2-Oxo-1,8-naphthyridine-3-carboxylic Acid Derivatives with Potent Gastric Antisecretory Properties

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The syntheses of 2-oxo-1,8-naphthyridine-3-carboxylic acid derivatives having potent gastric antisecretory properties in the pyloric-ligated (Shay) rat model are described. Two of the more potent compounds tested that were selected for more detailed dose–response evaluation were 4-amino-1-ethyl-1,2-dihydro-2-oxonaphthyridine-3-carboxylic acid ethyl ester (**35**) and 1-ethyl-1,2-dihydro-7-methyl-4-(4-methyl-1-piperazinyl)-2-oxo-1,8-naphthyridine-3-carboxylic acid ethyl ester (**77**). These compounds lowered total acid output in the rat in a dose-related fashion. Both compounds were more potent than cimetidine when tested in the rat. Both **35** and **77** showed inhibitory activity in food-stimulated acid secretion in the Pavlov-pouch, conscious dog. The mechanism of action for this series is not known. Details of structure–activity relationships are described.

The synthesis and in vivo antibacterial activity of 1,2,3,4-tetrahydro-4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives structurally resembling nalidixic acid have been reported.[1] Ring system modification resulted in the preparation of 1-ethyl-1,2-dihydro-4-hydroxy-7-methyl-2-oxo-1,8-naphthyridine-3-carboxylic acid ethyl ester (**20**), a compound showing no antibacterial activity. Tests to obtain a profile of pharmacological effects showed the compound active as both an antiallergic and gastric antisecretory agent in rat models. The antiallergy activity of **20** along with some related examples was confirmed by Hardtmann.[2] With our interests focused on the gastric antisecretory effect of **20**, synthetic efforts progressed to optimize the activity of these naphthyridine derivatives in attempts to arrive at a therapeutic agent for the treatment of peptic ulcer disease. Bolhofer and co-workers described the inhibition of gastric acid secretion in the rat of 2-oxo-1,8-naphthyridines, compounds of the same general heterocyclic class as those of the present report.[3] The work described by these authors and the intense interest in this area of medicinal chemistry prompts us to report the chemical synthesis and antisecretory properties of this series of compounds.[4a-c]

One modification of **20** found to enhance gastric antisecretory activity in the rat was replacement of the 4-hydroxy group by a 4-amino group. An early compound that showed high antisecretory potency relative to cimetidine[5] is 4-amino-1-ethyl-1,2-dihydro-2-oxo-1,8-naphthyridine-3-carboxylic acid ethyl ester (**35**). Systematic changes of ring substituents in **35** were undertaken to determine the effect on activity. A second beneficial modification, the replacement of the primary amino function by a tertiary amino group, e.g. piperazino or *N*-alkyl-substituted piperazino, led to the preparation of other potent gastric antisecretory agents. A typical example among these is 1-ethyl-1,2-dihydro-7-methyl-4-(4-methyl-1-piperazinyl)-2-oxo-1,8-naphthyridine-3-carboxylic acid ethyl ester (**77**). Details of structure–activity relationships are herein described. In addition, compounds **35** and **77** were further tested for their ability to inhibit gastric acid secretion in the dog and were found to be active.

Chemistry

The preparation of 1,8-naphthyridine derivatives bearing a 4-amino function required starting with suitably substituted 2-(alkylamino)nicotinonitriles (Table I, **1–13**). These were prepared, in general, from the corresponding 2-chloronicotinonitriles reacted with suitably substituted amines in refluxing ethanol (Scheme I). The 4-amino-1,8-naphthyridines shown in Table V were prepared in most cases by treating these nicotinonitriles with 1 equiv of ethyl malonyl chloride in anhydrous ether. The ether was removed, and the residue was subjected to Dieckmann-like ring closure conditions with sodium ethoxide (method I). Alternatively, when the substituted nicotinonitriles were treated with an excess of the sodium salt of diethyl malonate in refluxing ethanol for several hours, ring closure to the 4-amino-1,8-naphthyridines resulted, affording another method of preparing these derivatives (method II). In examples **42–44**, method II was used but di-*n*-butyl, bis[2-(diethylamino)ethyl], and di-*sec*-butyl malonates were used, respectively, instead of diethyl malonate. To prevent transesterification in these reactions, it was necessary to use the corresponding alcohols as reaction solvents. A few of the esters were hydrolyzed to the corresponding acids by alkaline hydrolysis, e.g. **40**, **41**, **54**, **61**, and **69**.

Several amides and substituted amides were prepared by reactions of the corresponding esters with ammonia or substituted amines, e.g. **45–47** and **55**. The hydrazide **48** was prepared from the corresponding ester and hydrazine in refluxing ethanol. The nitrile **56** was prepared by the dehydration of amide **55** with phosphorus oxychloride.

Various acylation reactions of the 4-amino function were carried out. For example, treatment of **35** with acetyl chloride for several hours gave the diacetyl derivative **59**. When **59** was treated with diethylamine, hydrolysis to the monoacetyl derivative resulted, giving **58**. The trifluoroacetyl derivative **57** was prepared from **35** by reaction with trifluoroacetic anhydride. Similarly, **60** was prepared from **35** with ethyl oxalyl chloride while **61** was prepared from **37** and chloroacetyl chloride.

Access to 1,8-naphthyridines bearing a secondary amino or tertiary amino group in the 4-position was readily available via displacement of a chloro group from the corresponding 4-chloro-substituted 1,8-naphthyridines (Table IV, **26–32**). The latter compounds were mostly

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(2) Hardtmann, G. E. U.S. Patent 4 128 649, 1978.
(3) Bolhofer, W. A.; Hoffman, J. M.; Habecher, C. N.; Pietruskiewicz, A. M.; Cragoe, E. F., Jr.; Torchiana, M. L. *J. Med. Chem.* **1979**, *22*, 301.
(4) A preliminary account of the present work appeared in the following patents: (a) Santilli, A. A.; Scotese, A. C. U.S. Patent 4 215 123, 1980. (b) Scotese, A. C.; Santilli, A. A. U.S. Patent 4 324 893, 1982. (c) Scotese, A. C.; Santilli, A. A. U.S. Patent 4 350 817, 1982.
(5) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Miles, P. D.; Parsons, M. E.; Prain, H. E.; White, G. R. *J. Med. Chem.* **1977**, *20*, 901.

