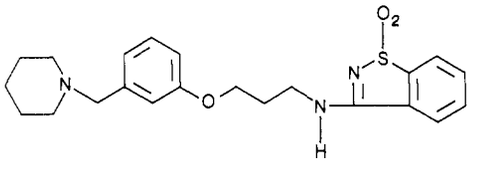
Syntheses and Gastric Acid Antisecretory Properties of the H_2-Receptor Antagonist *N*-[3-[3-(1-Piperidinylmethyl)phenoxy]propyl]thieno[3,4-*d*]isothiazol-3-amine 1,1-Dioxide and Related Derivatives

Arthur A. Santilli,* Anthony C. Scotese, Robert L. Morris, Guy A. Schiehser, Daniel M. Teller, Susan T. Nielsen, and Donald P. Strike

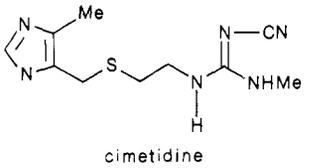
Research Division, Wyeth Laboratories, Inc., Radnor, Pennsylvania 19087. *Received October 13, 1987*

The synthesis and gastric acid antisecretory properties of several N-substituted thieno[3,4-*d*]isothiazol-3-amine 1,1-dioxides and analogues are described. Two of the more potent compounds, *N*-[3-[3-(1-piperidinylmethyl)-phenoxy]propyl]thieno[3,4-*d*]isothiazol-3-amine 1,1-dioxide (**6a**) and *N*-[4-[3-(1-piperidinylmethyl)phenoxy]-propyl]thieno[3,4-*d*]isothiazol-3-amine 1,1-dioxide (**6b**), showed greater potencies as H_2-receptor antagonists (in vitro) than ranitidine. They also had potent gastric acid antisecretory activities in vivo, inhibiting basal acid secretion in the rat (**6a**, **6b**), histamine-stimulated acid secretion in the dog (**6a**, **6b**), and food-stimulated acid secretion in the dog (**6a**). These were selected for further pharmacological evaluation.

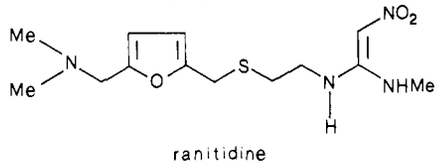
The introduction of cimetidine and ranitidine[1] as H_2-receptor antagonists for the control of peptic ulcer disease has been responsible for intense synthetic efforts by medicinal chemists in this therapeutic area to prepare highly efficacious drugs with greater potency. Previous reports from this laboratory indicated that *N*-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-1,2-benzisothiazol-3-amine 1,1-dioxide (Wy-45,086) is a potent H_2-receptor antagonist ($pA_2 = 8.1$) with confirmation of the gastric acid antisecretory activity of this drug in the rat and dog.[2a-c]



Wy-45,086



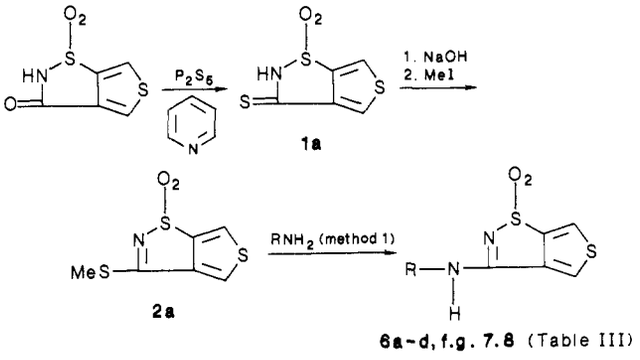
cimetidine



ranitidine

Substitution of the benzisothiazole group by a thieno-[3,4-*d*]isothiazole group afforded a still more potent member of this series, *N*-[3-[3-(1-piperidinyl)phenoxy]-propyl]thieno[3,4-*d*]isothiazol-3-amine 1,1-dioxide (**6a**).[2c,3] This substitution enhanced the gastric acid antisecretory activity of the resultant compound, and in both the rat and dog models its potencies exceeded those of Wy-45,086 and ranitidine. The present paper describes several synthetic pathways to **6a** along with the preparation of several of its structural variants. The effects of these structural changes on gastric acid secretion have been evaluated.

Scheme I



Chemistry

A key intermediate used for the preparation of **6a** and several analogues is 3-(methylthio)thieno[3,4-*d*]isothiazole 1,1-dioxide (**2a**) shown in Scheme I (Table I). The reaction of thieno[3,4-*d*]isothiazol-3(2*H*)-one 1,1-dioxide[4] with phosphorus pentasulfide in pyridine gave the corresponding thione (**1a**). Alkylation of the sodium salt of **1a** with methyl iodide afforded **2a**.

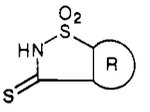
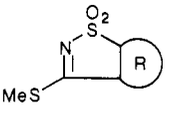
Displacement of methyl mercaptan from **2a** by reaction with 3-[3-(1-piperidinylmethyl)phenoxy]propanamine (**5a**)[5] afforded **6a** (method 1). The displacement of methyl mercaptan from **2a** by several other suitably substituted amines (Table II) provided access to several products given in Table III. The amines used to generate the H_2-receptor antagonists famotidine[6] and cimetidine[7] underwent similar displacement reactions with **2a**, giving **7** and **8**, respectively.

