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}; ^{1}H 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}; ^{1}H 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; ^{1}H 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 [^{3}H] 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.

(9) W. Stevens and A. VanEs, *Recl. Trav. Chim Pays-Bas*, **83**, 1287 (1964).
(10) H. I. Jacoby, A. C. Bonfilio, S. Gray, A. Staus, *Digestion*, **19**, 237 (1979).
(11) D. A. Brodie, *Gastroenterology*, **50**, 45 (1966).
(12) S. H. Snyder and H. I Yamamura, *Proc. Natl. Acad. Sci. U.S.A.*, **71**, 1725 (1974).

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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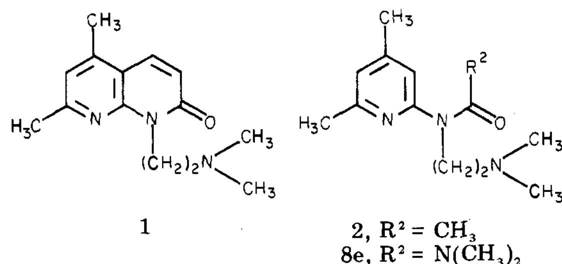


in the dog induced by gastrin tetrapeptide, gastric secretion stimulated by histamine was not inhibited at reasonable dose levels. Because of the involvement of histamine as an important mediator in the gastric secretory process, this series was considered to be devoid of drug potential. However, the naphthyridine structure served as the basis for development of a new structural type having greater inhibitory effectiveness against the major secretory agonists.

One modification, a 2-acetamidopyridine derivative, **2**, in which the pyridinone ring of the naphthyridinone nucleus was replaced by an acylamino function, showed promising activity in a primary antisecretory screen in dogs. A variant of **2** (**8e**) in which the acyl group was replaced by carbamoyl, showed further improvement in antisecretory activity. The pyridylurea derivative **8e** represented a new antisecretory structural type, and a number of analogues were prepared to evaluate this lead. The inhibitory effects on gastric secretion resulting from systematic change of substituents in the pyridine ring, the urea, and terminal-chain nitrogen, as well as a variation of the chain length, in **8e** were determined.

This report summarizes the major structural requirements for gastric antisecretory activity and provides a detailed comparison of one of the most potent compounds to cimetidine, an antisecretory agent in clinical use.

Chemistry. Most of the pyridylureas were made by reactions outlined in Scheme I. Basically, two alternate routes were employed for preparation of the final product **8**. In one, the final step involved an alkylation of a urea, while in the other, the final step was a carbamoylation. Both routes were satisfactory, and the choice was dependent mainly on availability of starting materials and reagents and the projected uses of intermediates for other syntheses. Compound **10**, obtained by carbamoylation of the anion of **9** with *N*,*N*-dimethylcarbamoyl chloride, was converted to its anion with lithium hydride and alkylated with benzylmethylaminoethyl chloride to give **8a**. In the other route, amine **7** was treated with butyllithium, and the anion was carbamoylated with *N*,*N*-dimethylcarbamoyl chloride to yield **8**.

Compounds of structure **7** were prepared by a number of routes. The majority were made by alkylation of the acetylated aminopyridine **5**. The acetyl products **6** were hydrolyzed, usually without purification, and the products **7** were purified by vacuum distillation. Yields and physical data are reported in Table I. For certain analogues of **7** (**7m–o**), halopyridines were more appropriate starting materials, and the aminoalkylamino group was introduced by displacement of halogen. The starting halopyridine, **25**, for **7o** included a cyano group, which was eliminated after formation of **26** by hydrolysis and decarboxylation. The preparation of the 4-methoxy derivative **7n** required a methoxide displacement of the nitro group of **28**, followed by an iron powder–acetic acid reduction of the *N*-oxide of **29**. Use of 2-chloro-4-nitropyridine instead of the *N*-oxide **27** in the amination reaction resulted in a preferential displacement of the nitro group.

The *N*-methylcarbamoyl derivative **12** was prepared by reacting **7g** with methyl isocyanate. The unsubstituted carbamoyl product **11** was prepared by hydrolysis of the cyanamide **23** obtained by reacting **7g** with cyanogen bromide.

Compounds with longer alkylene chains were prepared via aldehyde intermediates shown in Scheme II. This strategy provided a convenient access to compounds with various terminal dialkylamino substituents. The alkylation of **5g** with a protected alcohol, 4-chlorobutyl acetate, and the subsequent oxidation of the free alcohol **18** with pyridinium chlorochromate gave the aldehyde **19**. Reductive amination of **19** with diisopropylamine and sodium cyanoborohydride yielded the amine **20**, which, after hydrolysis, was converted to the pyridylurea **22** by reaction with *N*,*N*-dimethylcarbamoyl chloride.

In another route to longer-chain compounds, 2-amino-4,6-dimethylpyridine (**9**) was alkylated with 3,3-diethoxypropyl chloride to yield **13**, which was then acylated with *N*,*N*-dimethylcarbamoyl chloride. The acetal group of **14** was hydrolyzed with dilute acid, and the aldehyde **15** was reductively aminated with the amine and cyanoborohydride to yield the product **16**.

Biological Results and Discussion

A primary antisecretory evaluation of all compounds was performed in dogs stimulated with gastrin tetrapeptide, followed by secondary evaluation of the most potent compounds in related tests. Antisecretory activity in dogs is reported in Table II as percent decrease in the concentration of gastric acid after oral administration. All compounds were tested initially at a level of 20 mg/kg, and those with low or high activity were retested at 40 and 10 mg/kg, respectively.

