in an exact manner as described above for the synthesis of 4 by refluxing 1 (1.0 g, 3.82 mmol) with adipoyl dichloride (0.8 g, 4.37 mmol) in dry benzene (18 mL) for 2 h. The crude resulting product was purified by preparative TLC ($CHCl_3$–$Me_2CO$, 5:1) to give 370 mg of amorphous 5: IR (KBr) 1760 (lactone), 1730 (ester), 1705 (cyclopentenone), 1655 (C=C) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.67 (2 H, dd, $J$ = 2.0 and 6.0 Hz, H-2 and H-2′), 6.44 (2 H, d, $J$ = 3.0 Hz, $H_a$ and $H_{a'}$), 6.12 (2 H, d, $J$ = 3.0 Hz, $H_b$ and $H_{b'}$), 6.06 (2 H, dd, $J$ = 3.0 and 6.0 Hz, H-3 and H-3′), 4.90 (2 H, m, H-8 and H-8′), 1.28 (6 H, d, $J$ = 6.0 Hz, Me-10 and Me-10′), 1.00 (6 H, s, Me-5 and Me-5′); MS, $m/e$ 634.2771 ($M^+$) ($C_{36}H_{42}H_{10}$ requires 634.2778).

**Bis(plenolinyl) Malonate (7).** Compound 7 was prepared according to the aforementioned procedure described for the synthesis of 2 by refluxing plenolin (6; 0.5 g, 1.89 mmol) and malonyl dichloride (0.45 g, 3.21 mmol) in dry benzene (15 mL) for 1.5 h. The resulting pale yellow oil was purified by preparative TLC to yield 7 as colorless crystals (480 mg): mp 247–249 °C dec; IR (KBr) 1765 (lactone), 1735 (ester), 1700 (cyclopentenone) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.68 (2 H, dd, $J$ = 6.0 and 2.0 Hz, H-2 and H-2′), 6.0 (2 H, dd, $J$ = 6.0 and 3.0 Hz, H-3 and H-3′), 5.45 (2 H, s, H-6 and H-6′), 4.77 (2 H, m, H-8 and H-8′), 3.12 (2 H, s, $-COCH_2CO-$), 1.48 (6 H, d, $J$ = 6.0 Hz, Me-11 and Me-11′), 1.25 (6 H, d, $J$ = 6.0 Hz, Me-10 and Me-10′), 1.04 (6 H, s, Me-5 and Me-5′); MS, $m/e$ 596.2627 ($M^+$) ($C_{33}H_{40}O_{10}$ requires 596.2622).

**Bis(plenolinyl) Succinate (8).** Treatment of 6 (0.5 g, 1.89 mmol) with succinoyl dichloride (0.4 g, 2.58 mmol) in dry benzene (10 mL) by refluxing the mixture for 72 h in a similar manner as described above for the preparation of 3 afforded a crude oil. Purification of this oil by preparative TLC ($CHCl_3$–$Me_2CO$, 5:1) gave 275 mg of amorphous 8: IR ($CHCl_3$) 1780 (lactone), 1740 (ester), 1723 (cyclopentenone) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 7.74 (2 H, dd, $J$ = 6.0 and 2.0 Hz, H-2 and H-2′), 6.06 (2 H, dd, $J$ = 6.0 and 3.0 Hz, H-3 and H-3′), 5.44 (2 H, s, H-6 and H-6′), 4.77 (2 H, m, H-8 and H-8′), 2.43 (4 H, m, $-COCH_2CH_2CO-$), 1.47 (6 H, d, $J$ = 6.0 Hz, Me-11 and Me-11′), 1.23 (6 H, d, $J$ = 6.0 Hz, Me-10 and Me-10′), 1.02 (6 H, s, Me-5 and Me-5′); MS, $m/e$ 610.2772 ($M^+$) ($C_{34}H_{42}O_{10}$ requires 610.2778).

**Treatment of 2,3-Dihydrohelenalin (9) with Malonyl Dichloride. Bis(2,3-dihydrohelenalinyl) Malonate (10) and 2,3-Dihydrohelenalinyl Ethyl Malonate (14).** To a solution of 9 (532 mg, 2.02 mmol) in dry benzene (15 mL) was added a solution of malonyl dichloride (400 mg, 2.86 mmol) in dry benzene (10 mL). This mixture was refluxed for 1 h, then washed with $NaHCO_3$ and $H_2O$, dried ($MgSO_4$), and evaporated in vacuo to give a pale yellow oil (500 mg), which was subjected to preparative TLC ($CHCl_3$–EtOH, 20:1) to yield compounds 10 and 14. Compound 10 (140 mg, colorless crystals): mp 114–116 °C; IR (KBr) 1755 (lactone), 1740 (ester) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 6.40 (2 H, d, $J$ = 3.0 Hz, $H_a$ and $H_{a'}$), 6.03 (2 H, d, $J$ = 3.0 Hz, $H_b$ and $H_{b'}$), 5.38 (2 H, d, $J$ = 2.0 Hz, H-6 and H-6′), 4.81 (2 H, m, H-8 and H-8′), 3.56 (2 H, m, H-7 and H-7′), 3.29 (2 H, s, $-COCH_2CO-$), 1.06 (6 H, d, $J$ = 6.0 Hz, Me-10 and Me-10′), 0.77 (6 H, s, Me-5 and Me-5′); MS, $m/e$ 596.2627 ($M^+$) ($C_{33}H_{40}O_{10}$ requires 596.2622). Compound 14: IR (neat) 1775–1720 (lactone, ester and cyclopentanone) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 6.40 (1 H, d, $J$ = 3.0 Hz, $H_a$), 6.05 (1 H, d, $J$ = 3.0 Hz, $H_b$), 5.32 (1 H, d, $J$ = 2.0 Hz, H-6), 4.80 (1 H, m, H-8), 4.19 (2 H, q, $J$ = 7.0 Hz, $COCH_2CH_3$), 3.59 (1 H, m, H-7), 3.35 (2 H, s, $-COCH_2CO-$), 1.29 (3 H, t, $J$ = 7.0 Hz, $-COOCH_2CH_3$), 1.05 (3 H, d, $J$ = 6.0 Hz, Me-10), 0.78 (3 H, s, Me-5); MS, $m/e$ 378.1673 ($M^+$) ($C_{20}H_{26}O_7$ requires 378.1678).

