4-(Diphenylmethyl)-1-[(imino)methyl]piperidines as Gastric Antisecretory Agents

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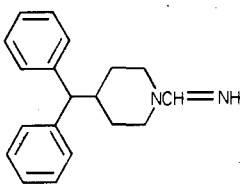
4-(Diphenylmethyl)-1-piperidinemethanimine (1) is a potent oral gastric antisecretory agent in rats but contains a strong anticholinergic component. Since a nonanticholinergic gastric antisecretory drug would be useful in the treatment of peptic ulcer disease, a program was initiated by us to find such an agent based on 1. Compound 1 contains structural elements common to the anticholinergics atropine and homatropine. Studies on the structure–activity relationships of these compounds and their derivatives have revealed certain modifications that diminish or abolish anticholinergic activity. The application of these modifications to the design of analogues of 1 afforded an antisecretory compound, 4-(diphenylmethyl)-1-[(octylimino)methyl]piperidine (**3h**, fenoctimine), which exhibited no anticholinergic activity. Fenoctimine is undergoing clinical trial as a gastric antisecretory drug.

In the course of biological screening, 4-(diphenylmethyl)-1-piperidinemethanimine (1) was found to be both



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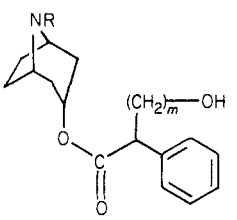
a potent suppressor of gastric acid secretion (acute gastric fistula) and a powerful anticholinergic (carbachol-induced gastric emptying) in the rat. The difference in ED_{50} values of antisecretory vs. anticholinergic activity (Table II) suggested that 1 contained an antisecretory component not due to anticholinergic activity. Since a gastric antisecretory compound that exerted little or no effect on cholinergic function would be valuable in the treatment of peptic ulcer disease, we used amidine 1 as the basis of a program to design and synthesize analogues in which anticholinergic activity would be minimized or eliminated and antisecretory activity would be optimized. The initial step in this program required a structural comparison of 1 and anticholinergic compounds, here represented by atropine (**2a**).



2a, R = CH_3; m = 1 (atropine)
b, R = C_2H_5; m = 1
c, R = $CH_2{=}CH_2$; m = 1
d, R = CH_3; m = 0 (homatropine)
e, R = $CH(CH_3)_2$; m = 0

This revealed that 1 contained structural elements common to **2a** and most anticholinergics, namely, a large lipophilic group (e.g., diphenylmethyl or benzyl) separated by 5–9 Å from a cationic terminus, such as protonated or quaternized nitrogen.[1] Once the commonalities of 1 and **2a** were established, various studies of structure–activity relationships of anticholinergic compounds were examined. Two of these studies involved the effect of atropine, homatropine (**2d**), also a potent anticholinergic, and their *N*-alkyl- or *N*-alkenyl-substituted analogues **2b,c,e**, on the acetylcholine-induced depression of cat blood pressure and showed that as the size of the substituent at the basic center increased, a substantial diminution of anticholinergic activity occurred, where **2b** and **2c** were 25 times less anticholinergic than **2a**, and **2e** was 10 times less anticholinergic than **2d**.[2,3] These structural changes of **2a** and **2d** suggested that similar modifications of 1 at the imino nitrogen or methanamine carbon might result in an antisecretory compound with little or no anticholinergic component. Accordingly, we undertook the synthesis of a series of amidines of general structure **3** (Table I), whose design was based on the successful anticholinergic-reducing modifications represented by **2b,c,e**. The methods of