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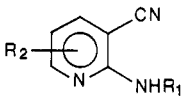
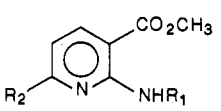
Table I. Physical Characteristics of 2-Aminonicotinonitrile Derivatives



no.	R^1	R^2	mp, °C	yield, %	recryst[e] solvent	formula	anal.
1[a]	H	H	164–166	17	A	$C_6H_5N_3$	C, H
2[b]	CH_3	H	81–84	44	B	$C_7H_7N_3$	C, H, N
3	CH_3CH_2	H	83–86	30	B	$C_8H_9N_3$	C, H, N
4	$CH_3(CH_2)_2$	H	33–35	22	C	$C_9H_{11}N_3$	C, H
5	$CH_2CH(CH_3)_2$	H	80–84	63	B	$C_{10}H_{13}N_3$	C, H, N
6	c-C_6H_{11}	H	87–89	28	B	$C_{12}H_{15}N_3$	C, H, N
7	$CH_2CH{=}CH_2$	H	60–62	61	D	$C_9H_9N_3$	C, H, N
8[c]	CH_3CH_2	6-CH_3	65–67	62	B	$C_9H_{11}N_3$	C, H
9	CH_2CH_2OH	6-CH_3	83–86	40		$C_9H_{11}N_3O\cdot{}^1/_2H_2O$	C, H
10	H	4,6-$(CH_3)_2$	250–253	57	E	$C_8H_9N_3$	C, H
11[d]	CH_3CH_2	4-CH_3, 6-CH_3CH_2NH	72–75	95	B	$C_{11}H_{16}N_4$	C, H, N
12	CH_3CH_2	4,6-$(CH_3)_2$	100–103	41	B	$C_{10}H_{13}N_3$	C, H
13	CH_3CH_2	5-CH_3CONH	196–198	49	E	$C_{10}H_{12}N_4O$	C, H, N
13a	CH_3CH_2	5-NH_2	94–96	99	B	$C_8H_{10}N_4$	C, H, N

[a] Reference 19. [b] Calcd: C, 63.14. Found: C, 62.41. [c] Calcd: C, 67.05. Found: C, 65.48. [d] Calcd: C, 64.68. Found: C, 64.16. [e] A = H_2O, B = heptane, C = pentane, D = petroleum ether, E = EtOH, F = EtOAc, G = EtOEt, H = hexane, I = 2-ethoxyethanol.

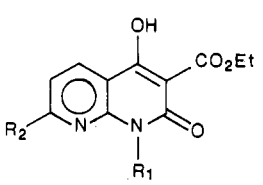
Table II. Physical Characteristics of 2-Aminonicotinonitrile Derivatives



no.	R^1	R^2	mp, °C	yield, %	recryst[b] solvent	formula	anal.
14[a]	H	CH_3			oil	$C_8H_{10}N_2O_2$	c
15	CH_3	H				$C_8H_{10}N_2O_2$	c
16	CH_3CH_2	H	140–145	56	F	$C_9H_{12}N_2O_2\cdot HCl$	C, H, N
17	CH_3	CH_3	63–66		B	$C_9H_{12}N_2O_2$	c
18	CH_3CH_2	CH_3	123–125	61	F–E	$C_{10}H_{14}N_2O_2\cdot HCl$	C, H, N
19	$CH_2CH{=}CH_2$	CH_3	140–142	80	F	$C_{11}H_{14}N_2O_2\cdot{}^1/_2H_2O$	C, H, N

[a] Reference 20. [b] See footnote e, Table I. [c] Used without purification.

Table III. Physical Characteristics and Antisecretory Activities of Substituted 1,2-Dihydro-4-hydroxy-2-oxo-1,8-naphthyridine-3-carboxylates



no.	R^1	R^2	mp, °C	yield, %	recryst[a] solvent	formula	anal.	TAO:[b] % of control	no. of animals
20	CH_3CH_2	CH_3	147–151	43	B	$C_{14}H_{16}N_2O_4$	C, H, N	53 ± 7	10
21	$CH_2CH{=}CH_2$	CH_3	113–115	8	B	$C_{15}H_{16}N_2O_4$	C, H, N	73 ± 8	9
22	CH_3CH_2	H	122–125	10	B	$C_{13}H_{14}N_2O_4$	C, H, N	63 ± 19	5
23	CH_3	H	158–160	46	E	$C_{12}H_{12}N_2O_4$	C, H, N		
24	CH_3	CH_3	143–145	48	F	$C_{13}H_{14}N_2O_4$	C, H, N	51 ± 11	7
25	H	CH_3	190–193	4	E	$C_{12}H_{12}N_2O_4$	C, H, N		

[a] See footnote e, Table I. [b] Total acid output values are mean ± SEM; animals received the drug, 32 mg/kg, administered intraduodenally.

prepared through the route given in Scheme I. Treatment of methyl 2-substituted aminonicotinates (Table II) with ethyl malonyl chloride followed by Dieckmann-like ring closure of the acylated intermediates produced naphthyridines **20–25** (Table III). These were converted to the corresponding 4-chloro-1,8-naphthyridines by the action of thionyl chloride or phosphorus oxychloride. One example, **26**, also was prepared from the corresponding 4-amino-1,8-naphthyridine derivative **49** by diazotization in hydrochloric acid solution. The various displacement reactions with primary or secondary amines were performed in refluxing ethanol. Displacement of the chloro group in **26** with ethoxide ion gave **83**. Quaternization of the free base of **77** with methyl chloride in refluxing acetone afforded **80**.

Discussion

As seen from the data given in Table V, many of the substituted 4-amino-2-oxo-1,8-naphthyridine-3-carboxylic acid derivatives were active antisecretory agents at 32 mg/kg, ID, in the pylorus-ligated rat. Cimetidine,[5] an H^2-receptor antagonist, gave a modest response as an antisecretory agent in the rat at 32 mg/kg (80 ± 10% of TAO of control). This dose, therefore, was used as the initial screening dose for comparison and for identifying active compounds. More potent compounds showed lower values