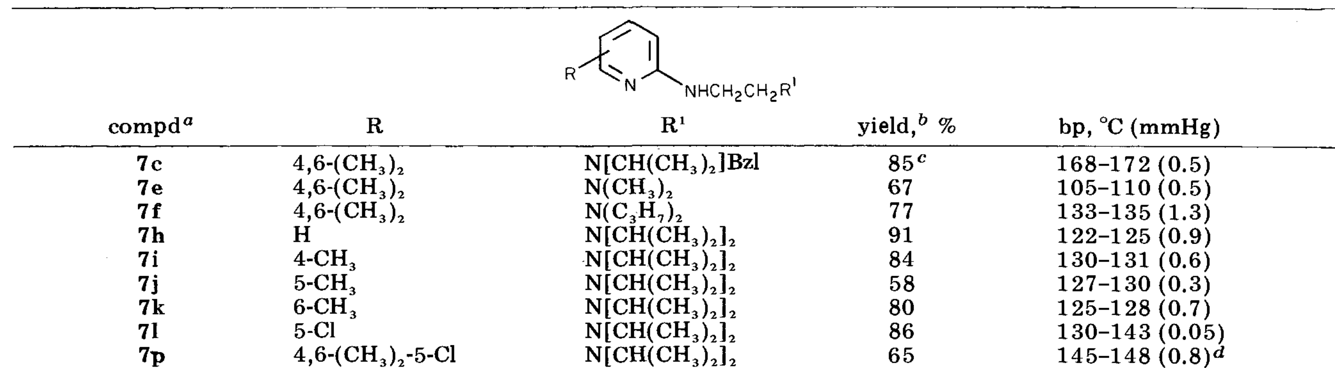
Representative compounds of the series were tested in vitro in rat uterus for reversal of the histamine effect on contraction, a response mediated by the histamine H_2 receptor.[2] Inhibitory activity, when observed, was weak compared with that of the cimetidine standard ($\leq$0.1 of cimetidine). It was concluded that in this structural series inhibition of gastric secretion does not result from competitive inhibition of the histamine H_2 receptor.

During the in vivo evaluation of the pyridylurea series, it became evident that the dialkylaminoethyl side chain could not be significantly modified without a decrease in potency. The analogues **8b,d,f,g**, **16**, and **22**, in which only the side chain of the lead structure **8e** is modified, clearly illustrate the effect of structural changes. The monoalkyl derivatives **8b** and **8d** had low activity. With increasing length of the di-*n*-alkyl groups as in the dipropyl analogue **8f**, potency decreases. Branching of the alkyl substituent, as in **8g**, was advantageous, as higher potency was attainable than with the corresponding *n*-alkyl counterpart. Lengthening of the alkylene chain caused a major decrease in potency as shown by the propylene (**16**) and butylene (**22**) analogues. Therefore, for maximal activity, the amino group must be disubstituted and separated from the urea nitrogen atom by an alkylene chain of two methylene units. This was consistently true for the series regardless of changes elsewhere in the structure. Comparative antisecretory data for other modifications of the pyridylurea structure are reported in Table II only for the diisopropylaminoethyl analogues.

Dimethyl substitution on the urea nitrogen (R^2, Table II) as exemplified by **8g** yielded maximum antisecretory

(1) Bolhofer, W. A.; Hoffman, J. M.; Habecker, C. N.; Pietruszkiewicz, A. M.; Cragoe, E. J., Jr.; Torchiana, M. L. *J. Med. Chem.* 1979, *22*, 301.

Table I. Properties of **7** Prepared from **5**



compd[a]	R	R^1	yield,[b] %	bp, °C (mmHg)
7c	4,6-$(CH_3)_2$	$N[CH(CH_3)_2]Bzl$	85[c]	168-172 (0.5)
7e	4,6-$(CH_3)_2$	$N(CH_3)_2$	67	105-110 (0.5)
7f	4,6-$(CH_3)_2$	$N(C_3H_7)_2$	77	133-135 (1.3)
7h	H	$N[CH(CH_3)_2]_2$	91	122-125 (0.9)
7i	4-CH_3	$N[CH(CH_3)_2]_2$	84	130-131 (0.6)
7j	5-CH_3	$N[CH(CH_3)_2]_2$	58	127-130 (0.3)
7k	6-CH_3	$N[CH(CH_3)_2]_2$	80	125-128 (0.7)
7l	5-Cl	$N[CH(CH_3)_2]_2$	86	130-143 (0.05)
7p	4,6-$(CH_3)_2$-5-Cl	$N[CH(CH_3)_2]_2$	65	145-148 (0.8)[d]

[a] R and R^1 as in compound **8** (Table II). [b] From corresponding **5**. [c] $ClCH_2CH_2N(CH_2C_6H_5)[CH(CH_3)_2]$ intermediate: Nickerson, M.; Gump, W. S. *J. Pharmacol. Exp. Ther.* 1949, *97*, 25. [d] Anal. ($C_{15}H_{26}ClN_3$) C, H, N.