Scheme I

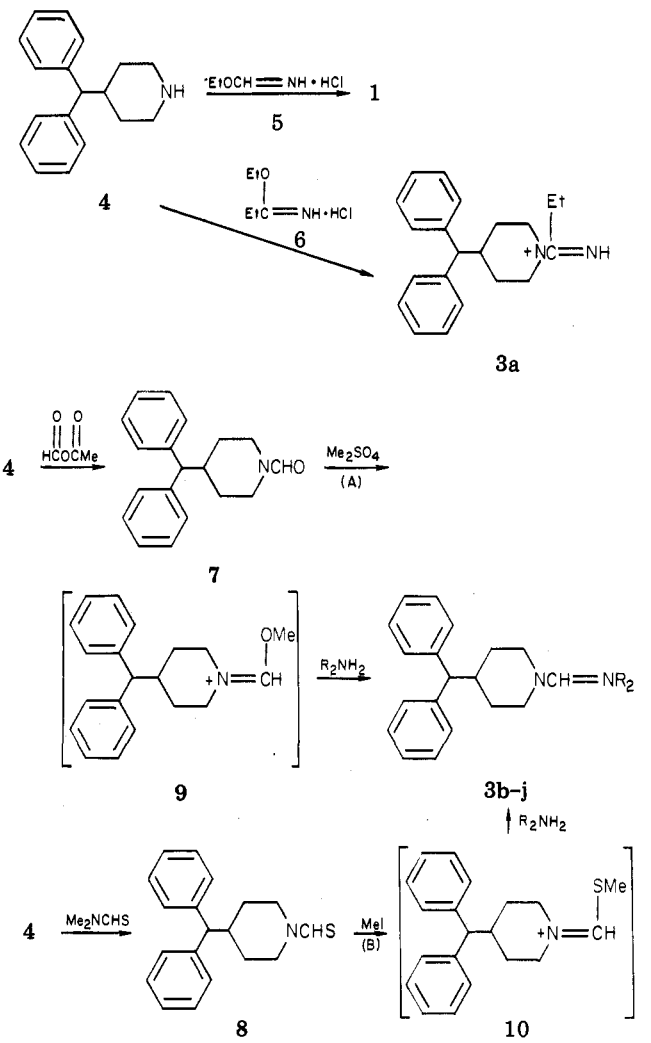


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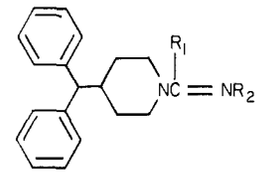
Table I. 4-(Diphenylmethyl)-1-[(imino)methyl]piperidines



compd	R_1	R_2	formula	mp, °C	recrystn solv	yield, %	anal.	synth method
1	H	H	$C_{19}H_{22}N_2 \cdot HCl \cdot 1.13H_2O$	217-219	toluene	43	C, H, N, H_2O[a]	
3a	C_2H_5	H	$C_{21}H_{26}N_2 \cdot HCl$	276.5-277.5	ethanol-ether	62	C, H, N	
3b	H	$CH(CH_3)_2$	$C_{22}H_{28}N_2 \cdot C_4H_4O_4 \cdot 0.63H_2O$[b]	175-178	ethanol	34	C, H, N, H_2O[c]	A
3c	H	$CH_2CH{=}CH_2$	$C_{22}H_{26}N_2 \cdot C_6H_{13}SO_3N$	179.5-181	acetone	49	C, H, N	A
3d	H	$3\text{-}CH_2C{\equiv}CH$	$C_{22}H_{24}N_2 \cdot HCl$	117-119	2-propanol-ether	38	C, H, N	B
3e	H	$(CH_2)_3CH_3$	$C_{23}H_{30}N_2 \cdot C_4H_4O_4$	194-196	ethanol-ether	27	C, H, N	A
3f	H	$(CH_2)_5CH_3$	$C_{25}H_{34}N_2 \cdot C_4H_4O_4$	179-181.5	2-propanol	33	C, H, N	A
3g	H	$(CH_2)_6CH_3$	$C_{26}H_{36}N_2 \cdot C_4H_4O_4 \cdot 0.50H_2O$	175-178	2-propanol	14	C, H, N, H_2O	A
3h	H	$(CH_2)_7CH_3$	$C_{27}H_{38}N_2 \cdot C_4H_4O_4 \cdot 0.63H_2O$	153 (sinter) 157-159	ethanol-water	10	C, H, N, H_2O	A
3i	H	$(CH_2)_8CH_3$	$C_{28}H_{40}N_2 \cdot C_4H_4O_4 \cdot 0.63H_2O$	142-144.5	ethanol-water	19	C, H, N, H_2O	A
3j	H	$(CH_2)_9CH_3$	$C_{29}H_{42}N_2 \cdot C_4H_6O_4$	104 (softens) 106-109	2-propanol-ether	14	C, H, N	A