**Bis(2,3-dihydrohelenalinyl) Succinate (11).** Compound 11 was prepared in an analogous manner as described above for the synthesis of 8. The crude oil resulting from a 36-h reflux of 9 (0.5 g, 1.89 mmol) with succinoyl dichloride (0.4 g, 2.58 mmol) in dry benzene (10 mL) was purified by preparative TLC ($CHCl_3$–$Me_2CO$, 4:1) to give 250 mg of amorphous 11: IR ($CHCl_3$) 1765 (lactone), 1752 (ester and cyclopentanone), 1669 (C=C) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 6.47 (2 H, d, $J$ = 3.0 Hz, $H_a$ and $H_{a'}$), 6.08 (2 H, d, $J$ = 3.0 Hz, $H_b$ and $H_{b'}$), 5.31 (2 H, d, $J$ = 2 Hz, H-6 and H-6′), 4.84 (2 H, m, H-8 and H-8′), 3.56 (2 H, m, H-7 and H-7′), 2.55 (4 H, m, $-COCH_2CH_2CO-$), 1.09 (6 H, d, $J$ = 6.0 Hz, Me-10 and Me-10′), 0.78 (6 H, s, Me-5 and Me-5′); MS, $m/e$ 610.2772 ($M^+$) ($C_{34}H_{42}O_{10}$ requires 610.2778).

**Bis(2,3,11,13-tetrahydrohelenalinyl) Malonate (13).** Compound 13 (285 mg) was obtained from an analogous method described above by reacting 12 (266 mg, 1 mmol) and malonyl dichloride (200 mg, 1.43 mmol): mp 118–120 °C; IR (KBr) 1750 (lactone), 1735 (ester) $cm^{-1}$; NMR ($CDCl_3$) $\delta$ 5.39 (2 H, s, H-6 and H-6′), 4.72 (2 H, m, H-8 and H-8′), 3.18 (2 H, s, $-COCH_2CO-$), 1.44 (6 H, d, $J$ = 6.0 Hz, Me-11 and Me-11′), 1.07 (6 H, d, $J$ = 6.0 Hz, Me-10 and Me-10′), 0.86 (6 H, s, Me-5 and Me-5′); MS, $m/e$ 600.2931 ($M^+$) ($C_{33}H_{44}O_{10}$ requires 600.2931).

**Biological Methods.** The antileukemic activity test against the lymphocytic leukemia P-388 maintained in our laboratory at UNC[2] was conducted in $BDF_1$ male mice (~22 g). In this screen, $10^6$ cells were implanted on day 0. The test compounds were administered intraperitoneally from 0.6 to 60 (mg/kg)/day for 2 weeks. T/C values were calculated according to the NIH protocol.[11] 5-Fluorouracil was used as the internal standard in the screen.

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# Gastric Antisecretory Agents. 1. Antisecretory and Antiulcer Activity of 5*H*-[1]Benzopyrano[2,3-*b*]pyridin-5-ylureas and 5*H*-[1]Benzothiopyrano[2,3-*b*]pyridin-5-ylureas

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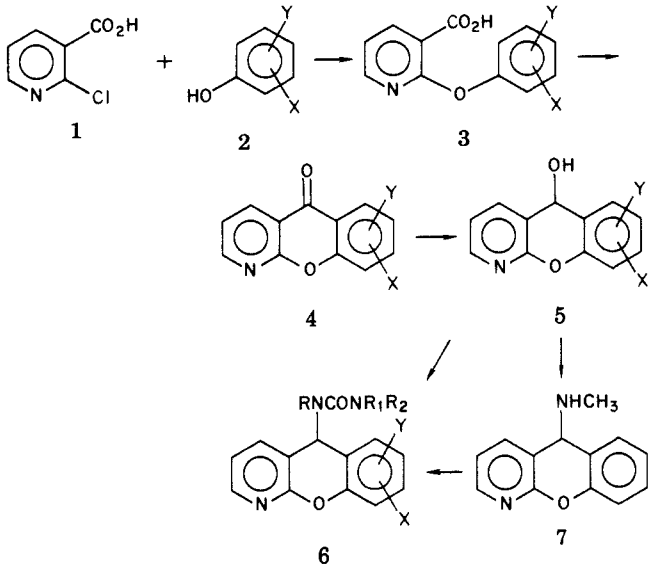
5*H*-[1]Benzopyrano[2,3-*b*]pyridin-5-ylureas and 5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-ylureas are a new class of gastric antisecretory agents and antiulcer agents. Certain compounds inhibit histamine-, dimaprit-, insulin-, and food-stimulated gastric acid secretion in dogs, as well as aspirin-induced ulcers in rats. Most compounds are antisecretory in the pylorus-ligated rat. Several compounds are comparably potent to cimetidine.