N-[3-[3-(1-Piperidinylmethyl)phenoxy]propyl]thieno-[2,3-*d*]isothiazol-3-amine 1,1-dioxide (**9**), an isomer of **6a**, was prepared in identical fashion from **5a**[5] and 3-(methylthio)thieno[2,3-*d*]isothiazole (**2b**). This intermediate was

(1) Domschke, W.; Lux, G.; Domschke, S. *Lancet* **1979**, *8111*, 320.
(2) (a) Nielsen, S. T. *Arch. Int. Pharmacodyn.* **1986**, *282*, 151. (b) Santilli, A. A., Teller, D. M., Scotese, A. C., Morris, R. L., Vogel, R. L., Nielsen, S. T. Presented in part at the 187th National Meeting of the American Chemical Society, St. Louis, MO, April 1984; Division of Medicinal Chemistry, MEDI 21. (c) Schiehser, G. A.; Strike, D. P. U.S. Patent 4 490 527, 1984.
(3) Santilli, A. A., Scotese, A. C., Morris, R. L., Schiehser, G. A., Teller, D. M., Vogel, R. L., Nielsen, S. T., Strike, D. P. Presented in part at the 188th National Meeting of the American Chemical Society, Philadelphia, PA, August 1984; Division of Medicinal Chemistry, MEDI 27.
(4) Rossy, P. A.; Hoffmann, W.; Müller, N. *J. Org. Chem.* **1980**, *45*, 617.
(5) Clitherow, J. W.; Bradshaw, J.; Mackinnon, J. W. M.; Price, B. J.; Martin-Smith, M.; Judd, D. B. U.S. Patent 4 318 913, 1982.
(6) Takeda, M.; Takagi, T.; Yashima, Y.; Maeno, H. *Arzneim.-Forsch.* **1982**, *32*, 734.
(7) Durant, G. J.; Emmett, J. C.; Ganellin, C. R.; Miles, P. D.; Parsons, M. E.; Prain, H. D.; White, G. R. *J. Med. Chem.* **1977**, *20*, 901.

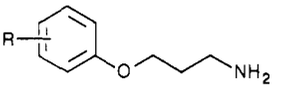
0022-2623/88/1831-1480$01.50/0

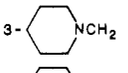
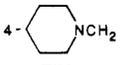
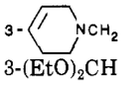
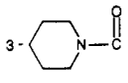
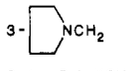
Table I. Physical Data for Thione and Methylthio Key Intermediates

no.	R	mp, °C	recryst solvent	formula	% yield	anal.
						
1a		196–198	H_2O	$C_5H_3NO_2S_3$	49	C, H, N
1b[a]		186–189		$C_5H_3NO_2S_3$	69	C, H, N
						
2a		184–186	EtOH	$C_6H_5NO_2S_3$	47	C, H, N
2b		165–167	EtOH	$C_6H_5NO_2S_3$	84	C, H, N

[a] Reference 8 describes the synthesis of the corresponding oxo intermediate.

Table II. Physical Data for Substituted Phenoxypropyl Amines



no.	R	mp, °C	recryst solvent	formula	% yield	anal.
5a[a]		136–141/0.1 mm		$C_{15}H_{24}N_2O$	73	C, H, N[b]
5b[a]		148–152/0.35 mm		$C_{15}H_{24}N_2O$	77	C, H, N[c]
5c		oil		$C_{15}H_{22}N_2O$	84	C,[d] H,[d] N
5d	3-$(EtO)_2CH$	oil		$C_{14}H_{23}NO_3$	79	C,[e] H, N[e]
5e		oil		$C_{15}H_{22}N_2O_2$	31	C,[f] H, N
5f[g]		oil		$C_{14}H_{22}N_2O$	81	
5g[h]	3-$(n\text{-}Pr)_2NCH_2$	200 dec	EtOH	$C_{16}H_{28}N_2O\cdot 2HCl$	38	C, H,[i] N[i]

[a] Reference 5. [b] N: calcd, 11.28; found, 10.67. [c] N: calcd, 11.28; found, 11.72. [d] C: calcd, 73.13; found, 72.44. H: calcd, 9.00; found, 8.33. [e] C: calcd, 66.37; found, 63.54. N: calcd, 5.53; found, 6.03. [f] C: calcd, 68.67; found, 68.16. [g] Reference 15. [h] Reference 2c. [i] H: calcd, 8.97; found, 8.31. N: calcd, 8.67; found, 8.26.

prepared by thiation of thieno[2,3-*b*]isothiazol-3(2*H*)-one 1,1-dioxide[8] followed by alkylation of the sodio salt of the resulting thione with methyl iodide.