[a] H_2O: calcd, 6.07; found, 6.94. [b] $C_4H_4O_4$ represents fumaric acid. [c] H_2O: calcd, 2.53; found, 3.04.

synthesis and the results of the evaluation of the antisecretory and anticholinergic activity of amidines **3** are reported in this paper.

Chemistry. Amidines **3** (Table I) were prepared as shown in Scheme I. Treatment of piperidine **4** with imidinium esters **5**[4] and **6**[5,6] afforded amidines **1** and **3a**, respectively. The N-substituted compounds **3b–j** were prepared by either method A or method B. Piperidine **4** was converted to formamide **7** by using acetic–formic anhydride, while thioformamide **8** was obtained from **4** and *N,N*-dimethylthioformamide. Generation of intermediate imidinium esters **9** (method A) and **10** (method B), without isolation, and subsequent reaction with an appropriate amine afforded amidines **3b–j**, which were isolated as the salts shown in Table I.

Results and Discussion

Compounds **1** and **3a–j** were evaluated in the acute gastric fistula rat, for antisecretory activity, and in the rat carbachol-induced gastric emptying test and cholinergic receptor binding assay, for anticholinergic activity. These methods are described under Experimental Section, and the results are shown in Table II and depicted graphically in Figure 1. For comparative purposes, data for the reference drugs atropine (**2a**) and cimetidine are included.

Substitution of an ethyl group for hydrogen on the methanimine carbon of **1** (compound **3a**) caused a decrease in antisecretory potency compared to anticholinergic activity, reflected by the low therapeutic ratio of **3a** (Table II). When R_1 on the amidine nitrogen was a three-carbon group (R_2 = H), i.e., isopropyl (**3b**), allyl (**3c**), or propargyl (**3d**), a slight separation between antisecretory and anticholinergic activity was observed with an approximate 30-fold decrease in oral potency compared to **1**. The therapeutic ratios of these compounds were greater than that of **3a** but were less than that of **1**. This trend continued for the *n*-butyl (**3e**) and *n*-hexyl (**3f**) analogues. An increase in the separation of activity was noted for the *n*-heptyl compound **3g**, which had a therapeutic index about equal to that of **1** and was greater than those of **3a–f**. Although **3g** represented an improvement over compounds **3a–f**, far more interesting results were obtained for amidine **3h** (R_1 = *n*-octyl), where potent (ED_{50} = 10.9 mg/kg) antisecretory activity was observed but where the large ED_{50} (176 mg/kg) for gastric emptying, representing a nonspecific block of this function, suggested that the anticholinergic component had been eliminated. An increase in the length of R_1 to nine (**3i**, R_1 = *n*-nonyl) and ten (**3j**, R_1 = *n*-decyl) carbon atoms resulted in lower therapeutic indexes, compared to **3h**, but still represented significant separation of activity. The ability of compounds **1** and **3a–j** to displace [^{3}H]quinuclidinyl benzilate from rat brain muscarinic receptors appeared to parallel their therapeutic ratios, with **3h** and **3i** showing little or no affinity for the cholinergic receptor (Table II).