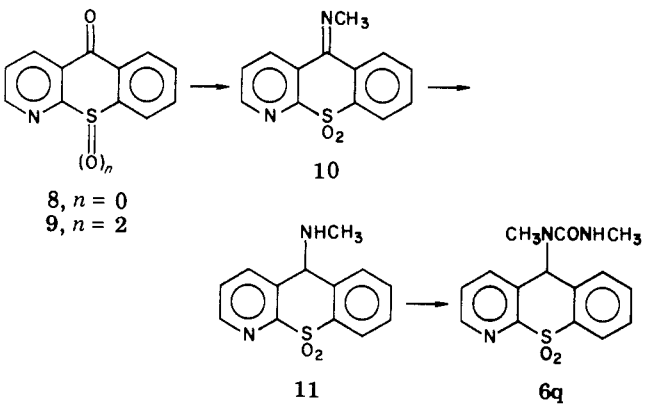
The introduction and wide acceptance of the histamine ($H_2$) receptor antagonist cimetidine[2] for the treatment of peptic ulcer disease has renewed interest in the drug therapy of this disease. The effectiveness of the histamine

0022-2623/81/1824-0927$01.25/0 

Scheme I



Scheme II



($H_2$) receptor antagonists provides support for the hypothesis that histamine is an essential mediator of gastric acid secretion.[3,4] In principle, any entity which inhibits histamine-stimulated gastric acid secretion in animals would be a potential antiulcer agent, whether or not it specifically blocks histamine at the $H_2$ receptor. We are reporting a new series of antisecretory and antiulcer agents, 5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-ylureas (**6**),[5,6] which are not competitive histamine ($H_2$) receptor antagonists and yet which do inhibit histamine-stimulated gastric acid secretion in dogs, as well as gastric acid secretion produced by other means of stimulation. Additionally, these compounds are antisecretory in the pylorus-ligated rat, and several compounds tested inhibit aspirin-induced ulcer formation in the rat.

**Chemistry.** The 5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-ylureas (**6**) were synthesized by several routes starting with the 5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-ols (**5**), which were prepared by $NaBH_4$ reduction of 5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-ones (**4**) Scheme I).[7]

**Method A.** The alcohol **5** was treated with a urea derivative in $HOAc/CH_3CN$ at reflux to give **6**.

**Method B.** The alcohol **5** was heated at 80 °C with a urea derivative in HCl/dimethylacetamide to give **6**.

**Method C.** The alcohol **5** was reacted with $CH_3NH_2$ in HOAc to give **7** which was treated with an isocyanate to give **6**.

**Method D.** The amine **7** was reacted with phosgene and triethylamine, followed by treatment with a secondary amine, to give **6**.

**Method E.** Compound **6n** was prepared from **6m** by reduction with $NaBH_4/CaCl_2$.

**Method F.** The sulfone **6r** was prepared according to Scheme II.

**Method G.** The trimethylurea derivative **6x** was synthesized from the dimethylurea derivative **6u** by alkylation of **6u** with $CH_3I$.

The 5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-ones (**4**) and the thio analogue **8** were prepared according to the general procedure of Villani et al.[7] (Scheme I), except that the condensation to give the phenoxynicotinic acids (**3**) was generally carried out in dimethylacetamide–xylene in the presence of $K_2CO_3$ and Cu powder. The cyclization of **3** to **4** was performed either with $CH_3SO_3H/P_2O_5$ (Eaton's reagent)[8] or by Villani's procedure.[7] The requisite N-3 and N-4 precursors to **6b** and **6c** were synthesized by known methods.[7,9]

**Biological Test Methods.** The compounds were evaluated for gastric antisecretory activity in two animal models (Tables I and II). The pylorus-ligated rat[10] was used as the primary screen to assess antisecretory activity and to identify potentially toxic compounds. In this test, the compounds were administered at a 40 mg/kg dose intraperitoneally (ip) at the time of ligation, and reduction in acid output was measured after 4 h. The secondary model was the inhibition of histamine-stimulated gastric acid secretion in adult mongrel dogs[11] with surgically prepared Heidenhain pouches. Selected compounds were tested against dimaprit-, food- and insulin-induced gastric secretion. Compounds were first administered at 5 kg/kg intravenously, and reduction in acid output, relative to the non-drug-treated control value in the same animal, was measured. Selected compounds were also tested at 8 mg/kg orally against histamine in the Heidenhain pouch dog. A tertiary screen involving inhibition of aspirin-induced ulcers in the rat[12] was also employed for some compounds.

## Results and Discussion

The antisecretory results for the rat and dog models are shown in Tables I and II. All 1,3-dimethylurea derivatives which have substituents on the benzopyrano[2,3-*b*]pyridine nucleus which are nitrogen positional isomers, or which are benzothiopyrano[2,3-*b*]pyridines are included in Table

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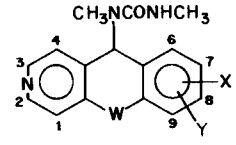
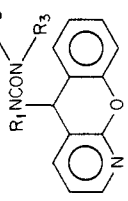
Table I. Inhibition of Gastric Acid Secretion by Substituted 1-[Benzopyranopyridin-5-yl]-1,3-dimethylurea Derivatives