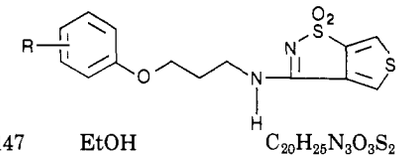
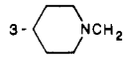
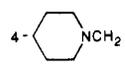
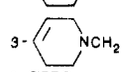
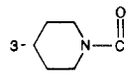
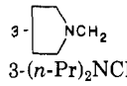
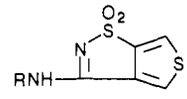
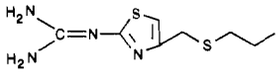
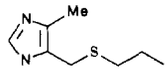
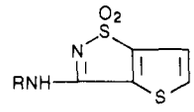
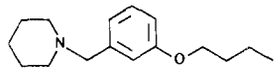
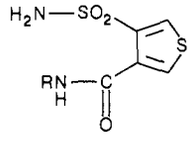
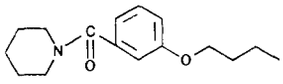
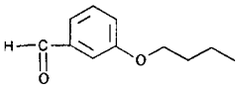
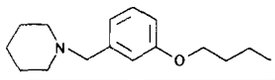
Interest in developing alternative pathways to **6a**, an early promising therapeutic agent, prompted us to explore several synthetic routes. For example, alkylation of the sodio salt of previously described 3-(1-piperidinylcarbonyl)phenol (**3**)[9] with *N*-(3-bromopropyl)phthalimide afforded 1-[3-[3-(1,3-dihydro-1,3-dioxo-2*H*-isoindol-2-yl)propoxy]benzoyl]piperidine (**4**). Treatment of the latter with excess hydrazine in ethanol afforded the expected amine (**5e**). The reaction of **5e** with 4-(aminosulfonyl)-3-thiophenecarbonyl chloride gave the corresponding amide, 4-(aminosulfonyl)-*N*-[3-[3-(1-piperidinylcarbonyl)phenoxy]propyl]-3-thiophenecarboxamide (**10**). Ring closure with phosphorus oxychloride gave **6e**. Reduction of the amide group in **6e** gave **6a** (method 2). This reduction was accomplished by first allowing **6e** to react with phosphorus oxychloride followed by treatment of the resulting intermediate with sodium borohydride. Intermediate **6e** was prepared alternatively via the reaction of **5e** with **2a**.

Other variations in the synthesis of **6a** utilizing 3-[3-(diethoxymethyl)phenoxy]propanamine (**5d**) are depicted in Scheme II. Treatment of 2-[3-[3-(1,3-dioxolan-2-yl)-phenoxy]propyl]-1*H*-isoindole-1,3(2*H*)-dione[10] with an excess of hydrazine in ethanol afforded **5d**. Under the conditions of the reaction, the formation of the diethyl acetal was somewhat unexpected. Displacement of methyl mercaptan in **2a** by **5d** under the usual conditions gave the corresponding diethyl acetal derivative (**13**), which upon acidification gave 3-[3-(thieno[3,4-*d*]isothiazol-3-ylamino)propoxy]benzaldehyde *S',S'*-dioxide (**6d**). Reductive amination of **6d** with piperidine and sodium borohydride gave **6a** (method 3).

Alternatively, treatment of **5d** with methyl 4-(aminosulfonyl)-3-thiophenecarboxylate[4] at steam-bath temper-

(8) Hromatka, O.; Binder, D., U.S. Patent 4 028 373, 1977.
(9) Tilly, G. *Chim. Ther.* **1967**, *2*, 57; *Chem. Abstr.* **1967**, *67*, 32432*s*.
(10) Clitherow, J. W.; Bradshaw, J.; Mackinnon, J. W. M.; Price, B. J.; Martin-Smith, M.; Judd, D. B.; Ger. Offen 2 917 026, 1979; *Chem. Abstr.* **1980**, *92*, P181197*n*.

Table III. Physical and Biological Data for N-Substituted Thieno[3,4-*d*]isothiazole-3-amine 1,1-Dioxides and Analogues

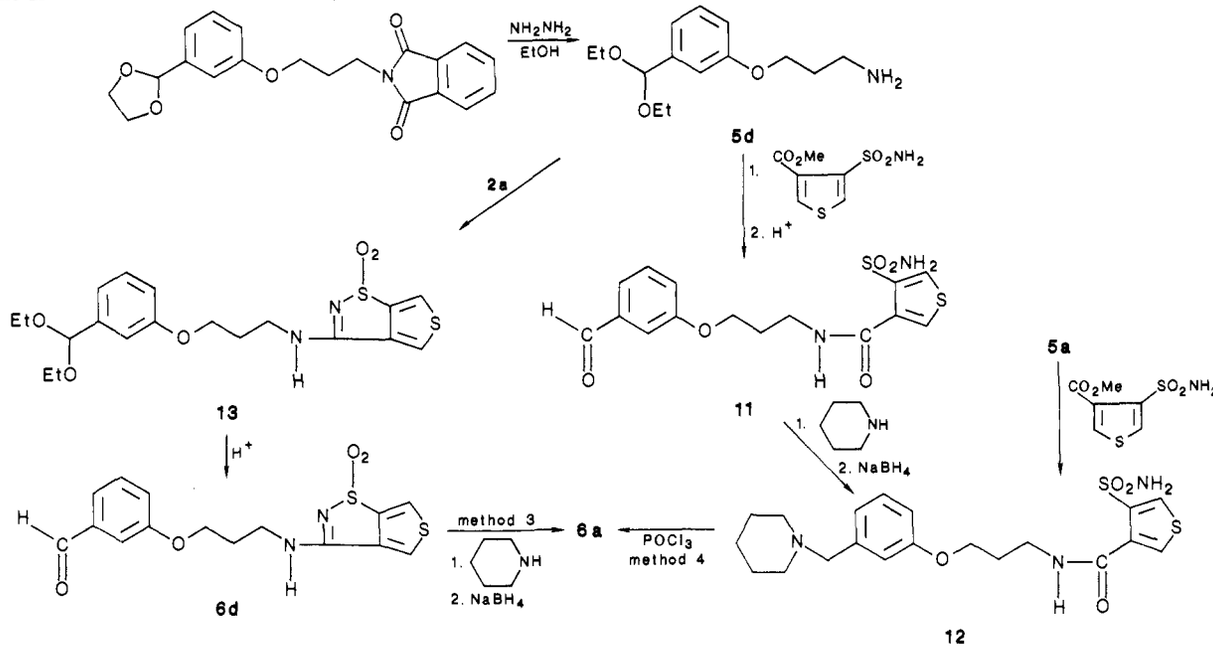
no.	R	mp, °C	recryst solvent	formula	% yield	anal.	inhibn of basal acid secretion in the pylorus-ligated rat: dose, mg/kg, id	inhibn of basal acid secretion in the pylorus-ligated rat: total acid output: % of control ± SEM[g]
								