Table II. Gastric Antisecretory Activity

compd	*n*	R	R^1	R^2	formula[a]	mp or bp, °C (mmHg)	recrystn solvent[b]	% inhibn of acid concn at the following po doses[c]		
								10 mg/kg	20 mg/kg	40 mg/kg
8b	2	4,6-$(CH_3)_2$	$NHCH_3$	$N(CH_3)_2$	$C_{13}H_{22}N_4O\cdot 2HBr$	170-172	C			20 ± 16 (3)
8c[d]	2	4,6-$(CH_3)_2$	$N[CH(CH_3)_2]Bzl$	$N(CH_3)_2$	$C_{22}H_{32}N_4O\cdot 2HBr$	203-204	A		not tested	
8d[e]	2	4,6-$(CH_3)_2$	$NHCH(CH_3)_2$	$N(CH_3)_2$	$C_{15}H_{26}N_4O\cdot HBr\cdot 0.5H_2O$[f]	128-130 dec	B		33 ± 11 (4)	42 ± 15 (3)
8e[d]	2	4,6-$(CH_3)_2$	$N(CH_3)_2$	$N(CH_3)_2$	$C_{14}H_{24}N_4O\cdot 2HCl$	202 dec	A	14 ± 6 (6)	58 ± 10 (6)	58 ± 8 (9)
8f[d]	2	4,6-$(CH_3)_2$	$N(C_3H_7)_2$	$N(CH_3)_2$	$C_{18}H_{32}N_4O$	142-145 (0.4)			22 ± 11 (4)	93 ± 7 (2)
8g	2	4,6-$(CH_3)_2$	$N[CH(CH_3)_2]_2$	$N(CH_3)_2$	$C_{18}H_{32}N_4O\cdot HCl$	190-192	A	70 ± 9 (12)	100 (14)	
16	3	4,6-$(CH_3)_2$	$N[CH(CH_3)_2]_2$	$N(CH_3)_2$	$C_{19}H_{34}N_4O\cdot 2HBr$	224 dec	A		0 (4)	35 ± 21 (4)
22	4	4,6-$(CH_3)_2$	$N[CH(CH_3)_2]_2$	$N(CH_3)_2$	$C_{20}H_{36}N_4O$	165-167 (0.7)			5 ± 2 (4)	3 ± 2 (4)
11	2	4,6-$(CH_3)_2$	$N[CH(CH_3)_2]_2$	NH_2	$C_{16}H_{28}N_4O\cdot HCl$	160-162	B		18 ± 9 (4)	CNS effects
12	2	4,6-$(CH_3)_2$	$N[CH(CH_3)_2]_2$	$NHCH_3$	$C_{17}H_{30}N_4O\cdot 2HCl$	179 dec	D		44 ± 11 (8)	CNS effects
8h[d]	2	H	$N[CH(CH_3)_2]_2$	$N(CH_3)_2$	$C_{16}H_{28}N_4O$	140-145 (0.4)			17 ± 11 (8)	82 ± 13 (2)
8i[d]	2	4-CH_3	$N[CH(CH_3)_2]_2$	$N(CH_3)_2$	$C_{17}H_{30}N_4O\cdot HCl\cdot 0.25H_2O$	133-136	A	79 ± 12 (4)	95 ± 4 (8)	
8j[d]	2	5-CH_3	$N[CH(CH_3)_2]_2$	$N(CH_3)_2$	$C_{17}H_{30}N_4O$	140 (0.05)			19 ± 8 (6)	33 ± 19 (2)
8k[d]	2	6-CH_3	$N[CH(CH_3)_2]_2$	$N(CH_3)_2$	$C_{17}H_{30}N_4O\cdot HCl$	156.5-157.5	A	54 ± 15 (6)	87 ± 11 (4)	
8l[d]	2	5-Cl	$N[CH(CH_3)_2]_2$	$N(CH_3)_2$	$C_{16}H_{27}ClN_4O$	147 (0.1)		44 ± 44 (2)	63 ± 9 (5)	
8m[d]	2	6-Cl	$N[CH(CH_3)_2]_2$	$N(CH_3)_2$	$C_{16}H_{27}ClN_4O\cdot HCl$	143.5-145.5	A		78 ± 13 (4)	
8n[d]	2	4-OCH_3	$N[CH(CH_3)_2]_2$	$N(CH_3)_2$	$C_{17}H_{30}N_4O_2$	168-170 (0.7)		64 ± 17 (4)	84 ± 9 (4)	
8o[d]	2	4-CH_3-6-Cl	$N[CH(CH_3)_2]_2$	$N(CH_3)_2$	$C_{17}H_{29}ClN_4O\cdot HCl$	172-175	A	52 ± 16 (2)	71 ± 12 (4)	
8p[d]	2	4,6-$(CH_3)_2$-5-Cl	$N[CH(CH_3)_2]_2$	$N(CH_3)_2$	$C_{18}H_{31}ClN_4O\cdot HCl$	175-176	A	62 ± 13 (6)	95 ± 5 (5)	

[a] Elemental analyses for C, H, N were within ±0.4% of the calculated values. [b] Recrystallization solvents: A = EtOH-ether; B = *i*-PrOH-ether; C = *i*-PrOH; D = CH_3CN-acetone. [c] Dose in terms of base weight of compound; number of animals in parentheses. [d] From corresponding **7** by the procedure used for **8g**. [e] From **8c** by the procedure used for **8b**. [f] Analyses were acceptable for 5.87% weight excess of HBr as $C_{15}H_{26}N_4O\cdot 2HBr$.