In addition to rats, where its antisecretory potency compared favorably with that of cimetidine, **3h** exhibited potent antisecretory activity in dogs, where it blocked the effects of histamine, gastrin tetrapeptide, and urecholine.[7] However, **3h** had no effect on the cholinergic function of these species (i.e., no tachycardia or mydriasis was observed), nor was it a histamine H_2 antagonist, suggesting that this compound is unique in controlling mammalian gastric acid secretion. Based on its pharmacological profile and demonstrated safety in animals, amidine **3h** (McN-4097, USAN name, fenoctimine) was selected to be evaluated in man. Clinical studies are now in progress.

Experimental Section

All melting points are uncorrected and were taken on Thomas-Hoover Uni-Melt or Laboratory Devices Mel-Temp melting point apparatuses in capillary melting point tubes. UV spectra were determined on a Carey 14 instrument. IR spectra were taken on a Perkin-Elmer 552 infrared spectrophotometer. The 90-MHz NMR spectra were obtained on a Perkin-Elmer R-32 nmr spectrometer with Me_4Si as an internal standard. The spectral data for each compound supported the assigned structure, and all

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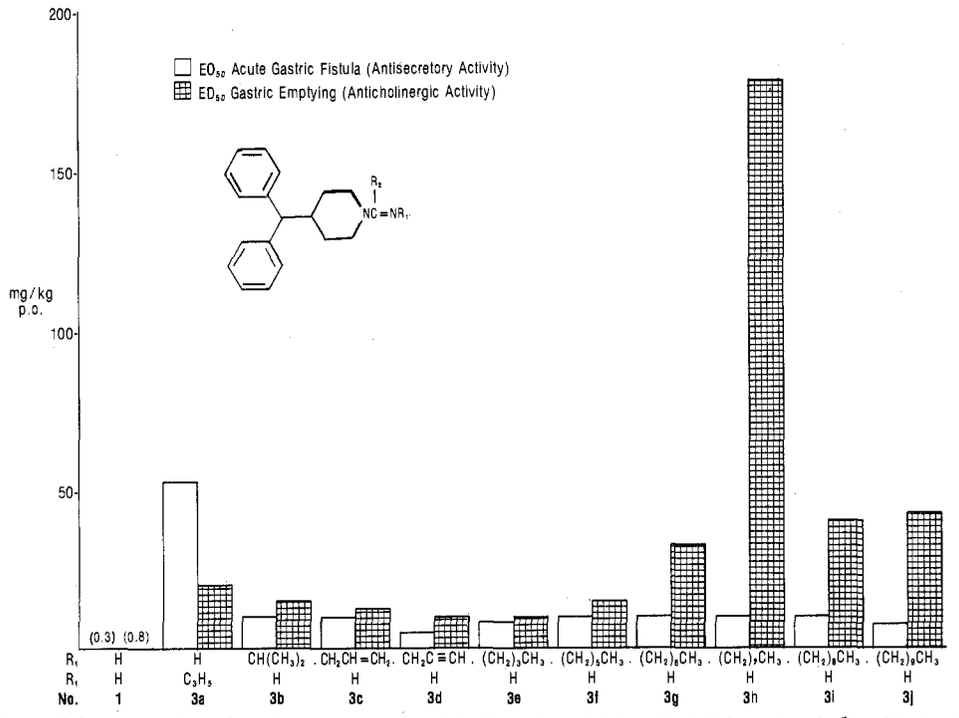

Figure 1. Comparison of the separation of antisecretory and anticholinergic activities of 4-(diphenylmethyl)-1-[(imino)methyl]piperidines. Confidence limits are given in Table II.