6a		145–147	EtOH	$C_{20}H_{25}N_3O_3S_2$	50	C, H, N	8[a]	16* ± 9
6b		137–139	EtOH	$C_{20}H_{25}N_3O_3S_2$	84	C, H, N	8[a]	21* ± 5
6c		131–134	EtOH	$C_{20}H_{23}N_3O_3S_2$	54	C, H, N	4	18* ± 6
6d	3-CHO	182–185	acetone–H_2O	$C_{15}H_{14}N_2O_4S_2$	89	C, H, N	4	89 ± 21
6e		232–234	EtOH	$C_{20}H_{23}N_3O_4S_2$	46	C, H, N	8	94 ± 26
6f		206–209	MeCN–Et_2O	$C_{19}H_{23}N_3O_3S_2 \cdot HCl$	32	C,[b] H, N	4	19* ± 12
6g	3-(*n*-Pr)$_2$NCH$_2$	184–187	EtOH	$C_{21}H_{29}N_3O_3S_2 \cdot HCl$	50	C, H, N	4	16* ± 3
								
7		223–225 dec	EtOH–petr ether	$C_{12}H_{14}N_6O_2S_4$	58	C, H, N[c]	4	83 ± 22
8		236–239	MeOH	$C_{12}H_{14}N_4O_2S_3$	66	C,[d] H, N	8	87 ± 16
								
9		132–135	EtOH	$C_{20}H_{25}N_3O_3S_2$	79	C, H, N	8	12* ± 6
								
10		70–80	amorphous, uncrystallized	$C_{20}H_{25}N_3O_5S_2 \cdot H_2O$	32	C,[e] H, N[e]		NT[f]
11		132–134	EtOH	$C_{15}H_{16}N_2O_5S_2$	40	C, H, N	8	94 ± 26
12		130–134	H_2O	$C_{20}H_{27}N_3O_4S_2 \cdot HCl \cdot H_2O$	4	C, H, N	8	36* ± 8

[a] See Figure 1 for additional data. [b] C: calcd, 51.63; found, 51.22. [c] N: calcd, 20.88; found, 20.45. [d] C: calcd, 42.09; found, 41.66. [e] C: calcd, 51.16; found, 51.58. N: calcd, 8.95; found, 8.45. [f] NT, not tested (intermediate). [g] An asterisk indicates significant difference from control, $p < 0.05$, by analysis of variance.

ature followed by acidification of the resulting product gave 4-(aminosulfonyl)-*N*-[3-(3-formylphenoxy)propyl]-3-thiophenecarboxamide (**11**). Reductive amination of **11** with piperidine and sodium borohydride afforded 4-(aminosulfonyl)-*N*-[3-[3-(1-piperidinylmethyl)phenoxy]-propyl]-3-thiophenecarboxamide (**12**). Ring closure with phosphorus oxychloride gave **6a** (method 4). Intermediate **12** was prepared alternatively from the reaction of **5a** with methyl 4-(aminosulfonyl)-3-thiophenecarboxylate.

Another procedure for the synthesis of **6a** involved the

Scheme II



alkylation of thieno[3,4-*d*]isothiazol-3-amine 1,1-dioxide (**14**) with sodium hydride and 1-[[3-(3-bromophenoxy)-phenyl]methyl]piperidine (**15**). The product thus afforded was **6a** (method 5).

Finally, catalytic reduction of the double bond of the tetrahydropyridinyl group in **6c** afforded **6a** (method 6).