| compd | N position | W | X | Y | mp, °C | recrystn solvent | formula[b] | method[c] | % yield | % reduction of gastric acid output: rat,[d] 40 mg/kg iv | dog: 5 mg/kg iv | dog: 8 mg/kg po |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| cimetidine | | | | | | | | | | 74 | 84 | 86 |
| **6a** | 1 | O | H | H | 166–168 | toluene | $C_{15}H_{15}N_3O$ | A | 60 | 95 | 70 | <30 |
| **6b** | 3 | O | H | H | 158–159 | $CH_3CN$ | $C_{15}H_{15}N_3O$ | A | 87 | 77 | <30 | |
| **6c** | 4 | O | H | H | 153–158 | EtOAc | $C_{15}H_{15}N_3O$ | B | 94 | 37 | 38[e] | 34 |
| **6d** | 1 | O | 6-$CF_3$ | H | 153–155 | toluene | $C_{16}H_{14}F_3N_3O_2$ | B | 56 | 71 | <30 | |
| **6e** | 1 | O | 8-$CF_3$ | H | 194–196 | $H_2O$ | $C_{16}H_{14}F_3N_3O_2$ | B | 93 | 46 | <30 | |
| **6f** | 1 | O | 7-F | H | 158–160 | *a* | $C_{15}H_{14}FN_3O_2$ | A | 17 | 68 | 63 | <30 |
| **6g** | 1 | O | 9-F | H | 189–191 | toluene | $C_{15}H_{14}FN_3O_2$ | A | 57 | 35[f] | <30 | |
| **6h** | 1 | O | 7-$CH_3$ | H | 149–153 | $CH_3CN$ | $C_{16}H_{17}N_3O_2$ | A | 36 | 71 | 62[e] | <30 |
| **6i** | 1 | O | 8-$CH_3$ | H | 175–177 | $CH_3CN$ | $C_{16}H_{17}N_3O_2$ | A | 50 | 81 | 75[e] | <30 |
| **6j** | 1 | O | 9-Cl | H | 159–160 | *a* | $C_{15}H_{14}ClN_3O_2$ | A | 20 | 60 | <30 | |
| **6k** | 1 | O | 7-$NO_2$ | H | 165–168 | EtOAc | $C_{15}H_{14}N_4O_4$ | B | 56 | 71 | <30 | |
| **6l** | 1 | O | 7-$OCH_3$ | H | 145–148 | toluene | $C_{16}H_{17}N_3O_3$ | A | 60 | 59 | 51 | <30 |
| **6m** | 1 | O | 7-$CO_2CH_3$ | H | 223–226 | $CH_3CN$ | $C_{17}H_{17}N_3O_4$ | A | 87 | <30 | <30 | |
| **6n** | 1 | O | 7-$CH_2OH$ | H | 191–193 | $CH_3CN$ | $C_{16}H_{17}N_3O_3$ | E | 61 | <30 | <30 | |
| **6o** | 1 | O | 8-$OCH_3$ | H | 98–111 | toluene | $C_{16}H_{17}N_3O_3 \cdot 0.5H_2O$ | C | 22 | 60 | 54[g] | <30 |
| **6p** | 1 | O | 7-Cl | 8-$CH_3$ | 162–164 | toluene | $C_{16}H_{16}ClN_3O_2$ | A | 30 | 65 | <30 | |
| **6q** | 1 | S | H | H | 158–160 | $CH_3CN$ | $C_{15}H_{15}N_3OS$ | A | 43 | 96 | 80[e] | <30 |
| **6r** | 1 | $SO_2$ | H | H | 200–202 | EtOAc | $C_{15}H_{15}N_3O_3S$ | F | 61 | <30 | <30 | |

[a] Chromatographed. [b] All new compounds had microanalyses for C, H, and N within 0.4% of theoretical values, except **6c** (C: calcd, 66.90; found, 66.19), **6g** (C: calcd, 66.66; found, 66.15), and 6o (C: calcd, 62.33; found, 62.81). [c] See Experimental Section. [d] $p \leq 0.05$. [e] Mean value for two determinations. [f] $p = 0.09$. [g] Acid output measured over 2 h.

Table II. Inhibition of Gastric Acid Secretion by Benzopyrano[2,3-*b*]pyridin-5-ylurea Derivatives



| compd | $R_1$ | $R_2$ / $R_3$ | mp, °C | recrystn solvent | formula[a] | method[b] | % yield | % reduction of gastric acid output: rat,[c] 40 mg/kg ip | dog: 5 mg/kg iv | dog: 8 mg/kg po |
|---|---|---|---|---|---|---|---|---|---|---|
| **6s** | H | $NH_2$ | 269–271 | $CH_3OH$ | $C_{13}H_{11}N_3O_2$ | A | 16 | 46 | 36[d] | |
| **6t** | H | $NHCH_3$ | 247–248 | EtOH | $C_{14}H_{13}N_3O_2$ | A | 48 | 54 | 31 ± 11[e] | |
| **6u** | H | $N(CH_3)_2$ | 210–215 | $CH_3CN$ | $C_{15}H_{15}N_3O_2$ | A | 57 | 95 | 35[d] | <30 |
| **6v** | $CH_3$ | $NH_2$ | 195–200 | EtOAc/$CH_3CN$ | $C_{14}H_{13}N_3O_2 \cdot 0.5H_2O$ | C | 32 | 70 | 30 | |
| **6w** | $CH_3$ | $N(CH_3)_2$ | 89–92 | IPE[f] | $C_{16}H_{17}N_3O_2$ | G | 59 | **96** | <30 | |
| **6x** | $CH_3$ | $NHC(CH_3)_3$ | 126–128 | IPE | $C_{18}H_{21}N_3O_2$ | C | 47 | 82 | 35 | <30 |
| **6y** | $CH_3$ | c-$N(CH_2CH_2)_2O$ | 131–134 | IPE | $C_{18}H_{19}N_3O_3$ | D | 35 | 95 | **64** | <30 |
| **6z** | $CH_3$ | c-$NC_5H_{10}$ | 114–116 | hexane | $C_{19}H_{21}N_3O_2$ | D | 54 | 72 | 31 | |
| **6aa** | $CH_3$ | c-$N(CH_2CH_2)_2N$-$CH_3$ | 134–137 | $CH_3CN$ | $C_{19}H_{20}N_4O_2 \cdot 0.5H_2O \cdot C_2H_2(COOH)_2$[g] | D | 15 | 94 | <30 | <30 |
| **6bb** | $CH_3$ | $NHC_6H_5$ | 186–188 | $CH_3CN$ | $C_{20}H_{17}N_3O_2$ | C | 43 | 45 | 55 | <30 |

[a] All new compounds had microanalyses for C, H, and N within 0.4% of theoretical value except **6v** (N: calcd, 15.89; found, 16.99). [b] See Experimental Section. [c] $p \leq 0.05$. [d] Mean value for two determinations. [e] Standard error from four determinations. [f] Diisopropyl ether. [g] Fumarate.