Scheme I

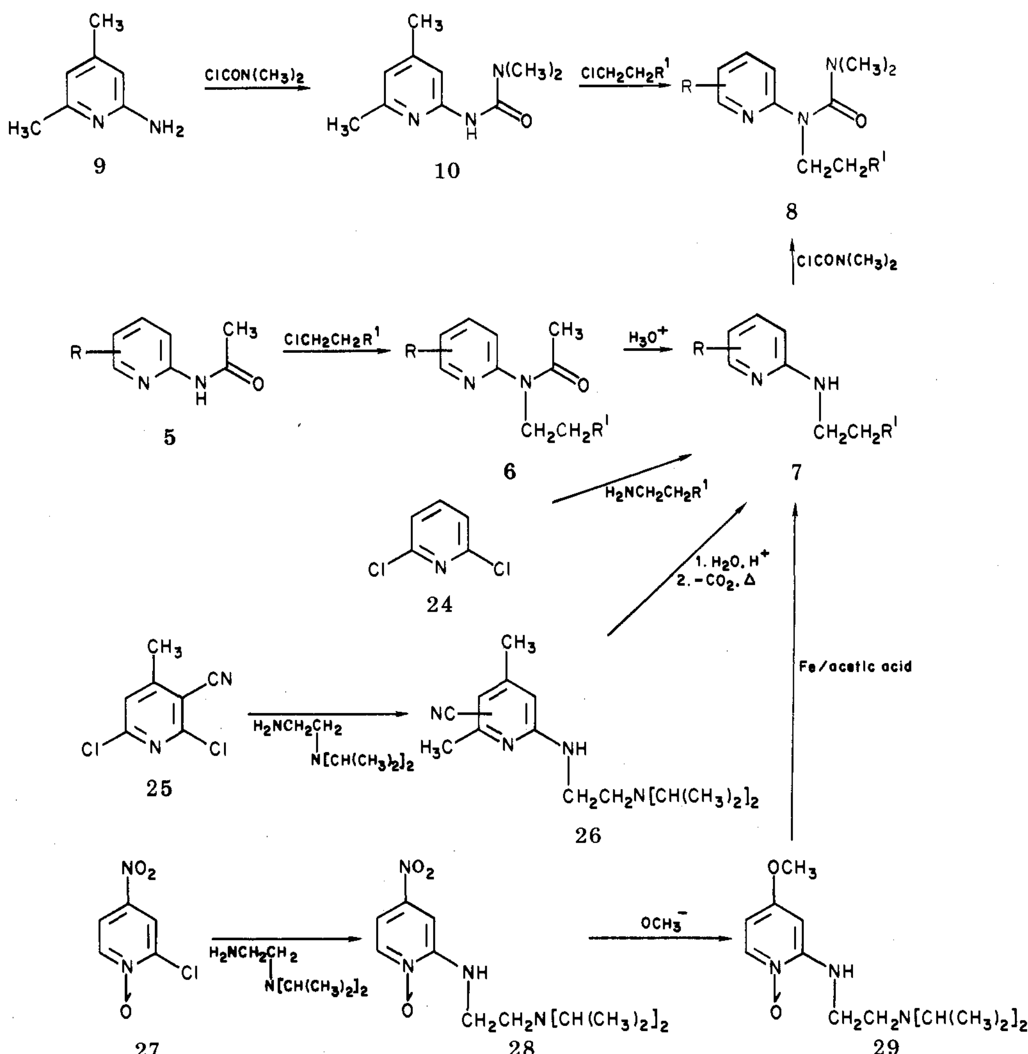


Table III. Comparison of 8g and Cimetidine in the Dog

compd	stimulant[b]	inhibn of gastric secretion: po ED_{50},[a] mg/kg (95% CL) volume	acid concn	acid output
8g	gastrin tetrapeptide	3.8 (2.1, 7.0)	6.8 (5.1, 9.0)	3.3 (2.0, 5.4)
	histamine	12.6 (6.2, 25.8)	9.6 (7.8, 11.9)	5.1 (4.0, 6.5)
cimetidine	gastrin tetrapeptide	3.9 (2.4, 6.4)	6.4 (4.9, 8.3)	3.6 (2.6, 4.9)
	histamine	3.5 (2.6, 4.7)	5.0 (3.3, 7.5)	2.6 (2.0, 3.5)

[a] Base weight of 8g. [b] Maximal stimulatory dose (see Experimental Section).

activity. Unsubstituted (**11**) or monosubstituted (**12**) analogues of **8g** were less active and showed CNS side effects, which precluded measurement of antisecretory activity at the 40 mg/kg dose.

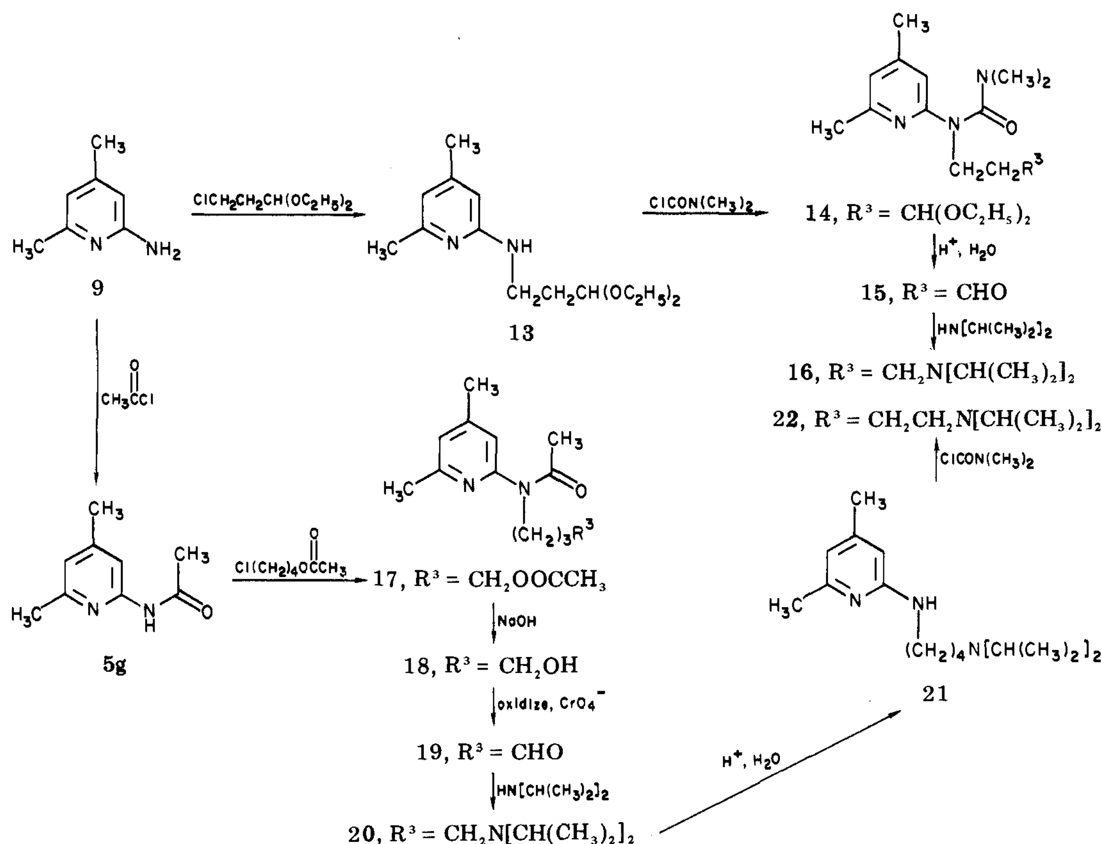
The position and type of substituent on the pyridine ring had a significant effect on antisecretory activity in this series. The 4-methyl (**8i**) and 6-methyl (**8k**) analogues had very high potency, while the 5-methyl (**8j**) analogue was considerably less active. The 6-chloro (**8m**) analogue was similar to the 6-methyl (**8k**) analogue; however, the 5-chloro (**8l**) analogue was considerably more potent than the 5-methyl (**8j**) analogue. The 4,6-dimethyl (**8g**) compound was one of the most potent in the series. Combination of methyl and chloro substitution as in the 4-methyl-6-chloro (**8o**) analogue did not prove superior to **8g**. An attempt was made to exploit the apparent potency-enhancing effect of a 5-chloro substituent by introducing this halogen into the 5-position of **8g** to give **8p**. Potency of **8g** was not enhanced. The 4-methoxy (**8n**) analogue was almost equivalent to the 4-methyl (**8i**) derivative in potency.