Scheme I

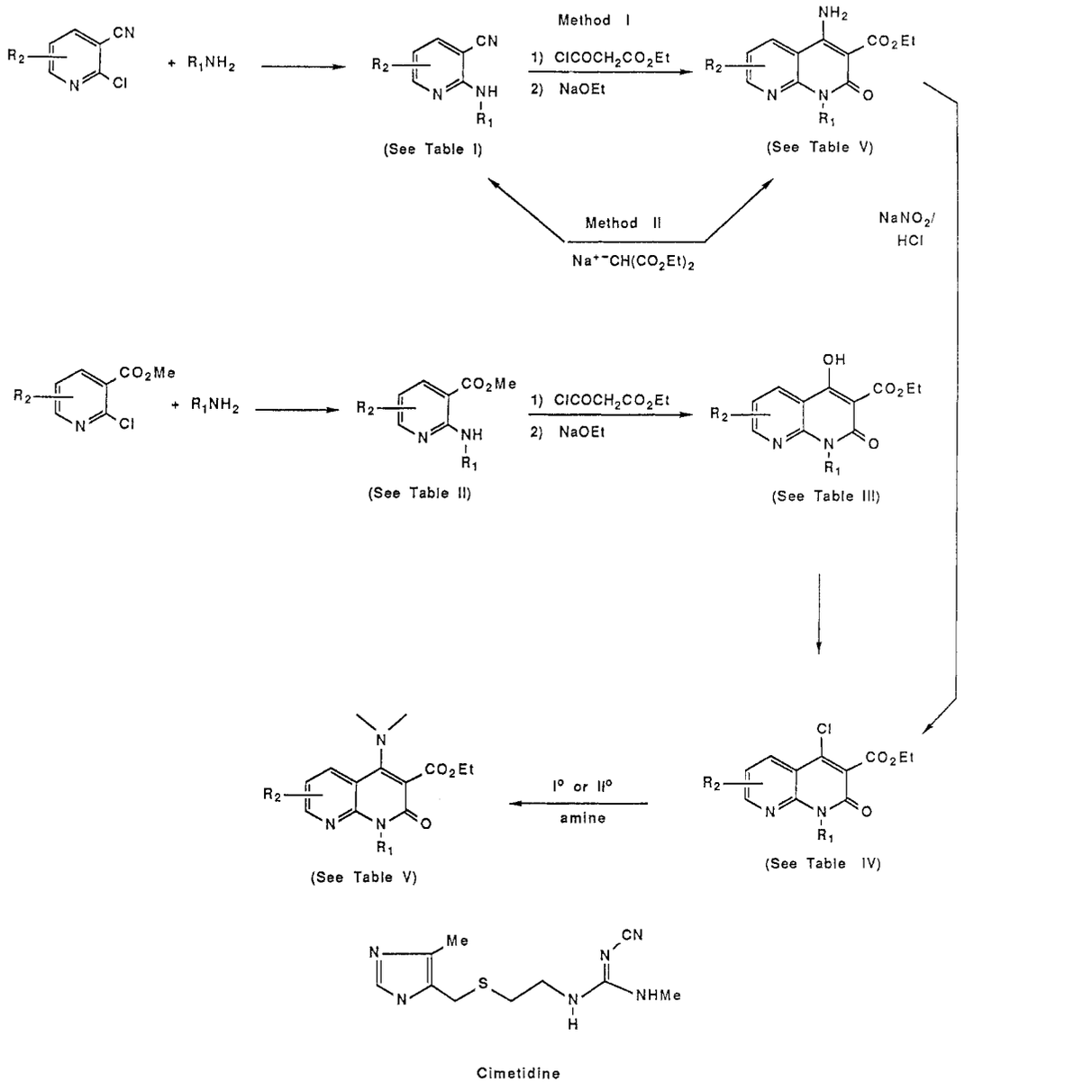
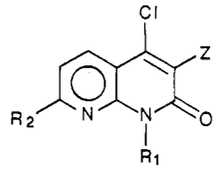


Table IV. Physical Characteristics and Antisecretory Activities of Substituted Ethyl 4-Chloro-1,3-dihydro-2-oxo-1,8-naphthyridine-3-carboxylates



no.	R^1	Z	R^2	mp, °C	yield, %	recryst[a] solvent	formula	anal.	TAO:[b] % of control	no. of animals
26	CH_3CH_2	$CO_2CH_2CH_3$	CH_3	143–144	41	B	$C_{14}H_{15}ClN_2O_3$	C, H, N	66 ± 11	9
27	CH_3CH_2	CN	CH_3	215–217	55	E	$C_{12}H_{10}ClN_3O$	C, H, N		
28	$CH_2CH{=}CH_2$	$CO_2CH_2CH_3$	CH_3	80–82	42	B	$C_{15}H_{15}ClN_2O_3$	C, H, N		
29	CH_3CH_2	$CO_2CH_2CH_3$	H	134–136	81	B	$C_{13}H_{13}ClN_2O_3$	C, H, N		
30	CH_3	$CO_2CH_2CH_3$	H	132–135	95	B	$C_{12}H_{11}ClN_2O_3$	C, H, N		
31	CH_3	$CO_2CH_2CH_3$	CH_3	180–184	75	F	$C_{13}H_{13}ClN_2O_3$	C, H, N		
32	H	$CO_2CH_2CH_3$	CH_3	160–163	81	E	$C_{12}H_{11}ClN_2O_3$	C, H, N		

[a] See footnote *e*, Table I. [b] Total acid output values are mean ± SEM; animals received the drug, 32 mg/kg, administered intraduodenally.

of percentage of TAO vs control at the test dose. Although the TAO (see the Biological Methods) is a product of gastric volume and acid concentration, these parameters were not individually quantified in the present paper. The compounds of this series, like cimetidine, reduced both gastric volume as well as acid concentration.

Replacing the 1-ethyl group of **35** by an alkyl group such as methyl (**34**), propyl (**36**), allyl (**37**), or isobutyl (**38**) also gave compounds with high activity. Having the 1-position unsubstituted (**33**) reduced activity. This decreased effect

was more pronounced when comparing the activity of **52** with **51**. The presence of a second amino function in the molecule as in **53** also had a deleterious effect on activity. Replacement of the 4-amino group by a hydroxyl group (**22**), a chloro group (**26**), or a 4-ethoxy group (**83**) either greatly diminished or eliminated activity.

Replacement of the carbethoxy group by a carboxyl group (**41**), carbamoyl group (**45**), alkylcarbamoyl group (**46**), or hydrazide group (**48**) maintained high activity.

Acetylation or diacetylation of the 4-amino group (**58**, **59**, or **62**) greatly reduced activity.

Several compounds having tertiary amino groups at the 4-position of the naphthyridine ring showed high potencies, e.g. pyrrolidino (**73** and **75**), morpholino (**76**), *N*-methylpiperazino (**66**, **68**, **70**, **74**, and **77**), and piperazino (**78**). Compound **80**, the quaternized derivative of **77**, was totally inactive. The presence of a carbethoxy group on the piperazinyl N as in **79** resulted in greatly diminished activity. A loss of activity was noted when comparing the activity of the ester **68** with that of the free carboxylic acid **69** at the equivalent dose levels employed.

Several compounds showed significantly greater potencies than cimetidine at the initial screening dose. The most potent compounds among the 4-amino series were, e.g., **34**, **35**, **37**, and **45**. Among the most potent in the 4-tertiary-amino series were those having a piperazino group, e.g., **78**, or *N*-alkyl-substituted piperazino group, e.g., **74** and **77**. Among these, one representative primary amino derivative and one tertiary amino derivative, e.g., **35** and **77**, was selected for further evaluation and comparison with cimetidine at several dose levels.

Dose-related responses of **35** and **77**, along with cimetidine are given in Table VI. These compounds were significantly more potent than the standard at doses as low as 2–4 mg/kg.

Both **35** and **77** inhibited food-stimulated gastric acid secretion in the Pavlov-pouch, conscious dog[6] (Table VII). Compound **35** showed 62 ± 11% reduction of TAO vs control at 16 mg/kg, po, producing emesis at higher doses. Compound **77** was more potent, giving a 40 ± 11% reduction at 4 mg/kg, po, but four of seven dogs had drug-induced emesis. Cimetidine had an ED_{50} = 6 mg/kg, po.