Biological Results and Discussion

The in vivo gastric acid antisecretory activities of these novel N-substituted thieno[3,4-*d*]isothiazol-3-amine 1,1-dioxides and related derivatives were initially assessed in the pylorus-ligated rat model. Shown in Table III are results obtained following administration to the animals of the test compounds at screening doses of 8 or 4 mg/kg. Excellent suppression of basal acid secretion was seen with both **6a** and **6b**, and additional experiments were conducted with both of these compounds (vide infra). Similarly, a potent inhibitory response was observed with compounds in which the piperidino group in **6a** was replaced with a pyrrolidinyl group (**6f**), a dipropylamino group (**6g**), or a 1,2,3,6-tetrahydropyridino group (**6c**). Surprisingly, neither **7** nor **8**, which have the thieno[3,4-*d*]isothiazole group attached to the pharmacophoric amino group present in famotidine and cimetidine, respectively, showed any appreciable antisecretory response in the rat model. Removal of the basic piperidinylmethyl group in **6a** and replacement with a formyl group as in **6d** rendered the compound inactive at 4 mg/kg. Similarly, elimination of the basicity of the piperidinyl group in **6d** by replacement of the contiguous methylene group attached to the benzene ring with a carbonyl group, as in **6e**, rendered the molecule inactive at 8 mg/kg. Cleavage of the thiophene[3,4-*d*]isothiazole group of **6a** to the open chain sulfamoyl derivative (**12**) also caused a sharply reduced potency.

Potency was maintained when the thieno[3,4-*d*]isothiazole portion of **6a** was replaced with the isomeric thieno[2,3-*d*]isothiazole group as in **9**.

Dose–response curves for two of the most interesting compounds, **6a** and **6b**, are shown, together with data from the reference standard ranitidine, in Figure 1. In the rat the two compounds clearly and dose-dependently inhibited basal gastric acid secretion with similar potencies, thus indicating that shifting the 3-piperidinylmethylene group from the 3-position (**6a**) of the benzene ring to the 4-

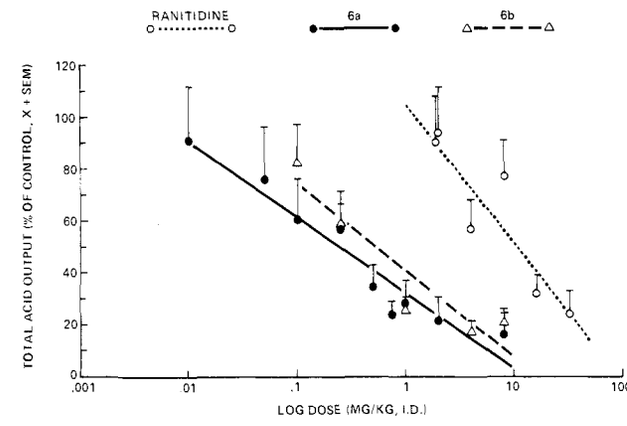


Figure 1. Comparison of the inhibitory effects of **6a**, **6b**, or ranitidine administered intraduodenally on basal acid secretion in the pylorus-ligated rat. Following pylorus ligation under methohexital anesthesia, drug (or vehicle) was administered to male Sprague–Dawley rats (10 per group) at the indicated dose. Rats were allowed to recover and then sacrificed 4 h later. Average total acid output was determined for control and drug treated groups, and the data are expressed as percent of control ± SEM.

position (**6b**) did not alter this parameter. Furthermore, it is evident that both **6a** and **6b** are more potent than ranitidine.

The activities of **6a** and **6b** were explored in depth in several additional models. In dogs prepared with innervated gastric pouches both **6a** and **6b** had excellent acid antisecretory activity. They dose-dependently inhibited acid secretion elicited by either (a) the secretagogue histamine (subcutaneous injection) or (b) consumption of a test meal. In Figure 2, data demonstrating efficacy against histamine stimulation is shown for ranitidine, the reference standard, and for **6a** and **6b**. Each of the three compounds had antisecretory activity over similar dose ranges. In contrast, when food was used as a stimulus, (comparing **6a** with ranitidine), compound **6a** appeared several fold more potent than ranitidine (respective ED_{50} values of 0.35 and 0.93 mg/kg; data not shown). In actuality, the enhanced potency of **6a** vis-à-vis ranitidine that was observed in the latter protocol may be more relevant for two reasons. First, food provides a more physiological stimulus than does histamine. Second, the time course for histamine-

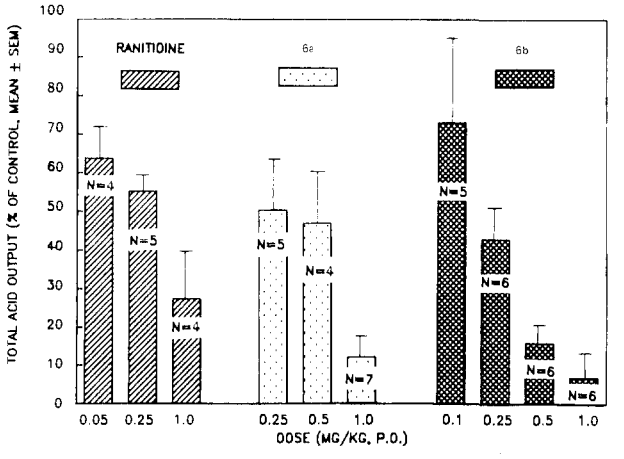


Figure 2. Inhibition of histamine-stimulated gastric acid secretion in the innervated gastric pouch dog by H_2-receptor antagonists. Saline (control) or drug treatment was administered to each dog prior to subcutaneous histamine injection, after which acid secretion was quantified. Data was expressed as percent of control, with each dog serving as its own control. A minimum of 3 days intervened between control and drug-treated experiments. Data shown is the mean value ± SEM, with the number of animals used in each experiment being indicated within each bar. For comparative purposes, data are shown for the two most interesting compounds (indicated by dotted bars), **6a** and **6b** (indicated by cross-hatched bars), in comparison to the reference standard ranitidine (indicated by hatched bars).