Table III. Inhibition of Aspirin-Induced Ulcers by 5*H*-[1]Benzopyrano[2,3-*b*]pyridine Derivatives

| compd | dose, mg/kg, po | % inhibn |
|---|---|---|
| cimetidine | 10 | 67[a] |
| 6a | 3 | 51[b] |
| 6a | 10 | 89[a] |
| 6a | 30 | 100[a] |
| 6q | 3 | 0 |
| 6q | 10 | 68[b] |
| 6q | 30 | 100[a] |
| 6u | 30 | 74[b] |
| 6w | 20 | 100[b] |

[a] $p < 0.01$. [b] $p < 0.05$.

I. Table II contains other substituted urea derivatives appended to the benzopyrano[2,3-*b*]pyridine nucleus.

Most of the compounds tested had significant antisecretory activity in the pylorus-ligated rat model; however, there is little correlation between activity in this model and activity in the dog. The number of "false positives" in the rat probably is due to the nonspecificity of this model. Agents with diverse pharmacological action (e.g., anticholinergic, $\alpha$ and $\beta$ adrenergic, and antihistaminic) will inhibit acid secretion in the pylorus-ligated rat.[13] No meaningful structure–activity relationships (SAR) can be derived from the rat data.

Inhibition of histamine-stimulated acid secretion in the dog is a more specific model with good correlation to activity in man.[14] Many of the present compounds possessed good antisecretory activity upon intravenous administration in the dog. Thus, the benzopyrano[2,3-*b*]pyridines **6a**,**f**,**h**,**i** and the benzothiopyrano[2,3-*b*]pyridine **6q** were all comparably active to simetidine. Of these, **6q** was the most active compound.

Of the substituted ureas (Table II), the morpholine derivative **6y** and the phenylurea **6bb** were the most active. The remainder of the compounds were only slightly active, resulting in less than 30–35% inhibition.

Little activity was observed when the compounds which were the most active by intravenous administration were tested orally in the dog at 8 mg/kg. Compound **6a** was orally active and exhibited a dose–response inhibition at 16 (35% inhibition) and 32 mg/kg (75% inhibition). Tremors and convulsive behavior in dogs were noted with **6q** at doses higher than 8 mg/kg.

The intravenous dog data in Table I suggest the following SAR. (1) The position of the nitrogen atom greatly influences activity, since **6a** is more active than **6c** while **6b** is inactive. (2) Ring substitution at positions 7 or 8 with electron-releasing substituents provides compounds with excellent antisecretory activity (**6h**,**i**,**l**,**o**). (3) Substitution with electron-withdrawing substituents (**6l**, **6k**, 6m, or **6n**) leads to inactive compounds. (4) Substitution at position 9 (**6g** or **6j**) leads to a loss of activity. (5) Oxidation of the sulfur (**6r**) eliminates activity.

Confirmation of the antiulcer properties of these compounds was obtained by testing several of the more active compounds (**6a**,**z**,**u**,**w**,**y**) in the rat for inhibition of aspirin-induced ulcers following oral administration (Table III). All compounds tested were at least as active as cimetidine at inhibiting experimental ulcers in rodents. In each example, antiulcer activity correlated better with rat antisecretory data than with dog antisecretory data.

(13) P. Bass and M. H. Patterson, *J. Pharmacol. Exp. Ther.*, **156**, 142 (1967).
(14) R. W. Brimblecombe, W. A. M. Duncan, G. J. Durant, J. C. Emmett, C. R. Ganellin, G. B. Leslie, and M. E. Parsons, *J. Pharmacol. Exp. Ther.*, 74, 339 (1978).

Table IV. Effects of 6a and 6q on Insulin-, Dimaprit-, and Food-Stimulated Canine Gastric Secretion

| | % reduction in gastric acid secretion | | | |
|---|---|---|---|---|
| | 6a | | 6q | |
| gastric acid stimulation | 5 mg/kg iv | 8 mg/kg po | 5 mg/kg iv | 8 mg/kg po |
| insulin hypoglycemia[a] | 79 ± 5 ($n$ = 5) | <30 ($n$ = 2) | 97 ± 0.3 ($n$ = 3) | 62 ± 14 ($n$ = 4) |
| dimaprit[b] | 58 ± 7 ($n$ = 5) | d | 78 ± 7 ($n$ = 4) | <30 ($n$ = 1) |
| feed[c] | 69 ± 12 ($n$ = 5) | <30 ($n$ = 4) | 78 ± 10 ($n$ = 2) | <30 ($n$ = 6) |

[a] Compound administered at time of 0.2 μg/kg insulin injection to dogs with gastric fistulas. [b] Compound administered 0.5 h postconstant iv infusion of 0.8 (μg/kg)/min dimaprit. [c] Compound administered at the same time as the presentation of 250 g of ground, cooked beef hearts. [d] Not tested.