On the basis of the foregoing results **8g** was selected for in vivo comparison to cimetidine as shown in Table III. Compound **8g** is equipotent with cimetidine as an antagonist of secretion stimulated by gastrin tetrapeptide, but it is not as potent for inhibition of histamine-stimulated secretion. This may reflect the ineffectiveness of the series on the histamine H_2 receptor in vitro.

In other biological tests involving gastric functions, **8g** enhanced mucus output in dogs and rats and showed a cytoprotective effect against alcohol-induced gastric necrosis in rats.[2] Metabolic studies on **8g** have been reported[3] and a toxicologic evaluation has been performed. In the

(2) Torchiana, M. L., Merck Sharp & Dohme Research Laboratories, West Point, PA, to be published.
(3) Hucker, H. B.; Stauffer, S. C.; White, S. D.; Arison, B. H.; Zacchei, A. G. *Drug Metab. Dispos.* 1982, *10*, 28.

Scheme II



latter study, chronic administration of **8g** to dogs resulted in a marked decrease in the number of parietal cells in the stomach.[4]

In summary, this study has shown that substituted pyridylureas constitute a new structural type having gastric antisecretory activity. The analogue **8g** was equipotent to cimetidine for inhibition of secretion induced by gastrin tetrapeptide but not by histamine.

Experimental Section

Melting points were determined in a capillary tube and are uncorrected. Analytical results are within ±0.4% of theoretical values unless otherwise stated. Structural identity of key intermediates and all products was confirmed by NMR spectra. Intermediates for which analyses are not reported were usually of high purity as indicated by TLC.

2-[[2-(Diisopropylamino)ethyl]amino]-4,6-dimethylpyridine (7g). Sodium hydride (57% in mineral oil; 19.80 g, 0.47 mol) was added in three portions over a 30-min period to a solution of *N*-(4,6-dimethyl-2-pyridyl)acetamide (**5g**; 77.2 g, 0.47 mol) [from acetylation of commercially available 2-amino-4,6-dimethylpyridine (**9**)] in 1.0 L of dimethylformamide under N_2. The thick reaction mixture was stirred for 30 min, and 100 g (0.5 mol) of 2-(diisopropylamino)ethyl chloride hydrochloride was added in three portions. After 30 min, a second quantity of sodium hydride (22.33 g, 0.53 mol) was added in three portions over 30 min, and the mixture was then stirred under N_2 at 75 °C for 2 h and at 90 °C for 3 h. Portionwise addition of reagents was necessary to control excessive thick foaming of the reaction. The mixture was cooled and 30 mL of EtOH was added. All solvent was removed by vacuum concentration to leave crude *N*-[2-(diisopropylamino)ethyl]-*N*-(4,6-dimethyl-2-pyridyl)acetamide (**6g**) as a dark, viscous oil. This oil was heated under reflux with 1 L of 6 N HCl for 5 h with stirring. Mineral oil was extracted with ether, and the aqueous layer was cooled in an ice bath and made strongly basic with 10 N NaOH. The product was extracted into ether. The dried (Na_2SO_4) extract was concentrated, and the residue was distilled to yield 101.8 g (87%) of **7g**, bp 125–126 °C (0.4 mm). Compounds **7c,e,f,h–l,p** were prepared similarly and are included in Table I.

***N*,*N*-Dimethyl-*N'*-[2-(diisopropylamino)ethyl]-*N'*-(4,6-dimethyl-2-pyridyl)urea Hydrochloride (8g).** A solution of *n*-butyllithium in hexane (0.41 mol) was added over 1.5 h to a well-stirred solution of 100 g (0.40 mol) of **7g** in 330 mL THF under N_2 at -5 °C. Dimethylcarbamoyl chloride (53.5 g, 0.50 mol) was then added over 1 h at -5 to 0 °C, and the mixture was stirred for 2 h at 0 °C. H_2O (20 mL) was added, and most of the solvent was removed by vacuum concentration. H_2O and CH_2Cl_2 (400 mL) were added, and the organic layer was separated, washed with Na_2CO_3 solution, dried (Na_2SO_4), and evaporated to yield an oil. This was dissolved in ether (400 mL), and ethanolic HCl was added to form the crystalline HCl salt **8g** (Table II).

Compounds **8c,e,f,h–p**, prepared in a similar manner from the corresponding amine **7** and purified as the hydro- or dihydrohalide salt or by distillation of the base, are included in Table II.

***N*,*N*-Dimethyl-*N'*-(4,6-dimethyl-2-pyridyl)urea (10).** Sodium hydride (57% in mineral oil, 38.0 g, 0.90 mol) was suspended in 600 mL of toluene at 75 °C under N_2, and 52.5 g (0.43 mol) of 2-amino-4,6-dimethylpyridine was added in small portions. The mixture was heated at 100 °C for 1 h and cooled to 90 °C, and a solution of 47.0 g (0.43 mol) of dimethylcarbamoyl chloride in 150 mL of toluene was added over 1.5 h. Heating was continued for 2 h. After the reaction mixture was cooled to room temperature, 150 mL of H_2O was added, and the organic layer was separated, dried (Na_2SO_4), and concentrated. The residue was

(4) Administration of compound **8g** (orally, gelatin capsules) to dogs for 3 months at dosage levels of 2.5, 7.5, or 22.5 mg/kg b.i.d. (six dogs per group) caused a statistically significant ($p \leq 0.05$) reduction in the number of parietal cells present in the stomach fundic mucosa of four of six dogs in each of the two highest dosage groups. Compared to mean control values, an approximate range of 25–60% reduction in parietal cells occurred in the individual affected dogs. No evidence of active parietal cell degeneration or necrosis or inflammation of the fundic mucosa was seen. The chief cell population was unaffected. Personal communication from J. A. Majka, Merck Sharp & Dohme Research Laboratories, West Point, PA 19486.

triturated with cyclohexane to give 74.0 g (85%) of 10, mp 105–108 °C. Anal. ($C_{10}H_{15}N_3O$) C, H, N.