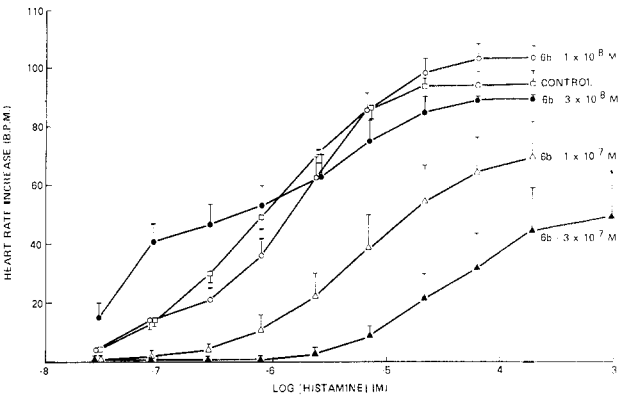


Figure 3. Effect of **6b** on the histaminic positive chronotropic response in isolated guinea pig right atria. Histamine dose–response curves were constructed first in the absence and then in the presence of the H_2 antagonist at the concentration indicated. Control values (n = 16) from the three experiments were pooled. For each experiment all determinations were carried out in quadruplicate. All data points are mean ± SEM.

stimulated gastric acid secretion is shorter than that for food, and so a greater potency in the latter protocol is indicative of a more sustained duration of action.

That this gastric acid antisecretory efficacy was based on H_2-antagonist properties was confirmed by using the isolated guinea pig right atrial assay. In this model histamine, in a H_2-receptor-dependent mechanism, elicits a positive chronotropic response. In the isolated guinea pig atrial assay, noncompetitive kinetics have previously been observed with certain H_2-receptor antagonists having, as part of their substructure, a [(piperidinylmethyl)phenoxy]propylamine moiety. In these reports the initial dose–response curve shifts elicited at low concentrations of antagonists were rightward and parallel, but as the antagonist concentration was increased, the dose–response curve shifts became increasingly nonparallel, accompanied by diminished maxima.[11] This phenomenon, observed with both **6a** and **6b**, effectively precludes accurate pA_2 value determination. However, initial shifts of the dose–response curves from the control curves were elicited by **6a** and by **6b** at submicromolar concentrations (see Figure 3 and ref 2a), which is indicative of high H_2-receptor-binding affinity. In conclusion, both **6a** and **6b** showed potent H_2-receptor-antagonist activity and both potently suppressed gastric acid secretion in the rat and the dog. No adverse findings were detected with either compound in ancillary cardiovascular, central nervous system, immunoinflammatory, or endocrinological testing (data not shown).

Experimental Section

Melting points were measured in a Thomas-Hoover oil bath melting point apparatus and are reported uncorrected. The IR spectra were recorded on a Perkin-Elmer Model 299 infrared spectrophotometer and the NMR spectra were measured on a Varian XL-100 or FT-80A spectrometer. All spectra were consistent with the assigned structures. Combustion analyses were performed on a Perkin-Elmer Model 240 elemental analyzer and were within ±0.4% of the theoretical values except as noted.

Biological Methods. Pylorus-Ligated Rat. Basal acid secretion in the rat was determined according to the method of Shay et al.[12] Male 190–260-g Charles River rats (strain SD/CD) were fasted for 24 h with access to tap water ad libitum until the test. Groups of 10 rats each were assigned to either control or drug treatment. Under methohexital anesthesia (40 mg/kg), a midline laparotomy was performed and a ligature tightly secured around the pylorus. Either control vehicle (0.25% aqueous methylcellulose) or drug in control vehicle was administered intraduodenally 1 mL/kg, immediately after ligating the pylorus. The abdominal incision was closed, and the rats were allowed to recover from anesthesia and then were sacrificed by CO_2 asphyxiation 4 h later.

The volume of gastric juice was recorded and the acid concentration of 1.0-mL sample aliquots was measured by electrometric titration to pH 7.0 with 0.1 N NaOH. The product of the gastric volume and acid concentration was used to calculate the total acid output. Total acid output after drug administration was compared with that obtained in control animals and results expressed as percent inhibition. Any samples having coprophagic contamination were excluded.

Thomas Modification of the Pavlov-Pouch Dog. Food- or histamine-stimulated acid secretion in the dog was determined with dogs prepared with modified Pavlov pouches as described by Thomas.[13] Female beagles weighing 9–13 kg were surgically prepared with innervated gastric pouches and allowed a recovery period of at least 2 weeks. The dogs were fasted for 18 h with access to tap water ad libitum until the test. Two samples of gastric secretions were collected at 15-min intervals to establish a base line. The control vehicle (0.9% saline) or drug in control vehicle was administered by oral gavage and two additional 15-min samples were taken. At 30 min after treatment, the dogs were given a 200-mL portion (185 g) of commercially prepared, 100% meat meal. Dogs routinely consumed the entire meal within 5 min, and any dog not consuming the entire meal within 15 min was excluded from the test. After the dogs were fed, gastric pouch samples were collected at 15-min intervals until the test was terminated 4 h later.