The mechanism by which this class of compounds exert antisecretory effects in the rat and dog is not known. Selected compounds of this series (**6a,b,f,g,m,p,q,t,w,z,bb**) were evaluated for histamine ($H_2$) receptor antagonism.[4] At a concentration of $5 \times 10^{-5}$ M, none of these compounds inhibited the histamine-stimulated chronotropic response of guinea pig right atria, thus ruling out histamine ($H_2$) receptor antagonism as the antisecretory mechanism of these compounds. Autonomic challenge studies showed **6a** to be devoid of anticholinergic, $H_1$, and α-, and β-adrenergic blocking properties. In order to profile further **6a** and **6q**, each compound was tested in the dog for inhibition of gastric acid secretion induced by insulin hypoglycemia,[11] dimaprit,[15] and a meat meal[10] (Table IV). Insulin triggers a vagal cholinergic response to the resulting hypoglycemia, dimaprit is a specific $H_2$ receptor agonist, and a meat stimulates secretion primarily by a release of gastrin in the Heidenhain pouch dogs employed. As shown in Table IV, both **6a** and **6q** were highly effective against all three challenges when administered intravenously. Compound **6q** was effective orally as an inhibitor of insulin hypoglycemia-stimulated gastric secretion but was inactive orally against other stimuli. Since insulin hypoglycemia induces gastric acid secretion through a central nervous system mechanism, this suggests that **6q** exerts its antisecretory effect through this system.[16] Inhibition of dimaprit-induced gastric secretion by **6a** and **6q** does not define their activity as being related to histamine ($H_2$) receptor antagonism.

In conclusion, we have described a new class of antisecretory agents, some members of which have intrinsic antisecretory and antiulcer activity equal to or better than cimetidine. The compounds in this series, unlike cimetidine, are much more potent following intravenous administration than when they are administered orally. Oral activity could be demonstrated at higher doses.

## Experimental Section

**General.** Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. All new compounds gave satisfactory microanalyses. IR, $^1$H NMR, and mass spectra were recorded for all new compounds, and the spectra support the structural assignments for these compounds. Distillation, concentration, or removal of organic solvents was done on a rotary evaporator under reduced pressure.

**Chemistry. Method A. 1-(5*H*-[1]Benzopyrano[2,3-*b*]pyridin-5-yl)-1,3-dimethylurea (6a).** A solution of **5** (X = Y = H; 19.9 g, 0.10 mol) and 1,3-dimethylurea (8.8 g, 0.10 mol) in 250 mL of $CH_3CN$ and 10 mL of HOAc was heated under reflux for 1 h. The solution was cooled and concentrated to remove the $CH_3CN$. Ice was added to the residual liquid followed by aqueous $K_2CO_3$ solution, and this mixture was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with saturated NaCl solution, dried ($K_2CO_3$), and concentrated to give an oil, which crystallized upon standing. This was recrystallized from 75 mL of toluene to give 17.4 g (65%) of **6a**: mp, sinters at 140 °C, melts at 145–150 °C. A second recrystallization from 75 mL of toluene gave 15.2 g of pure **6a**, mp 166–168 °C.

The thio analogue **6q** thus prepared had the following $^1$H NMR spectrum ($Me_2SO$-$d_6$): δ 2.45 (s, obscured by $Me_2SO$, $CH_3NCO$), 2.66 (d, $J$ = 4.5 Hz, 3 H, $CH_3NH$), 6.49 (br s, 1 H, NH), 6.89 (s, 1 H, $C_5$ H), 7.2–7.4 (m, 5 H, aryl H), 7.66 (dd, 1 H, $C_4$ H), 8.40 (dd, 1 H, $C_2$ H).

**Method B. 1,3-Dimethyl-1-[8-(trifluoromethyl)-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-yl]urea (6e).** Concentrated HCl (1.08 mL) was added to a magnetically stirred solution, under $N_2$, of 7.00 g (0.026 mol) of **5** (X = 8-$CF_3$; Y = H) and 9.23 g (0.10 mol) of 1,3-dimethylurea in 60 mL of dimethylacetamide (DMA) held in an oil bath at 80 °C. After stirring for 0.75 h, the reaction was poured into 300 mL of ice–$H_2O$ containing 1.8 g of $K_2CO_3$. The solid product was collected to give 8.21 g of **6e**.

The N-positional isomers of **6a–c** were thus prepared and gave $^1$H NMR spectra as follows. **6b** ($CDCl_3$): δ 2.40 (s, 3 H, $CH_3NCO$), 2.93 (d, $J$ = 4.5 Hz, 3 H, $CH_3NH$), 4.64 (br s, 1 H, NH), 6.9–7.4 (m, aryl H + $C_5$ H at 7.03), 8.42 (d, $J$ = 6 Hz, 1 H, $C_3$ H), 8.57 (s, 1 H, $C_1$ H). **6c** ($CDCl_3$): δ 2.42 (s, 3 H, $CH_3NCO$), 2.91 (d, $J$ = 5 Hz, 3 H, $CH_3NH$), 5.41 (br s, 1 H, NH), 6.69 (s, 1 H, $C_5$ H) 7.0–7.5 (m, aryl H), 8.40 (dd, $J$ = 4.5 Hz, 1 H, $C_2$ H).

**Method C. 3-(1,1-Dimethylethyl)-1-(5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-yl)-1-methylurea (6x).** $CH_3NH_2$ was bubbled into 175 mL of HOAc for 0.5 h and then 30.0 g (0.15 mol) of **5** (X = Y = H) was added to the warm solution. $CH_3NH_2$ was passed into the reaction for 0.25 h and it was heated on a steam bath for 4 h. Upon cooling, the solution was poured into cold NaOH solution and the product was extracted into 1 L of $Et_2O$. The $Et_2O$ was washed with three cold portions of 0.5 N $H_2SO_4$, and the acidic solution was rendered basic with 50% NaOH and extracted with 1 L of $Et_2O$. This was washed with brine, dried ($K_2CO_3$), and concentrated to give 23.1 g of **7** as a yellow oil: $^1$H NMR ($CDCl_3$) δ 1.77 (br s, 1 H, NH), 2.13 (s, 3 H, $CH_3$), 4.95 (s, 1 H, $C_5$ H), 7.0–7.5 (m, 5 H, aryl H), 7.80 (dd, $J$ = 8 Hz, 1 H, $C_4$ H), 8.28 (dd, $J$ = 5 Hz, 1 H, $C_2$ H). The oil was used without further purification.

