Hz, CH_3), 4.18 (q, 2 H, J = 7 Hz, $COOCH_2$),

(11) It has already been mentioned that the increasing of the size of *p*-alkoxy group enhances the potency. Such compounds reported previously, however, have simultaneously two *o*-methyl groups in the aromatic ring (see ref 4f and 4g).

(12) Compound **9** has a pK_a value of 7.75.

(13) Harris, A. S.; Estandia, A.; Ford, T. R.; Tillotson, R. F. *Circulation* **1951**, *4*, 522.

(14) Onset of action was 10–60 min (number of test animals were two).

1.20–3.34 (other aliphatic protons on the pyrrolizidine ring); mass spectrum, m/e 183 (M^+). Anal. ($C_{10}H_{17}NO_2$) C, H, N.

Synthesis of *N*-Aryl-8-pyrrolizidineacetamides (6a–s). Method A. To a stirred suspension of 1.5–2 equiv of sodium hydride (50% dispersion in oil) in 1,4-dioxane was added dropwise a solution of 1.5–2 equiv of the substituted aniline and the mixture was heated at 100 °C for 2 h. A solution of 1 equiv of compound **4** in 1,4-dioxane was added to the above-stirred mixture at room temperature and then heated at 100 °C for 2 h. The reaction mixture was poured into ice–water and extracted with ether. The ether layer was washed with 5% aqueous HCl, and the aqueous layer was neutralized with sodium bicarbonate followed by washing with ether. The resulting aqueous layer was basified with 20% NaOH and extracted with chloroform. The chloroform layer was washed with water, dried over magnesium sulfate, and evaporated to give an oily substance. This material was converted to the corresponding hydrochloride, or picrate, which was recrystallized from ethanol–ether to give colorless crystals (**6a–s**). The structures of the target compounds obtained by the above method were easily confirmed by their mass spectra [correct molecular ion], IR [1665–1685 cm^{-1} (amide C=O)], NMR ($CDCl_3$, as free base) [δ 1.2–4 (pyrrolizidine ring protons), 2.38–2.54 (s, 2 H, CH_2CO), 6.40–8.18 (introduced aromatic ring) are characteristic], and elemental analysis.

The structures, physical properties, and yields of the target compounds are summarized in Table I.

Method B. To a stirred solution of compound **5** (2.03 g, 0.012 mol) in chloroform (100 mL) was added dropwise oxalyl chloride (30 mL, 0.34 mol) at room temperature. The mixture was heated at 40 °C for 1 h and then evaporated under reduced pressure to give solid material. To a stirred solution of this material in chloroform (100 mL) was added at room temperature a substituted aniline (0.020 mol). After stirring for 1 h at room temperature, the solvent was evaporated to leave an oil. The products were purified by recrystallization or by column chromatography. When 2,6-xylidine was used as a substituted aniline, compound **6n**·HCl was obtained as crystals (81%).

***N*-(2,6-Dimethylphenyl)-8-pyrrolizidinecarboxamide (9). Method C.** To a stirred suspension of sodium hydride (50% dispersion in oil) (1.0 g, 0.0208 mol) in 1,4-dioxane was added slowly 2,6-xylidine (2.0 mL, 0.0162 mol) at room temperature, and then the mixture was heated to reflux for 2 h. A solution of compound 8 (2.0 g, 0.0109 mol) in 1,4-dioxane was added dropwise to the above reaction mixture with ice cooling and the mixture was heated under reflux for 5 h. The resulting mixture was poured into ice–water and extracted with ether. The ether layer was evaporated under reduced pressure, and the residue was converted to its hydrochloride. Purification by column chromatography on silica gel using methanol–chloroform (1:10) as eluent gave a solid, which was recrystallized from chloroform to afford compound **9** (2.39 g, 74%): mp 127–130 °C; IR (KBr) 1660 cm^{-1} (amide C=O). The free base gave the following physical data: NMR ($CDCl_3$) δ 2.20 (s, 6 H, protons of two methyl groups), 7.00 (br s, 3 H, aromatic protons), 1.20–3.34 (m, 12 H, other aliphatic protons on the pyrrolizidine ring); mass spectrum, m/e 258 (M^+).

Pharmacological Method. The antiarrhythmic activity of the target compounds in mice was evaluated essentially according to the method described by Lawson.[15]

Groups of 10 male mice (DDY strain) weighing 18–22 g were used and all compounds were injected subcutaneously. The volume of solution injected was 0.1 mL/10 g of body weight. Thirty minutes after drug administration, the mice were exposed to chloroform vapor in a glass beaker until respiratory arrest occurred. The animals were removed from the beaker immediately after respiratory arrest, and a lead II electrocardiogram was used to observe whether ventricular fibrillation took place or not, and then the heart was exposed for visual inspection of ventricular rhythm. At least three to four doses of drug were administered to obtain different degrees of protection against fibrillation. According to the method of Litchfield and Wilkoxon,[16] the antiarrhythmic ED_{50} value was calculated, at which 50% of animals were protected from ventricular fibrillation induced by chloroform. The acute LD_{50} value (24 h) was calculated by the up-and-down method described by Brownlee[17] in order to assess the therapeutic index (LD_{50}/ED_{50}).

Certain members of the series were selected for further testing in dogs with ventricular arrhythmias produced by coronary artery ligation according to the method of Harris.[13]

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Structure–Activity Relationships of Arylimidazopyridine Cardiotonics: Discovery and Inotropic Activity of 2-[2-Methoxy-4-(methylsulfinyl)phenyl]-1*H*-imidazo[4,5-*c*]pyridine[1]

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Recently several noncatecholamine, nonglycoside cardiotonic drugs have been discovered that possess both inotropic and vasodilator activities in experimental animals and man. Prototypical compounds include amrinone, sulmazole, and fenoximone. We investigated the structural requirements necessary for optimal inotropic activity in a series of molecules containing a heterocyclic ring fused to 2-phenylimidazole and discovered that 2-phenylimidazo[4,5-*c*]pyridines were generally 5–10-fold more potent than analogous 2-phenylimidazo[4,5-*b*]pyridines (e.g., sulmazole) or 8-phenylpurines. Furthermore, all imidazo[4,5-*c*]pyridine analogues we tested were orally active; in contrast, only one of the imidazo[4,5-*b*]pyridine derivatives, sulmazole, was significantly active. One of several highly active compounds in the [4,5-*c*] series was **50** (LY175326, 2-[2-methoxy-4-(methylsulfinyl)phenyl]-1*H*-imidazo[4,5-*c*]pyridine hydrochloride). The structure–activity relationship of this series is presented and compared to that of the imidazo[4,5-*b*]pyridine and purine series.

Congestive heart failure (CHF) afflicts approximately 3–4 million Americans, and the 2-year survival rate of patients with severe failure is 30% or less.[2,3] This high incidence and unacceptably poor prognosis underscore the

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