Table II. Antisecretory and Anticholinergic Activity of 4-(Diphenylmethyl)-1-[(imino)methyl]piperidines[a]

compd	AGF:[b] ED_{50} (rat), mg/kg, po	GE:[c] ED_{50} (rat), mg/kg, po	therapeutic ratio: GE/AGF	cholinergic receptor binding in vitro: I_{50}, nM	cholinergic receptor binding in vitro: rel potency (atropine = 100)
1	0.34 (0.26-0.42)	0.86 (0.7-1.1)	2.53	3	81.70
3a	54.5 (29.4-142)*	~20.00	~0.37	70	3.61
3b	8.6 (8.0-9.1)	15.1 (14.2-16)	1.76	1 600	0.15
3c	10.4 (9.1-11.9)	13.2 (9.4-18.2)	1.27	490	0.51
3d	5.4 (5.0-5.8)*	~8.00	~1.48	1 300	0.19
3e	7.6 (4.2-11.7)	10.3 (9.5-11.1)	1.36	1 600	0.15
3f	8.34 (4.9-21.8)*	15.00 (13.6-16.4)	1.80	1 900	0.13
3g	11.5 (9.3-14.4)	33.4 (27.5-41.9)	2.90	3 300	0.08
3h	10.9 (3.3-19.4)	176.00 (81-3189)	16.15	8 600	0.04
3i	10.8 (6.6-18.4)	40.4 (34.4-41.4)	3.74	>10 000	
3j	7.8 (7.0-8.8)	43.1 (33.1-58.1)	5.52	3 800	0.06
2a	0.64 (0.44-0.89)	0.35 (0.25-0.48)	0.55	1.3	100.00
cimetidine	7.6 (5.7-10.8)	160[d]	>21.05		

[a] 95% confidence limits are given in parentheses. Parentheses marked with asterisk indicates 90% confidence limits. [b] AGF = acute gastric fistula. [c] GE = gastric emptying, carbachol induced. [d] Highest dose tested.

elemental and Karl-Fischer analyses were within 0.4% of the calculated values, except as indicated.

4-(Diphenylmethyl)-1-piperidinemethanimine Hydrochloride Hydrate (1). A mixture of 10.0 g (0.04 mol) of 4-(diphenylmethyl)piperidine, 5.80 g (0.053 mol) of ethyl formimidate hydrochloride[4] (5), and 100 mL of absolute ethanol was stirred under a drying tube at 25 °C for 0.75 h and filtered, and the solvent was evaporated in vacuo, furnishing an oil. This material was heated in toluene, which caused solidification. Recrystallization from ethanol–ether and then from methylene chloride–toluene afforded 5.76 g (43%) of a white solid: mp 217–219 °C; IR ($CHCl_3$) ν_{max} 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.87 (s, 1, CH=N).

4-(Diphenylmethyl)-1-(1-iminopropyl)piperidine Hydrochloride (1:1) (**3a**). To a solution of 10.00 g (0.04 mol) of 4-(diphenylmethyl)piperidine in 50 mL of absolute EtOH was added 5.60 g (0.041 mol) of **6**.[5,6] A precipitate formed over several minutes, and the resulting mixture was stirred overnight at 25 °C. Filtration yielded colorless crystals, which were recrystallized twice from ethanol–ether to afford 8.43 g (62%) of **3a**: mp 276–277.5 °C; IR (KBr) ν_{max} 1680 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 2.58 (q, J = 7 Hz, 2, CH_2CH_3), 1.12 (t, J = 7 Hz, 3, CH_3).

Method A. A mixture of 4.46 g (0.016 mol) of 1-formyl-4-(diphenylmethyl)piperidine (**7**) and 2.00 g (0.015 mol) of dimethyl sulfate was heated at 100 °C for 3 h until the mixture became homogeneous.[8] The thick, clear oil was cooled, dissolved in 30 mL of CH_2Cl_2, and treated with 0.016 mol of amine, and the resulting solution was stirred for 3 h at 25 °C. After the mixture was cooled to 0 °C, 6 mL of 3 N NaOH was added with vigorous stirring, and the CH_2Cl_2 phase was separated, dried over anhydrous K_2CO_3, and evaporated. The residue was characterized as a salt.