*tert*-Butyl isocyanate (5.0 mL) in 25 mL of $Et_2O$ was added over 2 min under $N_2$ to a stirred solution of 5.10 g (0.024 mol) of **7** in 75 mL of $Et_2O$. After 10 min the mixture was filtered to remove a small amount of solid, the filtrate was concentrated, and the residue was chromatographed on silica gel with $Et_2O$ to give an oil, which was crystallized from diisopropyl ether to afford 3.50 g of **6x**.

**Method D. 5-[*N*-(4-Morpholinylcarbonyl)-*N*-methylamino]-5*H*-[1]benzopyrano[2,3-*b*]pyridine (6y).** A solution of **7** (8.10 g, 0.038 mol) and $Et_3N$ (8 mL) in 50 mL of toluene was added dropwise over 0.5 h to a cold (–10 to –15 °C) 12.5% benzene solution of phosgene (0.048 mol) in 45 mL of toluene. The reaction was allowed to warm to 25 °C over 3 h. $Et_2O$ was added, the mixture was filtered, and the solids were washed with ether. To half of the combined filtrate (175 mL) was added morpholine (10 mL), holding the temperature of the reaction at 10–15 °C. The mixture was concentrated and the residue was partitioned between $CHCl_3$ and $H_2O$. The $CHCl_3$ was washed successively with two 75-mL portions of cold 0.5 N $H_2SO_4$, saturated $NaHCO_3$, and brine. Drying ($K_2CO_3$) and removal of the $CHCl_3$ gave a semisolid residue, which was recrystallized from diisopropyl ether to give 2.15 g of **6y**.

**Method E. 1,3-Dimethyl-1-[7-(hydroxymethyl)-5*H*-[1]benzopyrano[2,3-*b*]pyridin-5-yl]urea (6n).** A mixture of **6m**

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(4.0 g, 0.012 mol), $NaBH_4$ (4.0 g), and $CaCl_2$[17] (4.0 g) in 200 mL of THF was allowed to stir for 6 h. The mixture was cooled in an ice bath and a solution of 5.5 g sodium/potassium tartrate[18] in 13 mL of $H_2O$ was added dropwise. After 1 h, the mixture was filtered, the solids were washed with $CH_2Cl_2$, and the combined filtrate and washings were dried ($K_2CO_3$) and concentrated to give 3.58 g of a solid, which was recrystallized from $CH_3CN$ (150 mL) to afford 2.40 g of **6n**.

**Method F. 1,3-Dimethyl-1-(10,10-dioxo-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-yl)urea (6r).** A mixture of 8 (30.0 g, 0.14 mol) and *m*-chloroperbenzoic acid (0.33 mol) in 1.5 L of $CH_2Cl_2$ was heated under reflux for 2 h. After the solution cooled, the $CH_2Cl_2$ was washed successively with 1 L of 15% $Na_2SO_3$, four 1-L portions of 5% NaOH, and brine. Removal of the solvent gave 31.2 g of **9**. A sample was recrystallized from $CH_3CN/CHCl_3$ to give pure **9**: mp 264–265 °C; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 7.8–8.1 (m, 3 *H*), 8.1–8.4 (m, 2 H), 8.67 (dd, $J$ = 8 Hz, 1 H, $C_4$ H), 9.09 (dd, $J$ = 4 Hz, 1 H, $C_2$ H). Anal. Calcd for $C_{12}H_7NOS$: C, 58.77; H, 2.88; N, 5.71. Found: C, 58.79;H, 2.55; N, 5.84.

A solution of $TiCl_4$ (9.3 g, 0.049 mol) in 80 mL of toluene was added to a stirred mixture at −20 °C containing 20.0 g (0.08 mol) of **9** and 1.1 mol of $CH_3NH_2$. After heating under reflux for 3 h under a dry ice condenser, the mixture was filtered and the solid were washing with 500 mL of hot toluene and with 150 mL of $CHCl_3$. The filtrate was treated with Darco and the solvent was removed to give 18.9 g of **10**. A sample was crystallized from toluene to give pure **10**: mp 149–155 °C; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 3.77 and 3.82 (2 s, 3 *H*, *syn*- and *anti*-$NCH_3$), 7.6–8.9 (m, aryl H). Anal. Calcd for $C_{13}H_{10}N_2O_2S$: C, 60.45; H, 3.90; N, 10.85. Found: C, 60.63; H, 3.74; N, 10.89.

$NaBH_4$ (4.1 g) was added to a stirred mixture of 10.0 g (0.039 mol) of **10** in 250 mL of $CH_3OH$ at 5 °C. The mixture was held at 20–25 °C and excess $NaBH_4$ was added until no **10** was present as shown by TLC. The reaction was poured into brine and filtered, and the solids were washed with 1:1 brine/$CH_3OH$. Extraction of the combined filtrate and washings with $CHCl_3$ and recrystallization of the residue from $CH_3CN/Et_2O$, following removal of the $CHCl_3$, gave 4.0 g of **11**: mp 134–138 °C; $^1H$ NMR ($Me_2SO$-$d_6$) $\delta$ 2.21 (s, 3 *H*, $CH_3$), 5.07 (s, 1 H, $C_5$ H), 7.4–8.1 (m, aryl H), 8.23 (dd, $J$ = 9 Hz, 1 H, $C_4$ H), 8.72 (dd, $J$ = 5 Hz, 1 H, $C_2$ H). Anal. Calcd for ($C_{13}H_{12}N_2O_2S$): C, 59.98; H, 4.65; N, 10.76. Found: C, 59.75; H, 4.57; N, 10.70.