Neither **35** nor **77** were found to be H_2-receptors antagonists as determined by the right guinea pig atrium assay.[7] The mechanism of action for this series is not known. Preliminary experiments indicated that both **35** and **77** gave some protection against cold-restraint stress-induced gastric ulcer formation in the rat.[8] Whether or not this effect can be related to a cytoprotective mechanism is not presently known.

Compounds **35** and **77** showed only weak activity as antiallergy agents and therefore were not further explored in this regard.

The unfavorable emetic responses of **35** and **77** in the dog model precluded their selection for further development as possible clinical candidates.

In summary, 2-oxo-1,8-naphthyridine-3-carboxylic acids, esters, and hydrazides with a 4-amino function and a 1-alkyl group showed gastric antisecretory activities in the rat significantly greater than the standard, cimetidine, at the initial test dose. A high order of activity in this series was maintained by the substitution of a piperazino or 4-methylpiperazino moiety for the primary amino function at the 4-position of the naphthyridine. These derivatives were highly potent when tested as free bases or as hydrochloride salts. Two of the more potent compounds, **35** and **77** were tested and found to be more potent than cimetidine in a dose-related fashion.

Compound **77** was more potent than **35** in inhibiting food-stimulated gastric acid secretion in the dog. Further development of these drugs was not pursued, however, because of their emetic potential. The mechanism of action for this series is not known.

Experimental Section

Melting points were measured in a Thomas-Hoover oil bath melting point apparatus and are reported uncorrected. The IR spectra were recorded on a Perkin-Elmer Model 299 infrared spectrophotometer and the NMR spectra were measured on a Varian A-60 or a JEOL Model C-60 H6 spectrometer. All spectra were consistent with the assigned structures. Combustion analyses were performed on a Perkin-Elmer Model 240 elemental analyzer and were within ±0.4% of the theoretical values except as noted.

Biological Methods. Pylorus-Ligated Rat. Tests for the effect of selected compounds on gastric acid secretion were performed by using the pyloric ligated (Shay) rat technique. Male Charles River rats of Sprague–Dawley strain and 190–240 g of body weight were deprived of food for 24 h, but permitted access to tap water ad libitum until the test. Groups of 10 rats each were assigned for either control or drug treatment. Pyloric ligation was performed according to a modified procedure of Shay and co-workers.[9] Under ether anesthesia, a midline laparotomy was made, and a ligature was secured around the pylorus. Control vehicle or drugs in control vehicle were administered intraduodenally in a 1 mL/kg volume of 0.25% aqueous methylcellulose. All drug doses were prepared as 100% of the active moiety and administered at a 32 mg/kg dose. The abdominal incision was closed with wound clips, and the rats (two per cage) were allowed to recover from anesthesia. After 4 h, the rats were sacrificed by CO_2 asphyxiation, their stomachs were removed, and the gastric contents were collected into graduated tubes. The gastric samples were centrifuged for 10 min. Samples contaminated with food or fecal matter were discarded. The volume of gastric juice was recorded, and the acid concentration of 1.0-mL-sample aliquots was measured by electrometric titration to pH 7 with 0.1 N NaOH. The product of the gastric volume (mL/4 h) and acid concentration (mequiv/mL) is the calculated total acid output (TAO, mequiv/4 h). An analysis of variance was used to determine statistically significant ($p < 0.05$) deviations between control and drug-treated groups.

Thomas Modification of the Pavlov-Pouch Dog.[6] Female beagles weighing 9–13 kg were surgically prepared with innervated gastric pouches and allowed a recovery period of at least 2 weeks. The dogs were fasted for 18 h with access to tap water ad libitum until the test. Two samples of gastric secretion were collected at 15-min intervals to establish a base line. The control vehicle (0.9% saline) or drug in control vehicle was administered by oral gavage, and two additional 15-min samples were taken. At 30 min after treatment, the dogs were given a 200-mL portion (185 g) of commercially prepared, 100% meat meal. After feeding, gastric pouch samples were collected at 15 min intervals until the test was terminated 4 h later.

The volume of secreted gastric juice was recorded, and the acid concentration of 1.0-mL aliquots was measured by electrometric titration to pH 7.0 with 0.1 N sodium hydroxide.

The product of the gastric volume and acid concentration was used to calculate the total acid output (TAO). A mean ± SEM value was calculated for each time period, and the sum over a 3.25-h time period was calculated to provide the TAO. Total acid output after drug administration was compared with that after saline (control value), and the results were expressed as the percent inhibition.

General Chemical Methods. The following intermediates used in the present study were previously described: methyl 2-chloro-6-methylnicotinate,[10] methyl 2-chloronicotinate,[11] 2-

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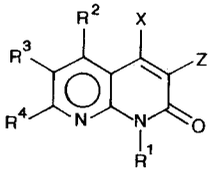
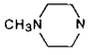
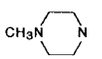
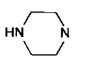
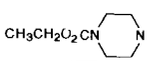
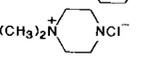
(7) Black, J. W.; Duncan, W. A. M.; Durant, C. J.; Ganellin, C. R.; Parsons, E. M. *Nature (London)* **1972**, *236*, 385.
(8) Hanson, H. M.; Brodie, D. A. *J. Appl. Physiol.* **1960**, *15*, 291.
(9) Shay, H.; Sun, D. C. H.; Gruenstein, M. A. *Gastroenterology* **1954**, *26*, 906.
(10) Mariella, R. P.; Havlik, A. J. *J. Am. Chem. Soc.* **1952**, *74*, 1915.

Table V. Physical Characteristics and Antisecretory Activities of 4-Amino- or 4-Substituted-1,2-dihydro-2-oxo-1,8-naphthyridine-3-carboxylic Acid Derivatives