***N,N*-Dimethyl-*N'*-[2-[(benzylmethyl)amino]ethyl]-*N'*-(4,6-dimethyl-2-pyridyl)urea (8a).** A mixture of 1.0 g (0.125 mol) LiH and 7.7 g (0.04 mol) of 10 in 80 mL of dioxane was heated at 100 °C for 3 h. 2-[(Benzylmethyl)amino]ethyl chloride hydrochloride[5] (4; 8.8 g, 0.04 mol) was added, and heating was continued for 24 h. The reaction was filtered and concentrated, and the residue was dissolved in CH_2Cl_2. The product was extracted into dilute HCl and the solution was made basic. The oil was extracted into CH_2Cl_2, and after the extract was dried (Na_2SO_4) and concentrated, 13.2 g (97%) of **8a** remained. This material was used without further purification for the preparation of **8b**.

***N,N*-Dimethyl-*N'*-[2-(methylamino)ethyl]-*N'*-(4,6-dimethyl-2-pyridyl)urea Dihydrobromide (8b).** A solution of crude **8a** (10.0 g, 0.029 mol) in 60 mL of acetic acid, containing 3.0 g of 10% Pd on C, was hydrogenated on a Parr apparatus until 1 equiv of H_2 was taken up. After the catalyst was removed, the solvent was evaporated and the residue was dissolved in H_2O. The solution was made basic with Na_2CO_3 and extracted with CH_2Cl_2. The extract was concentrated, the residue was dissolved in ether, and the salt was precipitated by adding HBr gas. Recrystallization from isopropyl alcohol gave 3.1 g (26%) of **8b** (Table II).

Compound **8c** was similarly debenzylated to give **8d**.

***N*-[2-(Diisopropylamino)ethyl]-*N*-(4,6-dimethyl-2-pyridyl)urea Hydrochloride (11).** A mixture of 19.95 g (0.08 mol) of **7g** and 12.72 g (0.12 mol) of cyanogen bromide in 125 mL of THF was stirred for 72 h at room temperature under N_2. The solvent was evaporated, and the residue was dissolved in ether. This was washed with saturated $NaHCO_3$ and H_2O and then dried (Na_2SO_4) and concentrated. The oily residue was chromatographed on silica gel, and the product fractions (determined by TLC) were combined and crystallized from EtOH–H_2O to give 6.22 g (28%) of *N*-[2-(diisopropylamino)ethyl]-*N*-(4,6-dimethyl-2-pyridyl)cyanamide (**23**), mp 57–59 °C. Anal. ($C_{16}H_{26}N_4$) C, H, N.

Sodium methoxide (1.9 g) was added to a solution of 6.9 g (0.01 mol) of **23** in 75 mL of dry methanol, and the mixture was stirred at room temperature until TLC indicated **23** was totally reacted. The mixture was diluted with ether and washed with H_2O. The ether was dried and concentrated to yield 7.0 g of an oil, which NMR showed was the *O*-methylisourea corresponding to **23**. This was dissolved in 20 mL of MeOH, and 3.8 mL of concentrated HCl was added. The mixture was concentrated, and the residue was dissolved in CH_2Cl_2. The solution was washed with aqueous Na_2CO_3, dried, and evaporated to give 7.5 g of 11. This was dissolved in 2-propanol–ether (1:25), and 4.5 mL of 6 N ethanolic HCl was added. The HCl salt of 11 slowly crystallized, and 7.3 g, mp 160–162 °C, was obtained.

***N*-Methyl-*N'*-[2-(diisopropylamino)ethyl]-*N'*-(4,6-dimethyl-2-pyridyl)urea Dihydrochloride (12).** A mixture of 8.0 g (0.032 mol) of **7g** and 3.64 g (0.064 mol) of methyl isocyanate in 50 mL of benzene was stirred at room temperature for 48 h and then concentrated. The residual oil was dissolved in ether, ethanolic HCl was added, and the crystalline product was recrystallized from CH_3CN–acetone to give 9.2 g (75.8%) of 12.

6-Chloro-2-[[2-(diisopropylamino)ethyl]amino]pyridine (7m). A solution of 14.8 g (0.1 mol) of 2,6-dichloropyridine and 28.8 g (0.2 mol) of 2-(diisopropylamino)ethylamine in 50 mL of pyridine under N_2 was heated under reflux for 64 h. The reaction mixture was concentrated, 10 N NaOH was added to the residue, and the mixture was extracted with benzene. The benzene solution was dried (Na_2SO_4) and concentrated to an oil, which was distilled to give 18 g (70%) of **7m** boiling at 127–129 °C (0.5 mm).

6-Chloro-2-[[2-(diisopropylamino)ethyl]amino]-4-methylpyridine (7o). The reaction of 3-cyano-2,6-dichloro-4-methylpyridine[6] (37.4 g, 0.2 mol) with 2-(diisopropylamino)ethylamine (34.6 g, 0.24 mol) was performed essentially by the method for **7m** to give 44.0 g of an approximately 1:1 isomeric mixture (**26**) of **6-chloro-5-cyano-2-[[2-(diisopropylamino)ethyl]amino]-4-methylpyridine** and **2-chloro-5-cyano-6-[[2-(diisopropylamino)ethyl]amino]-4-methylpyridine** as an oil. The oil was dissolved in 220 mL of 50% (v/v) H_2SO_4 and stirred at reflux for 18 h. After cooling, the reaction mixture was added to cold saturated Na_2CO_3 in excess. The mixture was extracted with CH_2Cl_2, and this extract was concentrated to an oil. This oil was lixiviated with 300 mL of hot hexane. When the solution cooled (–60 °C), 13.1 g of crystalline product was obtained. Recrystallization from hexane yielded 10.6 g (20%) of **7o**, mp 64–66.5 °C.