$CH_3NCO$ (1.3 g, 0.023 mol) was added to 4.0 g (0.015 mol) of **11** in 100 mL of $CH_3CN$. After stirring for 0.5 h, the solution was cooled and concentrated, and the residue was recrystallized from EtOAc to give 3.0 g of **6r**.

**Method G. 1-(5*H*-[1]Benzopyrano[2,3-*b*]pyridin-5-yl)-1,3,3-trimethylurea (6w).** Compound **6u** (4.5 g, 0.017 mol) was added to a suspension of 0.96 g (0.020 mol) of 50% NaH (washed free of oil with petroleum ether) in 50 mL of 1,2-dimethoxyethane held in an ice bath. The ice bath was removed and the mixture was stirred for 3 h. NaH (0.5 g) was added, and the mixture was heated under reflux for 2 h, cooled in an ice bath, and treated with $CH_3I$ (10 mL). After 0.75 h, $CH_3OH$ (2 mL) was added, the reaction was concentrated, and the residue was chromatographed on silica gel with EtOAc. The main fraction was recrystallized from diisopropyl ether to give **6w**.

**Biology. Heidenhain Pouch Dog.** Mongrel dogs, weighing between 12 and 18 kg, were surgically prepared with Heidenhain pouches. Any one dog fasted for 18 h was used for experimentation 1 day a week. Compounds were dissolved in 3 mL of 0.4% methylcellulose/saline solutions for intravenous studies and in 5 mL for oral studies. A dose of histamine of 0.4 ($\mu$g/kg)/min was found to produce 50–60% maximal acid output (AO), and this dose of histamine was selected as the most appropriate stimulant. The gastric secretions were collected at 30-min intervals for 0.5 to 1 h before the start of the infusion of histamine and for 4 to 5 h thereafter. The volume of each 30-min collection was recorded and an aliquot was used for titration to determine the acid concentration. The AO was calculated by multiplying the volume times the acid concentration. One hour after the start of the histamine infusion, the test compound was given either intravenously or orally by gavage. The respective 30-min acid outputs were summated for 3 h after drug administration. The AO collected over the 3-h period after drug administration was divided by the 3-h AO collected in control experiments. This value times 100 yields the percentage of control AO. Percent inhibition = 100 − percent of control. Unless otherwise noted in Tables I and II, each compound was tested in a single dog. Each animal served as its own control because the response to a set dose of histamine depends upon the size of the pouch, and the pouch size is not constant across animals. In our laboratories, the mean plus or minus SE for acid output in control studies was 10.56 ± 1.15 mequiv/3 h. Cimetidine, iv, had an $ID_{50}$ of 0.66 mg/kg with 95% confidence limits of 0.16–2.60 mg/kg. Cimetidine, po, had an $ID_{50}$ value of 1.25 mg/kg with 95% confidence limits of 0.58–2.52.

**Pylorus-Ligated Rat.** Charles River CD (outbred albino) male rats, 150 to 200 g of body weight, were employed for gastric secretion studies using the pylorus ligation technique. Rats that fasted for 24 h were anesthetized with a short-acting barbiturate anesthetic, Brevital. While under surgical level anesthesia, the abdomen was opened and a ligature was securely tied around the pylorus. The stomach was returned to the abdomen and the incision was closed with auto-clips. Test compounds were dissolved in a 2.5% Tween 80 solution and were administered intraperitoneally in doses of 0.5 mL/200 g of body weight. Four hours after drug administration, the animals were killed and the stomachs were removed. The contents of the stomach were collected and the volume was recorded. An aliquot was removed and the acid concentration was determined by automatic titration against 0.1 N NaOH to a pH end point of 7.0. The AO was calculated by multiplying the volume of gastric content in liters times the acid concentration in milliequivalents per liter, yielding AO values in milliequivalents/4 h. Six rats were used for each test compound and eight rats for the control. Percent inhibition was calculated as follows: 100 − [100 × (mean test AO/mean control AO)]. Results were statistically analyzed by Student's $t$ test. The mean plus or minus SE acid output in our control studies using this procedure was 0.61 ± 0.04 mequiv/4 h.

**Aspirin-Induced Ulcer.** Rats that fasted for 24 h were treated orally with test compounds made up of 0.4% methylcellulose–saline solutions (0.5 mL/100 g of body weight) 1 h before the oral administration of 100 mg/kg of aspirin in the 0.4% methylcellulose–saline solution. Four hours after aspirin administration, the rats were killed, and the stomachs were removed and opened along the greater curvature. The number of ulcers per rat was counted under a 2× magnifier light. Percent inhibition was calculated as follows: 100 − [100 × (mean number of test lesions/mean number of control lesions)]. Eight rats were used for each test compound, and the results were analyzed by Student's $t$ test.

**Insulin Hypoglycemia, Dimaprit, and Food.** Dogs prepared with simple gastric fistulas[17] were employed for studying the effects of compounds on insulin hypoglycemia induced gastric secretion. The compounds were given iv or po at the time of injection of 0.2 unit/kg of regular insulin.[10] Gastric collections were made for 3 h thereafter, and the percent reduction of acid output as compared to control studies in the same animals was calculated. Dogs with Heidenhain pouches were used for studying the effects of selected compounds on dimaprit and food-stimulated gastric secretion. Dimaprit was infused iv at 0.8 ($\mu$g/kg)/min starting 30 min before the administration of test compounds. Data were analyzed as above. In the feeding experiments, test compounds were given at the same time as a meal consisting of 250 g of ground cooked beef hearts. Data were analyzed as above.

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