When histamine was used as the secretagogue, drug or vehicle, as indicated above, was administered by oral gavage 30 min prior to administration of histamine diphosphate in saline (64 μg/kg histamine base, sc). Two samples at 15-min intervals were col-

(11) Lumma, W. C., Jr.; Anderson, P. S.; Baldwin, J. J.; Bolhofer, W. A.; Habecker, C. N.; Hirshfield, J. M.; Pietruszkiewicz, A. M.; Randall, W. C.; Torchiana, M. L.; Britcher, S. F.; Clineschmidt, B. V.; Denny, G. H.; Hirschmann, R.; Hoffman, J. M.; Phillips, B. T.; Streeter, K. B. *J. Med. Chem.* **1982**, *25*, 210.

(12) Shay, H.; Sun, D. C. H.; Gruenstein, M. A. *Gastroenterology* **1954**, *26*, 906.

(13) Thomas, E. J. *Proc. Soc. Exp. Biol. Med.* **1942**, *50*, 58.

lected during this time period. For duration of action studies, drug or vehicle was administered (po) the indicated number of hours plus 30 min before histamine.

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

The product of the gastric volume and acid concentration was used to calculate the total acid output (TAO). A mean ± SEM value was calculated for each time period, and the sum over a 3.25-h time period for experiments involving food stimulation or over a 1-h time period for experiments involving histamine stimulation was calculated to provide the TAO. Total acid output after drug administration was compared with that after saline (control value), and results were expressed as the percent inhibition.

Isolated Guinea Pig Right Atria. Isolated guinea pig right atria were prepared as described by Black et al.[14] Male guinea pigs from Charles River weighing 250–325 g were sacrificed by cervical dislocation. The right atria were dissected free and suspended in 10-mL isolated tissue baths under a 1-g tension load. Contraction rates were monitored via a Grass Model FT03 force displacement transducer. Krebs–Henseleit buffer of the following composition was used: 117.5 mM NaCl, 5.4 mM KCl, 2.5 mM $CaCl_2$, 1 mM $NaH_2PO_4 \cdot H_2O$, 25 mM $NaHCO_3$, 11.1 mM glucose. The Krebs–Henseleit bath solution was oxygenated (95:5 O_2–CO_2) and maintained at 32 °C. After a 1-h equilibration period, cumulative histamine dose–response curves were carried out. The tissues were then washed, the heart rate was allowed to return to basal level, and then, following addition of the histamine H_2 receptor antagonist to each tissue and a 30-min equilibration period, the histamine dose–response curve was repeated. Regression analysis of the log (dose ratio, 1) versus the log of the antagonist concentration gave the intercept and slope with 95% confidence limits. The H_2-receptor-antagonist potency was reported as the pA_2 value, i.e., the negative log molar concentration that produced a dose ratio of 2.

General Chemical Methods. The following intermediate amines used in the present study were previously described: **5a**,[5] **5b**,[5] **5f**,[15] **5g**,[2c] 2-guanidino-4-[[(2-aminoethyl)thio]methyl]thiazole hydrochloride,[16] 4-[[(2-aminoethyl)thio]methyl]-5-methylimidazole dihydrobromide,[7] 3-(1-piperidinylmethyl)phenol.[5]

Thieno[3,4-*d*]isothiazole-3(2H)-thione 1,1-Dioxide (1a). To a mixture of 5.6 g (0.03 mol) of thieno[3,4-*d*]isothiazol-3(2*H*)-one 1,1-dioxide[4] in 50 mL of dry pyridine was added portionwise 5.6 g (0.016 mol) of P_2S_5 over 3 min. The viscous mixture, in an atmosphere of N_2, was slowly heated in an oil bath by gradually raising the temperature of 80 °C over the course of 30 min. This temperature was maintained for 25 min. The reaction mixture was cooled to 50 °C and was then added dropwise into 200 mL of ice-cooled H_2O. The aqueous solution was filtered and acidified to pH 1 in an ice bath. The resulting product amounted to 3.0 g (49%). An analytical sample was obtained by recrystallization from water, mp 196–198 °C.

3-(Methylthio)thieno[3,4-*d*]isothiazole 1,1-Dioxide (2a). To a mixture of 0.9 g (0.0044 mol) of **1a** in 4 mL of EtOH was added a solution of 0.35 g (0.0044 mol) of 50% NaOH solution in 3 mL of H_2O. To the viscous mixture was added 0.62 g (0.0044 mol) of MeI. The mixture was heated under reflux for 5 min and then was filtered to give 0.35 g of product. On cooling, a second crop (0.1 g) of product was obtained (47%). An analytical sample was obtained by recrystallization from EtOH, mp 184–186 °C.

***N*-[3-[3-(1-Piperidinylmethyl)phenoxy]propyl]thieno[3,4-*d*]isothiazol-3-amine 1,1-Dioxide (6a) (Method 1).** To a solution of 83 g (0.038 mol) of **2a** in 20 mL of EtOH was added 9.4 g (0.038 mol) of 3-[3-(1-piperidinylmethyl)phenoxy]propylamine (**5a**)[5] in 20 mL of EtOH. The reaction mixture was heated under reflux for 2 h. The product that crystallized on cooling in ice was recrystallized from EtOAC, giving 8.0 g (50%) of product.