2-[[2-(Diisopropylamino)ethyl]amino]-4-methoxypyridine (7n). A mixture of 2-chloro-4-nitropyridine *N*-oxide[7] (20.9 g, 0.12 mol) and 2-(diisopropylamino)ethylamine (34.8 g, 0.24 mol) in 200 mL of EtOH was heated under reflux for 3.5 h. The mixture was concentrated, and the residue was repeatedly extracted with hot cyclohexane. When the solution cooled, 20.9 g (62%) of **2-[[2-(diisopropylamino)ethyl]amino]-4-nitropyridine *N*-oxide (28)** crystallized, mp 94–97 °C. This nitro intermediate (10.0 g, 0.0355 mol) was heated under reflux in 100 mL of MeOH with 3.0 g (0.055 mol) of sodium methoxide for 4 h. The reaction mixture was concentrated, and the residue was dissolved in $CHCl_3$, washed with H_2O, dried (Na_2SO_4), and concentrated to give a nearly quantitative yield of **2-[[2-(diisopropylamino)ethyl]amino]-4-methoxypyridine *N*-oxide (29)** as an oil. The oil (10.4 g) was dissolved in 65 mL of HOAc and refluxed with 16.5 g of iron powder for 3 h. The mixture was filtered and concentrated. The residue was dissolved in CH_3OH, treated with excess KOH pellets, filtered, and concentrated. The residue was dissolved in $CHCl_3$, washed with H_2O, dried (Na_2SO_4), and concentrated to yield **7n** (8.7 g) as an oil.

4,6-Dimethyl-2-[(3,3-diethoxypropyl)amino]pyridine (13). Sodium hydride (7.3 g, 57% in mineral oil, 0.167 mol) was added to 20.4 g (0.167 mol) of 2-amino-4,6-dimethylpyridine in 160 mL of xylene under N_2. The mixture was gradually heated to reflux, 33.3 g (0.20 mol) of 3,3-diethoxypropyl chloride in xylene was added, and heating under reflux was continued for 18 h. The reaction was cooled, filtered, and concentrated. The oil was distilled, and 14.2 g (34%) of 13 was collected at 115–120 °C (0.2 mm).

***N,N*-Dimethyl-*N'*-(2-formylethyl)-*N'*-(4,6-dimethyl-2-pyridyl)urea (15).** Carbamoylation of 14.0 g (0.056 mol) of 13 was carried out essentially as described for the preparation of **8g**, and 18.4 g (ca. 100%) of ***N,N*-dimethyl-*N'*-(3,3-diethoxypropyl)-*N'*-(4,6-dimethyl-2-pyridyl)urea (14)** was obtained as an oil. A mixture of 17.2 g of the oil and 145 mL of 1.5 N HCl was stirred for 16 h under N_2. The reaction was neutralized with saturated Na_2CO_3, and the oil was extracted with CH_2Cl_2. The extract was dried and concentrated to yield 12.2 g of noncrystalline 15.

***N,N*-Dimethyl-*N'*-[3-(diisopropylamino)propyl]-*N'*-(4,6-dimethyl-2-pyridyl)urea Dihydrobromide (16).** To a solution of 9.86 g (0.04 mol) of 15 in 75 mL of MeOH under N_2 there was added successively 4.0 g of 3A molecular sieves, 20.2 g (0.2 mol) of diisopropylamine (with cooling), 10 mL of 6 N ethanolic HCl and 1.78 g (0.027 mol) of sodium cyanoborohydride.[8] The reaction was stirred at room temperature for 48 h, 6 mL of 6 N ethanolic HCl was added, and the mixture was concentrated. Methylene chloride and aqueous Na_2CO_3 were added to the residue. The organic layer was dried (Na_2SO_4) and concentrated to give 12.2 g of an oil. After chromatography on silica, 5.9 g of purified 16 base was obtained. This was dissolved in ether, and HBr was passed in to form the HBr salt. Recrystallization yielded 6.6 g (33.7%) of 16.

***N*-(4,6-Dimethyl-2-pyridyl)-*N*-(4-hydroxybutyl)acetamide (18).** Sodium hydride (12.9 g; 57% NaH in mineral oil; 0.31 mol) was added in four portions to a solution of 49.2 g (0.3 mol) of *N*-(4,6-dimethyl-2-pyridyl)acetamide (**5g**) in 700 mL of DMF with warming to 48 °C. 4-Chlorobutyl acetate (46.7 g, 0.31 mol) was added, and the reaction mixture was stirred at 90 °C for 3 h. Acetic acid (20 mL) and 12 N HCl (25 mL) were added to the reaction, and the mixture was concentrated. H_2O (500 mL) was added, and the mixture was made alkaline with Na_2CO_3. It was

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extracted with CH_2Cl_2, which was dried (Na_2SO_4) and concentrated to a residue of 58.5 g. The oil was distilled, and 41 g (49%) of **N-(4,6-dimethyl-2-pyridyl)-N-(4-acetoxybutyl)acetamide** (17), bp 172–174 °C (1 mm) was obtained.

NaOH (1 N, 150 mL) was added to a solution of 41 g (0.147 mol) of the ester, 17, in 150 mL of EtOH, and the mixture was stirred for 1 h. The EtOH was removed by vacuum concentration, and the residual aqueous solution was made alkaline with Na_2CO_3. The oily product was extracted with CH_2Cl_2, and the extracts were dried (Na_2SO_4) and concentrated to yield 35.9 (~100%) of 18 as an oil.

N-(4,6-Dimethyl-2-pyridyl)-N-(3-formylpropyl)acetamide (19). The alcohol, 18 (24.8 g, 0.106 mol), in 100 mL of CH_2Cl_2 was added to a suspension of 8.62 g (0.04 mol) of pyridinium chlorochromate in 200 mL of CH_2Cl_2 under N_2. After 2 h, 250 mL of saturated Na_2CO_3 was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine and then stirred with 15 g of Florosil. The mixture was filtered, and the filtrate was dried (Na_2SO_4) and concentrated to obtain 23.7 g (95%) of 19 as an oil.

N-(4,6-Dimethyl-2-pyridyl)-N-[4-(diisopropylamino)butyl]acetamide (20). The reductive amination of 19 (11.7 g, 0.05 mol) was performed as described for the preparation of 16. Concentration of the solvent extract from the reaction workup yielded 14.7 g (92%) of 20 as an oil.