no.	R^1	Z	X	R^2	R^3	R^4	mp, °C	yield, %	recryst[a] solvent	formula	anal.	TAO:[b] % of control	no. of animals
33	H	$CO_2CH_2CH_3$	NH_2	H	H	H	264–267	21	E	$C_{11}H_{11}N_3O_3$	C, H, N	44 ± 10	10
34	CH_3	$CO_2CH_2CH_3$	NH_2	H	H	H	203–206	36	E	$C_{12}H_{13}N_3O_3$	C, H, N	21 ± 4	10
35	CH_3CH_2	$CO_2CH_2CH_3$	NH_2	H	H	H	210–212.5	23	F	$C_{13}H_{15}N_3O_3$	C, H, N	18 ± 10	10
36	$CH_3(CH_2)_2$	$CO_2CH_2CH_3$	NH_2	H	H	H	165–168	55	F	$C_{14}H_{17}N_3O_3$	C, H, N	30 ± 5	10
37	$CH_2CH{=}CH_2$	$CO_2CH_2CH_3$	NH_2	H	H	H	161–164	50	F	$C_{14}H_{15}N_3O_3$	C, H, N	22 ± 4	9
38	$CH_2CH(CH_3)_2$	$CO_2CH_2CH_3$	NH_2	H	H	H	157–160	21	F	$C_{15}H_{19}N_3O_3$	C, H, N	28 ± 5	8
39	c-C_6H_{11}	$CO_2CH_2CH_3$	NH_2	H	H	H	172–175	7	F	$C_{17}H_{21}N_3O_3$	C, H, N	48 ± 7	9
40	H	CO_2H	NH_2	H	H	H	297–300 dec	21	A	$C_9H_7N_3O_3$	C, H, N	72 ± 9	10
41	CH_3CH_2	CO_2H	NH_2	H	H	H	245–248	34	E	$C_{11}H_{11}N_3O_3$	C, H, N	37 ± 6	10
42	CH_3CH_2	$CO_2(CH_2)_3CH_3$	NH_2	H	H	H	117–120	6	F	$C_{15}H_{19}N_3O_3$	C, H, N	26 ± 7	8
43	CH_3CH_2	$CO_2(CH_2)_2N(CH_2CH_3)_2$	NH_2	H	H	H	153–156	16	E–G	$C_{21}H_{28}N_4O_7$ (maleate salt)	C, H, N	40 ± 5	7
44	CH_3CH_2	$CO_2CHCH_3CH_2CH_3$	NH_2	H	H	H	157–159	6	F	$C_{15}H_{19}N_3O_3$	C, H, N	42 ± 8	9
45	CH_3CH_2	$CONH_2$	NH_2	H	H	H	231–232	83	E	$C_{11}H_{12}N_4O_2$	C, H, N	19 ± 4	10
46	CH_3CH_2	$CONHCH_2CH_3$	NH_2	H	H	H	196–198	64	E	$C_{13}H_{16}N_4O_2$	C, H, N	28 ± 4	7
47	CH_3CH_2	$CONH(CH_2)_2N(CH_2CH_3)_2$	NH_2	H	H	H	147–149	79	E–D	$C_{17}H_{25}N_5O_2$	C, H, N	56 ± 7	10
48	CH_3CH_2	$CONHNH_2$	NH_2	H	H	H	275–277 dec	59	E	$C_{11}H_{13}N_5O_2$	C, H, N	29 ± 8	5
49	CH_3CH_2	$CO_2CH_2CH_3$	NH_2	H	H	CH_3	196–198	24	F	$C_{14}H_{17}N_3O_3$	C, H, N	33 ± 5	8
50	CH_2CH_2OH	$CO_2CH_2CH_3$	NH_2	H	H	CH_3	168–170	60	E	$C_{14}H_{17}N_3O_4 \cdot {}^1/_3H_2O$	C, H	74 ± 12	9
51	H	$CO_2CH_2CH_3$	NH_2	CH_3	H	CH_3	288–290 dec	30	E	$C_{13}H_{15}N_3O_3$	C, H, N	89 ± 21	10
52	CH_3CH_2	$CO_2CH_2CH_3$	NH_2	CH_3	H	CH_3	178–180	36	E	$C_{15}H_{19}N_3O_3$	C, H, N	50 ± 16	8
53	CH_3CH_2	$CO_2CH_2CH_3$	NH_2	CH_3	H	CH_3CH_2NH	195–197	13	F	$C_{16}H_{22}N_4O_3$	C, H, N	58 ± 11	10
54	CH_3CH_2	CO_2H	NH_2	H	CH_3CONH	H	304–306 dec	20	E	$C_{13}H_{14}N_4O_4 \cdot {}^1/_2H_2O$	C, H, N	82 ± 10	8
55	CH_3CH_2	$CONH_2$	NH_2	H	H	CH_3	263–266	4	E	$C_{12}H_{14}N_4O_2$	C, H, N	55 ± 9	9
56	CH_3CH_2	CN	NH_2	H	H	CH_3	>300	6	E	$C_{12}H_{12}N_4O$	C, H, N	62 ± 6	10
57	CH_3CH_2	$CO_2CH_2CH_3$	$NHCOCF_3$	H	H	H	195–197	42	F–D	$C_{15}H_{14}F_3N_3O_4$	C, H, N	22 ± 4	10
58	CH_3CH_2	$CO_2CH_2CH_3$	$NHCOCH_3$	H	H	H	148–150	46	F	$C_{15}H_{17}N_3O_4$	C, H, N	67 ± 12	7
59	CH_3CH_2	$CO_2CH_2CH_3$	$N(COCH_3)_2$	H	H	H	133–135	36	F	$C_{17}H_{19}N_3O_5$	C, H, N	59 ± 8	9
60	CH_3CH_2	$CO_2CH_2CH_3$	$NHCOCO_2CH_2CH_3$	H	H	H	163–167	37	E	$C_{17}H_{19}N_3O_6$	C, H, N	28 ± 3	8
61	$CH_2CH{=}CH_2$	CO_2H	$NHCOCH_2Cl$	H	H	H	145–148	26	F	$C_{14}H_{12}ClN_3O_4$	C, H, N	63 ± 6	9
62	CH_3CH_2	$CO_2CH_2CH_3$	$N(COCH_3)_2$	CH_3	H	CH_3	137–140	47	E	$C_{19}H_{23}N_3O_5$	C, H, N	76 ± 11	8
63	CH_3CH_2	$CO_2CH_2CH_3$	$NHCH_2CH_3$	H	H	CH_3	132–136	27	B	$C_{16}H_{21}N_3O_3$	C, H, N	36 ± 6	8
64	CH_3CH_2	$CO_2CH_2CH_3$	$NH(CH_2)_3N(CH_3)_2$	H	H	CH_3	75	15		$C_{19}H_{28}N_4O_3 \cdot HCl \cdot H_2O$	C, H, N	77 ± 10	10
65	CH_3CH_2	$CO_2CH_2CH_3$	$NHCH_2CHOHC_6H_5$	H	H	CH_3	178–181	33	F	$C_{22}H_{25}N_3O_4$	C, H, N	111 ± 14	9
66	CH_3	$CO_2CH_2CH_3$		H	H	H	231–234	4	E	$C_{17}H_{22}N_4O_3 \cdot HCl \cdot {}^1/_2H_2O$	C, H, N	25 ± 5	9
67	CH_3	$CO_2CH_2CH_3$		H	H	H	118–120	17	E–D	$C_{16}H_{19}N_3O_3$	C, H, N	51 ± 7	10
68	CH_3CH_2	$CO_2CH_2CH_3$		H	H	H	231–234 dec	44	E	$C_{18}H_{24}N_4O_3 \cdot HCl$	C, H, N	17 ± 8	6