Method B. 4-(Diphenylmethyl)-1-[(2-propynylimino)methyl]piperidine Hydrochloride (1:1) (**3d**). A solution of 2.95 g (0.01 mol) of **8**, 1.42 g (0.01 mol) of iodomethane, and 10 mL of $CHCl_3$ was refluxed for 45 min, cooled to room temperature, and treated with 0.55 g (0.01 mol) of propargylamine. After heating and stirring for 1 h under reflux, the reaction mixture was cooled, filtered, and evaporated in vacuo to give a foamy solid, which was dissolved in CH_2Cl_2 and stirred vigorously with 6 mL of 3 N NaOH solution. The organic layer was separated, dried over anhydrous K_2CO_3 and filtered. The filtrate was concentrated to an oil, which solidified upon trituration with ether. This material was dissolved in CH_2Cl_2, and treated with ethereal HCl,

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and the organic solvents were removed. The residue was recrystallized twice from 2-propanol–ether (using charcoal to remove color) to give 1.34 g (38%) of white crystals: mp 117–119 °C; IR (KBr) ν_{max} 2119 and 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.38 (s, 1, CH=N), 2.46 (t, J = 2 Hz, 1, C≡CH).

1-Formyl-4-(diphenylmethyl)piperidine (7). 4-(Diphenylmethyl)piperidine (22.00 g, 0.088 mol) was added portionwise to acetic–formic anhydride,[9] prepared from 17.30 mL of acetic anhydride and 8.77 mL of 97% formic acid, at 0 °C, and the resulting mixture was stirred at 25 °C overnight. Chloroform was added, and the solution was treated with saturated $NaHCO_3$ solution until the aqueous layer was basic (pH 8). The organic layer was separated, dried over anhydrous K_2CO_3, and filtered, and the filtrate was evaporated to an oil, which was crystallized from ethanol to give 17.30 g (71%) of white crystals, mp 128–130 °C. Recrystallization from ethanol afforded material melting at 131–134 °C: IR (KBr) ν_{max} 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.96 (s, 1, CH=O), 4.34 (d, J = 13 Hz, 1, C-2 equatorial H syn to carbonyl O), 3.52 (d, J = 13 Hz, 1, C-6 equatorial H anti to carbonyl O), 2.99 (t of d, J = 12 and 3 Hz, respectively, 1, C-6 axial H anti to carbonyl O), 2.57 (t of d, J = 12 and 3 Hz, respectively, 1, C-2 axial H syn to carbonyl O). Anal. ($C_{19}H_{21}NO$) C, H, N.

4-(Diphenylmethyl)-1-piperidinecarbothioaldehyde (8). A solution of 20.0 g (0.08 mol) of 4-(diphenylmethyl)piperidine, 14.2 g (0.16 mol) of *N,N*-dimethylthioformamide, and 50 mL of toluene was refluxed for 12 h, cooled, and washed with water. The organic layer was separated, dried, and concentrated to an oil, which, upon trituration with ether, gave a solid. Recrystallization from ethanol afforded colorless crystals: mp 152–154 °C; ^1H NMR ($CDCl_3$) δ 9.12 (s, 1, CH=S), 5.12 (d, J = 13 Hz, 1, C-2 equatorial H syn to thiocarbonyl S), 3.70 (d, J = 13 Hz, 1, C-6 equatorial H anti to thiocarbonyl S), 3.33 (t of d, J = 13 and 3 Hz, respectively, 1, C-6 axial H anti to thiocarbonyl S), 2.79 (t of d, J = 13 and 3 Hz, respectively, 1, C-2 axial H syn to thiocarbonyl S). Anal. ($C_{19}H_{21}NS$) C, H, N.

Pharmacological Methods. The ED_{50} values for gastric antisecretory and gastric empyting activity were determined with at least five animals per dosage group and at least three dosage groups per ED_{50}.

Gastric antisecretory activity was evaluated in the acute gastric fistula rat.[10] In this preparation, drug or vehicle (0.5% methocel solution) was administered po 1 h before surgery.