N,N-Dimethyl-N′-[4-(diisopropylamino)butyl]-N′-(4,6-dimethyl-2-pyridyl)urea (22). The acetamide 20 was deacetylated by acid hydrolysis as described for the preparation of **7g** from **6g**. The oil was distilled to give a 50% yield of **4,6-dimethyl-2-[[4-(diisopropylamino)butyl]amino]pyridine** (21), bp 142–148 °C (0.7 mm), from 20. Carbamoylation of 21 was performed essentially in the manner described for the preparation of **8g**, and the 22 base was distilled to give a 61% yield.

N-(5-Chloro-4,6-dimethyl-2-pyridyl)acetamide (5p). N-Chlorosuccinimide (32.8 g, 0.247 mol) was added to a stirred solution of 37.0 g (0.225 mol) of N-(4,6-dimethyl-2-pyridyl)-acetamide (**5g**) in 500 mL of CCl_4 under N_2. The mixture was heated under reflux for 3.5 h and then cooled to 0 °C. The crystalline **5p** and insoluble succinimide byproduct were collected. The succinimide was removed by washing the mixed solid with H_2O, leaving 35.8 g (80%) of **5p**, mp 221–223 °C, after recrystallization from ethanol.

Biological Methods. Antisecretory studies were performed in unanesthetized female beagle dogs with a chronic gastric fistula. Compounds were administered in 50 mL of aqueous (1%) methylcellulose directly into the stomach through the fistula cannula (referred to herein as oral administration) 60 min prior to administration of the gastric stimulant. Gastric output was collected continuously by gravity drainage through the fistula cannula for three 30-min periods after administration of a maximal secretory dose of gastrin tetrapeptide (64 μg/kg sc) or histamine dihydrochloride [64 μg (base)/kg sc)]. Output volume (milliliters) was measured to the nearest 0.1 mL, and acid concentration (milliequivalents per liter) was determined by titration of an aliquot to pH 7 with 0.01 N NaOH; acid output (milliequivalents) was calculated as the product of output volume and acid concentration. Data were expressed as the percent change in the gastric secretion parameter relative to a placebo trial in the same animal. ED_{50} and confidence limits determined for the period of maximal output (0–30 min) were calculated by analysis of variance according to Finney.[9] Dogs used for the detailed study of **8g** had an esophagostomy which was occluded during the experiment because preliminary trials indicated that salivary secretions evoked by **8g** could interfere with the gastric analysis. Esophagostomy does not affect gastric secretory results.

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Registry No. 4, 23510-18-1; **5g**, 5407-88-5; **5p**, 84369-60-8; **6g**, 84369-57-3; **7c**, 84369-44-8; **7e**, 63763-27-9; **7f**, 75308-69-9; **7g**, 63763-73-5; **7h**, 23826-74-6; **7i**, 24573-36-2; **7j**, 75308-61-1; **7k**, 75329-50-9; **7l**, 75308-62-2; **7m**, 75398-05-9; **7n**, 75329-45-2; **7o**, 75308-59-7; **7p**, 84369-61-9; **8a**, 84369-62-0; **8b**, 63763-60-0; **8b** (base), 75308-30-4; **8c**, 63764-42-1; **8c** (base), 84369-65-3; **8d**, 63764-43-2; **8d** (base), 81523-89-9; **8e**, 63763-62-2; **8e** (base), 63763-75-7; **8f**, 75308-70-2; **8g**, 63763-54-2; **8g** (base), 75308-65-5; **8h**, 84369-63-1; **8i**, 63764-52-3; **8i** (base), 75329-86-1; **8j**, 63764-40-9; **8k**, 75329-51-0; **8k** (base), 75329-92-9; **8l**, 63764-41-0; **8m**, 63764-50-1; **8m** (base), 75329-89-4; **8n**, 75329-46-3; **8o**, 63764-39-6; **8o** (base), 75329-87-2; **8p**, 63764-44-3; **8p** (base), 75308-66-6; **10**, 63763-52-0; **11**, 84369-45-9; **11** (base), 81523-91-3; **12**, 63763-74-6; **12** (base), 81523-90-2; **13**, 84369-46-0; **14**, 84369-47-1; **15**, 84369-48-2; **16**, 84369-49-3; **16** (base), 84369-64-2; **17**, 84369-50-6; **18**, 84369-51-7; **19**, 84369-52-8; **20**, 84369-53-9; **21**, 84369-54-0; **22**, 84369-55-1; **23**, 84369-56-2; **23** (O-methylisourea), 84369-58-4; **26** (isomer 1), 75308-58-6; **26** (isomer 2), 84369-59-5; **28**, 75329-43-0; **29**, 75329-44-1; 2-amino-4,6-dimethylpyridine, 5407-87-4; 3,3-diethoxypropyl chloride, 35573-93-4; 2,6-dichloropyridine, 2402-78-0; 3-cyano-2,6-dichloro-4-methylpyridine, 875-35-4; 2-chloro-4-nitropyridine N-oxide, 14432-16-7; 2-(diisopropylamino)ethyl chloride hydrochloride, 4261-68-1; dimethylcarbamoyl chloride, 79-44-7; 2-(diisopropylamino)ethylamine, 121-05-1; diisopropylamine, 108-18-9; 4-chlorobutyl acetate, 6962-92-1; pyridinium chlorochromate, 26299-14-9.

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Synthesis and Antineoplastic Activity of 3′-Azido and 3′-Amino Analogues of Pyrimidine Deoxyribonucleoside

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Several new 3′-azido and 3′-amino nucleosides (8, 9, 12, and 13) have been synthesized and their biological activities evaluated. Among them, 3′-amino-2′,3′-dideoxycytidine (13) was found to exhibit potent cytotoxic activity against both L1210 and S-180 cells in vitro with an ID_{50} of 0.7 and 4.0 μM, respectively. Furthermore, 13 has also shown antitumor activiy against L1210 tumor bearing mice with a T/C × 100 value of 283.

Modification of the sugar moiety of nucleosides may produce marked changes in their spectrum of biological activity and degree of selective toxicity, as well as in their chemical and physical properties. Baker et al.[1] first re-

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