69	CH_3CH_2	CO_2H		H	H	CH_3	217–219	12		$C_{17}H_{22}N_4O_3 \cdot {}^1/_4H_2O$	C, H, N	89 ± 13	7
70	H	$CO_2CH_2CH_3$		H	H	CH_3	172–175	19	F	$C_{17}H_{22}N_4O_3$	C, H, N	34 ± 8	8
71	CH_3CH_2	$CO_2CH_2CH_3$	$(CH_3CH_2)_2N$	H	H	CH_3	82–85	47	D	$C_{18}H_{25}N_3O_3$	C, H, N	55 ± 8	6
72	CH_3CH_2	$CO_2CH_2CH_3$	$CH_3N(CH_2)_2OH$	H	H	CH_3	111–113	33	F	$C_{17}H_{23}N_3O_4$	C, H, N	59 ± 7	9
73	CH_3	$CO_2CH_2CH_3$		H	H	CH_3	108–111	55	B	$C_{17}H_{21}N_3O_3$	C, H, N	32 ± 6	8
74	CH_3	$CO_2CH_2CH_3$		H	H	CH_3	278–280 dec	14	E	$C_{18}H_{24}N_4O_3 \cdot HCl \cdot {}^1/_2H_2O$	C, H, N	9 ± 3	10
75	CH_3CH_2	$CO_2CH_2CH_3$		H	H	CH_3	113–115	37	B	$C_{18}H_{23}N_3O_3$	C, H, N	29 ± 4	8
76	CH_3CH_2	$CO_2CH_2CH_3$		H	H	CH_3	127–130	43	B	$C_{18}H_{23}N_3O_4$	C, H, N	22 ± 3	10
77	CH_3CH_2	$CO_2CH_2CH_3$		H	H	CH_3	285–287	40	E	$C_{19}H_{26}N_4O_3 \cdot HCl$	C, H, N	7.5 ± 2.5	3
78	CH_3CH_2	$CO_2CH_2CH_3$		H	H	CH_3	137–139	22	B	$C_{18}H_{24}N_4O_3$	C, H, N	10 ± 2	5
79	CH_3CH_2	$CO_2CH_2CH_3$		H	H	CH_3	140–143	59	F	$C_{21}H_{28}N_4O_5$	C, H, N	70 ± 11	10
80	CH_3CH_2	$CO_2CH_2CH_3$		H	H	CH_3	250–254 dec	10		$C_{20}H_{29}ClN_4O_3$	C, H, N	123 ± 15	9
81	$CH_2CH{=}CH_2$	$CO_2CH_2CH_3$		H	H	CH_3	97–103	69	B	$C_{19}H_{23}N_3O_3$	C, H, N	59 ± 10	9
82	CH_3CH_2	CN		H	H	CH_3	211–213 dec	92	I	$C_{16}H_{18}N_4O$	C, H, N	67 ± 10	9
83	CH_3CH_2	$CO_2CH_2CH_3$	CH_3CH_2O	H	H	CH_3	77–79	33	B	$C_{16}H_{20}N_2O_4$	C, H, N	46 ± 8	10

[a] See footnote *e*, Table I. [b] Total acid output values are mean ± SEM; animals received the drug, 32 mg/kg, administered intraduodenally.

Table VI. Dose-Related Antisecretory Responses of Compounds **35** and **77** vs Cimetidine in the Pylorus-Ligated Rat

compound	dose, mg/kg	TAO:[a] % of control	no. of animals
35	0.5	100 ± 13	9
	2	58 ± 8	9
	4	55 ± 7	10
	8	35 ± 6	10
	16	17 ± 2	9
77	2	85 ± 12	10
	4	66 ± 11	8
	8	45 ± 9	10
	16	28 ± 5	8
cimetidine	4	106 ± 13	10
	8	77 ± 9	10
	16	73 ± 10	8
	32	80 ± 10	9
	64	60 ± 7	9

[a] Total acid output values are mean ± SEM; animals received the drug by intraduodenal route.

Table VII. Dose-Related Inhibition of Food-Stimulated Gastric Acid Secretion by Compounds **35** and **77** vs Cimetidine in the Gastric Pouch Dog

compound	dose, mg/kg (po)	TAO: % of control (X ± SEM)	no. of animals
35	4	92 ± 5	5
	8	97 ± 14	6
	16	62 ± 11[a]	5
	32[b]		
77	2	95 ± 31	3
	4	40 ± 11[c]	3
cimetidine	6[d]	50 (ED_{50})	

[a] Significantly different from control, $p < 0.05$ (Student's paired t-test). [b] Five of eight animals showed drug-induced emesis. [c] Four of seven animals were excluded from data analysis because of drug-induced emesis. [d] 95% confidence interval (3.38–8.42).

chloro-6-methylnicotinonitrile,[12] 2-chloronicotinonitrile,[13] 2-chloro-4,6-dimethylnicotinonitrile,[14] 2,6-dichloro-4-methylnicotinonitrile,[15] 2-(ethylamino)-5-nitronicotinonitrile,[16] bis[β-(diethylamino)ethyl] malonate,[17] di-*sec*-butyl malonate,[18] and 2-aminonicotinonitrile.[19]

4-Amino-1-ethyl-1,2-dihydro-2-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (35). Method A. A stirred mixture of 4 g (0.03 mol) of 2-chloronicotinonitrile in 200 mL of saturated $EtNH_2$ solution was heated under reflux for 5 h. The solution was cooled and diluted with 400 mL of H_2O. The precipitate of 2-(ethylamino)nicotinonitrile (**3**, Table I) that formed amounted to 1.3 g (30%) and was used directly as follows:

To a solution of 4.4 g (0.03 mol) of **3** in 200 mL of anhydrous Et_2O was added 2.25 g (0.015 mol) of ethyl malonyl chloride. After 2 h of stirring at room temperature, the mixture was filtered. The filtrate was evaporated in a rotary evaporator, and the residue was dissolved in 20 mL of EtOH. This solution was added to a solution of 0.69 g (0.03 g atom) of sodium in 100 mL of EtOH. After being stirred for 5 min at room temperature, the mixture was diluted with H_2O and acidified with concentrated HCl. The formed precipitate was collected, air-dried, and recrystallized from AcOEt to provide 1.8 g (23%) of the desired product **35** (Table V).

Method B. To a solution of 2.01 g (0.09 g-atom) of sodium in 75 mL of absolute EtOH was added 14.4 g (0.09 mol) of diethyl malonate. The solution was stirred at room temperature for 5 min. Then 4.4 g (0.03 mol) of **3** was added, and the mixture was heated under reflux for 6 h. The cooled mixture was diluted with 75 mL of H_2O and then acidified with concentrated HCl. The precipitate thus formed amounted to 3.29 g (42%). Two recrystallizations from EtOH provided 1.1 g of pure product, mp 203–207 °C.