Female Sprague–Dawley rats (Charles River, Inc.) weighing 120–160 g were deprived of food for at least 18 h. The rats were anesthetized with diethyl ether in an anesthesia jar, and after laparotomy, a flanged polyethylene tube was inserted into the fundal portion of the stomach. The wound was closed, and the rats were placed in a plastic cage with a slit to allow the cannula to pass through. A 10-mL collecting tube was attached, and the collection was begun. The first 30-min sample was discarded, and then two 1-h samples were collected. Each sample was centrifuged, the volume was determined, and a 1-mL aliquot was removed for titration to pH 7 using 0.01 N NaOH. Results are expressed as volume (milliliters), titratable acidity (milliequivalents per liter), and total acid output (milliequivalents of H^+). ED_{50}'s were calculated by the method of least-squares regression analysis and represent the dose (milligrams per kilogram) required to produce an average of 50% inhibition in total acid output vs. controls in the animals tested for a particular compound.

Anticholinergic activity was determined in vivo by measuring the effect of the compounds on carbachol-induced gastric emptying in the rat.[11]

Twenty-four hour food-deprived female Sprague–Dawley rats weighing 80–100 g were dosed orally with drug or vehicle. Thirty minutes later, ten 1-mm polystyrene beads were placed in the rats stomach by using a polyethylene tube. One hour after drug or vehicle administration, the rats were injected with 80 mcg/kg of carbachol subcutaneously and then sacrificed after 15 min. The number of beads remaining in the stomach were counted. Vehicle-treated rats emptied greater than 90% of the beads. The ED_{50}'s, which were calculated by least-squares regression analysis, are the doses (milligrams per kilogram) that caused an average of 50% inhibition of gastric emptying compared with controls.

An in vitro determination of anticholinergic activity of the compounds was obtained by measuring their ability to displace [^3H] quinuclidinyl benzilate from rat brain muscarinic receptor by the method of Snyder and Yamamura.[12]

Acknowledgment. The authors gratefully acknowledge the assistance of B. Price, S. Gray, C. Schneider, and A. Staus for the preparation and testing of the compounds. We also thank M. Mutter, J. Rogers, and R. Acchione for spectral data.

Registry No. 1, 72964-09-1; **3a**, 72964-10-4; **3a** (free base), 84132-05-8; **3b**, 84132-06-9; **3c**, 84132-07-0; **3d**, 72964-52-4; **3e**, 84132-08-1; **3f**, 84132-09-2; **3g**, 84132-10-5; **3h**, 84132-11-6; **3i**, 84132-12-7; **3j**, 84132-13-8; **4**, 19841-73-7; **5**, 16694-46-5; **6** (free base), 1070-17-3; **7**, 72964-01-3; **8**, 72964-02-4; acetic–formic anhydride, 2258-42-6; *N,N*-dimethylthioformamide, 758-16-7.

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Inhibitors of Gastric Acid Secretion: Antisecretory 2-Pyridylurea Derivatives

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A series of aminoalkyl-substituted pyridylureas has been prepared and evaluated as inhibitors of gastric acid secretion. *N,N*-Dimethyl-*N'*-[2-(diisopropylamino)ethyl]-*N'*-(4,6-dimethyl-2-pyridyl)urea (**8g**) was the most potent example of the class. Comparison of this compound with cimetidine showed it to be equipotent in dogs stimulated with gastrin tetrapeptide but approximately half as potent in dogs stimulated with histamine. Inhibition of secretion does not appear to result from antagonism of the histamine H_2 receptor, since the compounds show only weak inhibition of the H_2 receptor in vitro.

A previous report from these laboratories described the preparation of a series of 1,8-naphthyridin-2(1*H*)-ones, exemplified by **1**, for gastric antisecretory evaluation.[1] Although these compounds inhibited gastric acid secretion

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