1-Ethyl-1,2-dihydro-4-[(trifluoroacetyl)amino]-2-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (57). A stirred solution of 0.5 g (0.002 mol) of **35** in 20 mL of trifluoroacetic anhydride was heated under reflux for 3 h. The reaction solution was ice cooled and filtered. The resulting product amounted to 0.3 g (42%) of analytically pure product (Table V).

4-(Diacetylamino)-1-ethyl-1,2-dihydro-2-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (59). A stirred mixture of 6 g (0.02 mol) of **35** in 100 mL of acetyl chloride was heated under reflux for 24 h. The mixture was filtered, and the filtrate was removed in a rotary evaporator. The residue was recrystallized from 20 mL of AcOEt to afford 2.9 g (36%) of product (Table V).

4-(Acetylamino)-1-ethyl-1,2-dihydro-2-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (58). To a warm solution of 3.45 g (0.01 mol) of **59** in 30 mL of EtOH was added 0.95 g (0.013 mol) of diethylamine over a 1-min period. The solution was allowed to stand at room temperature for 3 h. The solvent was removed in a rotary evaporator. The residue was triturated with 10 mL of AcOEt. The resulting solid was recrystallized from AcOEt, giving 1.4 g (46%) of product (Table V).

4-Amino-1-ethyl-1,2-dihydro-2-oxo-1,8-naphthyridine-3-carboxamide (45). An autoclave charged with 10 g (0.038 mol) of **35** in 100 mL of concentrated NH_4OH solution was heated on a steam bath for 1.5 days. The reaction mixture was cooled in ice and poured into 500 mL of H_2O. The product amounted to 7.3 g (83%). Recrystallization from EtOH gave 5 g of product (Table V).

4-Chloro-1-ethyl-1,2-dihydro-7-methyl-2-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (26). To a cold solution of 5.4 g (0.12 mol) of anhydrous $EtNH_2$ in 5 mL of EtOH was added 11.1 g (0.06 mol) of methyl 2-chloro-6-methylnicotinate.[10] The mixture was heated in a glass autoclave over a steam bath for 5 h and then was evaporated in a rotary evaporator. The residue was added to 100 mL of H_2O, and the mixture was basified with concentrated NH_4OH. The mixture was then extracted with 100 mL of $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$, was filtered, and was evaporated to give 7.1 g (61%) of **18** as an oil. The HCl salt was prepared from ethanolic HCl and was recrystallized from AcOEt–EtOH (Table II).

To a solution of 3.98 g (0.02 mol) of **18** (free base) in 50 mL of anhydrous EtOEt was added 1.5 g (0.01 mol) of ethyl malonyl chloride. The mixture was stirred at room temperature for 1 h. The mixture was filtered, and the filtrate was evaporated in a rotary evaporator. The residue was added to a solution of 0.23 g of Na in 50 mL of EtOH and warmed for 5 min. The mixture was cooled in ice, and the insoluble material was collected on a filter and was dissolved in H_2O. Acidification of the aqueous solution with glacial HOAc afforded **20**. Recrystallization from heptane gave 1.2 g (43%) of pure product (Table III).

A stirred mixture of 7 g (0.02 mol) of **20** in 100 mL of $SOCl_2$ was heated under reflux for 3 h. The $SOCl_2$ was removed in a rotary evaporator, and the residue was recrystallized from AcOEt to give 3.0 g (41%) of desired product **26** (Table IV).

Alternative Method for Preparing 26. To a solution of 27.5 g (0.1 mol) of **49** in 500 mL of concentrated HCl solution was added over 5 min a solution of 34.5 g (0.5 mol) of $NaNO_2$ in 60 mL of H_2O. The mixture was stirred at room temperature for 30 min and was then poured into 1 L of cold H_2O. The precipitate was collected, air-dried, and recrystallized from AcOEt, giving 20.0 g (68%) of product, mp 144–146 °C.

1-Ethyl-1,2-dihydro-7-methyl-4-(4-methyl-1-piperazinyl)-2-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester Hydrochloride (77). A stirred mixture of 5.8 g (0.02 mol) of **26**, 2.0 g (0.02 mol) of *N*-methylpiperazine, and 2.12 g (0.02 mol) of Na_2CO_3 in 50 mL of EtOH was heated under reflux for 6 h. The mixture was filtered, and the filtrate was evaporated in a rotary evaporator. The residue was triturated with 50 mL of 20% Na_2CO_3 solution and was extracted with 75 mL of Et_2O. The Et_2O layer was dried over $MgSO_4$, filtered, and diluted with 50 mL of EtOH. The solution was acidified with ethereal HCl solution. The resulting precipitate was collected on a filter and recrystallized from EtOH, giving 3.2 g (40%) of product **77** (Table V).

1-Ethyl-1,2-dihydro-4-ethoxy-7-methyl-2-oxo-1,8-naphthyridine-3-carboxylic Acid Ethyl Ester (83). To a solution of 0.11 g (0.005 g atom) of Na in 20 mL of EtOH was added 1.47 g (0.005 mol) of **26**. The mixture was heated under reflux for 4 h. The mixture was cooled and diluted with H_2O. The resulting precipitate was collected, dried, and recrystallized from heptane to give 0.5 g (33%) of product (Table V).

4-Chloro-1-ethyl-1,2-dihydro-7-methyl-2-oxo-1,8-naphthyridine-3-carbonitrile (27). A mixture of 1 g (0.004 mol) of **20** in 20 mL of saturated ethanolic NH_3 solution was heated in an autoclave on a steam bath for 4 h. The reaction mixture was cooled and filtered. The precipitate was triturated with 50 mL of 20% aqueous HOAc. The insoluble product was removed by filtration and recrystallized from EtOH, giving 0.49 g (49%) of 1-ethyl-1,2-dihydro-4-hydroxy-7-methyl-2-oxo-1,8-naphthyridine-3-carboxamide (mp 240–242 °C). Anal. ($C_{12}H_{13}N_3O_3$) C, H, N.

A stirred mixture of 10 g (0.04 mol) of the latter product in 200 mL of $POCl_3$ was heated under reflux for 3 h. The $POCl_3$ was removed under suction in a rotary evaporator. To the residue was added 400 mL of ice water. The insoluble material was collected on a filter and recrystallized from EtOH, giving 5.5 g (55%) of product (Table IV).

5-Amino-2-(ethylamino)nicotinonitrile (13a). To a suspension of 4 g (0.02 mol) of 2-(ethylamino)-5-nitronicotinonitrile[16] in 75 mL of EtOH containing 4.8 g (0.08 g-atom) of iron powder was added dropwise over 10 min 30 mL of concentrated HCl. The mixture was heated under reflux for 1.5 h and was filtered. The filtrate was cooled in ice, and the resulting HCl salt was collected and dissolved in H_2O, and the solution was basified with 50%

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NaOH solution to afford 3.2 g (99%) of 5-amino-2-(ethylamino)nicotinonitrile, which was used directly in the next step. An analytical sample, mp 94–96 °C, was obtained by recrystallization from heptane (Table I).

5-(Acetylamino)-2-(ethylamino)nicotinonitrile (13). To a solution of 1.6 g (0.01 mol) of 5-amino-2-(ethylamino)-nicotinonitrile in 75 mL of anhydrous EtOH was added 0.78 g (0.01 mol) of acetyl chloride. The mixture was stirred at room temperature for 30 min and filtered. The precipitate was triturated with 100 mL of 15% Na_2CO_3 solution. The product amounted to 1.0 g (49%) after recrystallization from EtOH, mp 196–198 °C (Table I).

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Registry No. 1, 24517-64-4; 2, 52583-87-6; 3, 52583-89-8; 4, 74611-49-7; 5, 77276-32-5; 6, 77276-34-7; 7, 77276-35-8; 8, 77276-41-6; 9, 110457-38-0; 10, 5468-34-8; 11, 51560-67-9; 12, 110457-39-1; 13, 110457-40-4; 13A, 110457-41-5; 14, 31686-93-8; 15, 110457-42-6; 16, 76336-07-7; 17, 76335-99-4; 18, 76335-93-8; 19, 78997-37-2; 20, 76335-91-6; 21, 69407-71-2; 22, 76336-05-5; 23, 77276-17-6; 24, 69407-72-3; 25, 76336-15-7; 26, 76336-09-9; 27, 76336-11-3; 28, 77276-37-0; 29, 77276-63-2; 30, 77276-18-7; 31, 77276-20-1; 32, 110457-43-7; 33, 77276-16-5; 34, 77276-24-5; 35, 77276-25-6; 36, 77276-31-4; 37, 77276-36-9; 38, 77276-33-6; 39, 77289-97-5; 40, 77289-98-6; 41, 77276-28-9; 42, 77289-99-7; 43, 110457-45-9; 44, 110457-46-0; 45, 110457-47-1; 46, 110457-48-2; 47, 110457-49-3; 48, 77276-27-8; 49, 77276-42-7; 50, 110457-50-6; 51, 110457-51-7; 52, 110457-52-8; 53, 110457-53-9; 54, 110457-54-0; 55, 77276-45-0; 56, 77276-44-9; 57, 77276-40-5; 58, 110457-55-1; 59, 77276-29-0; 60, 110457-56-2; 61, 77276-39-2; 62, 110457-57-3; 63, 77276-53-0; 64, 82360-79-0; 65, 110457-58-4; 66, 82360-72-3; 67, 77276-19-8; 68, 82360-74-5; 69, 77276-61-0; 70, 110457-59-5; 71, 77276-47-2; 72, 110457-60-8; 73, 77276-21-2; 74, 82360-73-4; 75, 77276-46-1; 76, 77276-48-3; 77, 77276-49-4; 78, 77276-54-1; 79, 77276-56-3; 80, 110457-61-9; 81, 77276-38-1; 82, 76336-12-4; 83, 76336-08-8; di-*n*-butyl malonate, 1190-39-2; bis[2-(diethylamino)ethyl malonate, 92862-11-8; di-*sec*-butyl malonate, 32260-07-4; methyl 2-chloro-6-methylnicotinate, 53277-47-7; methyl 2-chloronicotinate, 40134-18-7; 2-chloro-6-methylnicotinonitrile, 28900-10-9; 2-chloronicotinonitrile, 6602-54-6; 2-chloro-4,6-dimethylnicotinonitrile, 14237-71-9; 2-(ethylamino)-5-nitronicotinonitrile, 31309-09-8; ethyl malonyl chloride, 36239-09-5; diethyl malonate, 105-53-3; *N*-methylpiperazine, 109-01-3; 1-ethyl-1,2-dihydro-4-hydroxy-7-melthyl-2-oxo-1,8-naphthyridine-3-carboxamide, 76335-95-0; 2-chloro-6-(ethylamine)-4-methylnicotinonitrile, 51561-60-5.

Thromboxane Synthetase Inhibitors and Antihypertensive Agents. 4. *N*-[(1*H*-Imidazol-1-yl)alkyl] Derivatives of Quinazoline-2,4(1*H*,3*H*)-diones, Quinazolin-4(3*H*)-ones, and 1,2,3-Benzotriazin-4(3*H*)-ones

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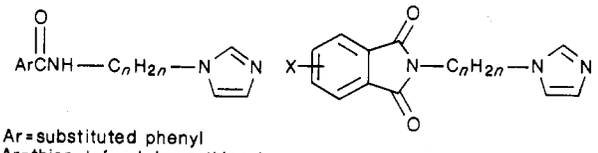
The quinazolinedione, quinazolinone, and 1,2,3-benzotriazinone title compounds were prepared as analogues of *N*-[(1*H*-imidazol-1-yl)alkyl]-1*H*-isoindole-1,3(2*H*)-diones which were the subject of a previous report from our laboratories. These compounds were evaluated as thromboxane (TX) synthetase inhibitors and as antihypertensive agents. While each series of compounds had activity both as TX synthetase inhibitors and as antihypertensives, the best compounds were *N*-[(1*H*-imidazol-1-yl)alkyl]quinazoline-2,4(1*H*,3*H*]-diones (V). In general these compounds were all selective enzyme inhibitors at least equipotent with the standard dazoxiben. These compounds were also very active antihypertensive agents as determined in SHR. The SAR is discussed for both types of activity. Compound **20a** was further evaluated for TX formation inhibiting properties in several other platelet types both in vitro and ex vivo and is between 100 and 1000 times more potent than dazoxiben.

Our laboratory has continued to pursue the goal of developing novel therapeutic agents that might be useful in the treatment of cardiovascular disorders. An ongoing series of *N*-[(1*H*-imidazol-1-yl)alkyl] and *N*-[(1*H*-1,2,4-triazol-1-yl)alkyl] derivatives of aryl amides I,[2] heteroaryl amides II,[3] and isoindole-1,3(2*H*)-diones III[4] was found to have interesting levels of thromboxane (TX) synthetase inhibiting activity as well as antihypertensive effects.



I: Ar = substituted phenyl
II: Ar = thienyl, furyl, benzothienyl benzofuryl, pyridyl, indolyl

III

Although TX synthetase inhibitors may well find clinical utility in the treatment of ischemia, arrhythmias, and sudden cardiac death,[5] we were particularly intrigued by the possibility that an agent that was a selective TX synthetase inhibitor might in fact produce antihypertensive effects by reducing levels of the potent vasoconstrictor TX and concomitantly raising the levels of the endogenous vasodilator prostacyclin (PGI_2) by the shunting of endoperoxides in the arachidonic acid cascade. While this attractive proposal seemed to have some merit initially for I,[2] it did not seem to generalize for the heterocyclic analogues II.[3] Isoindole-1,3(2*H*)-diones III,[4] on the other hand, did seem to have a unique biological profile with the most

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