Preparation of 6a·HCl. To a warm solution of 12.5 g (0.03 mol) of **6a** in 125 mL of EtOH was added a saturated solution of HCl gas in Et_2O. HCl was bubbled into the mixture until pH 1 was reached. The resulting precipitate was recrystallized from 50% aqueous EtOH, thus affording 9.6 g (70%) of product, mp 260–262 °C. Anal. ($C_{20}H_{25}N_3O_3S_2 \cdot HCl$) C, H, N.

4-(Aminosulfonyl)-3-thiophenecarbonyl Chloride. A mixture of 1 g (0.005 mol) of 4-(aminosulfonyl)-3-thiophenecarboxylic acid[9] in 20 mL of $SOCl_2$ was heated under reflux for 4 h. The mixture was cooled to room temperature and was filtered. The filtrate was stripped on a rotary evaporator and the residue was dissolved in 170 mL of anhydrous Et_2O. The solution was diluted with 200 mL of petroleum ether and the resulting precipitate was collected to give 0.4 g (35%) of product, mp 262–265 °C. Anal. ($C_5H_4ClNO_3S_2$) H, N; C: calcd, 26.61; found, 27.24.

1-[3-[3-(1,3-Dihydro-1,3-dioxo-2*H*-isoindol-2-yl)propoxy]benzoyl]piperidine (4). To a suspension of 0.09 g (0.0024 mol) of 60% NaH in 10 mL of dry DMF was added dropwise over 5 min a solution of 0.5 g (0.0024 mol) of 1-(3-hydroxybenzoyl)-piperidine (**3**)[10] in 10 mL of dry DMF. The mixture was stirred at room temperature for 5 min and then 0.64 g (0.0024 mol) of *N*-(3-bromopropyl)phthalimide was added. The mixture was stirred at room temperature for 1 h and was diluted with H_2O to the cloudy point. The resulting precipitate was collected, giving 0.5 g (53%) of product. The analytical sample was obtained from EtOH, mp 120–122 °C. Anal. ($C_{23}H_{24}N_2O_4$) C, H, N.

1-[[3-(3-Aminopropoxy)phenyl]carbonyl]piperidine (5e). To a warm solution of 0.5 g (0.001 mol) of **4** in 200 mL of absolute EtOH was added 1 mL of hydrazine. The mixture was stirred at room temperature for 1 h and was filtered. The filtrate was allowed to stand at room temperature for 18 h and again was filtered. The filtrate was evaporated in a rotary evaporator and the residue was partitioned between 50 mL of Et_2O and 50 mL of H_2O. The Et_2O phase was dried over $MgSO_4$, filtered, and evaporated to give 0.08 g (31%) of crude oily product. Purification by HPLC gave the analytical sample.

4-(Aminosulfonyl)-*N*-[3-[3-(1-piperidinylcarbonyl)phenoxy]propyl]-3-thiophenecarboxamide Hydrate (10). To a solution of 0.26 g (0.001 mol) of **5e** in 30 mL of dry THF was added 0.23 g (0.001 mol) of 4-(aminosulfonyl)-3-thiophenecarbonyl chloride. After a 15-min interval the THF was removed in a rotary evaporator and the residue was dissolved in 50 mL of $CHCl_3$. The $CHCl_3$ solution was extracted with 50 mL of 10% aqueous NaOH solution and then was acidified with 10% HCl solution followed by a rinse with H_2O. The $CHCl_3$ solution was dried over $MgSO_4$, filtered, and then evaporated in a rotary evaporator to give 0.15 g (32%) of an amorphorous product, mp 70–80 °C.

1-[3-[3-(Thieno[3,4-*d*]isothiazol-3-ylamino)propoxy]benzoyl]piperidine *S',S'*-Dioxide (6e). Method A. A mixture of 0.52 g (0.002 mol) of **5e** and 0.44 g (0.002 mol) of **2a** in 20 mL of EtOH was heated under reflux for 1 h. The mixture was filtered to give 0.4 g (46%) of product. An analytical sample was obtained from EtOH, mp 232–234 °C.

Method B. A stirred mixture of 0.15 g (0.000 32 mol) of **10** in 15 mL of $POCl_3$ was heated under reflux for 30 min. The reaction solution was evaporated in a rotary evaporator and the residue was triturated with 20 mL of H_2O. Approximately 5 mL of EtOH was added, which resulted in crystallization. The product amounted to 0.065 g (47%). Recrystallization from EtOH gave the analytical sample, mp 230–232 °C, whose IR spectrum was identical with that of the product made by method A. A mixture melting point of the two samples showed no depression.

Preparation of 6a·HCl from 6e (Method 2). A mixture of 0.2 g (0.000 46 mol) of **6e** in 10 mL of $POCl_3$ was warmed to give a solution. The solution was evaporated at room temperature with a vacuum pump. To the residue was added 10 mL of 1,2-dimethoxyethane. The resulting solution was cooled in ice and 0.07 g (0.0018 mol) of $NaBH_4$ was added. The reaction mixture was allowed to stand at room temperature for 1 h and 5 mL of 10% HCl was added dropwise. The mixture was evaporated with a vacuum pump and 20 mL of H_2O was added. The mixture was heated under reflux for 20 min, cooled, and filtered. The filtrate was basified with 10% Na_2CO_3 solution. The resulting precipitate was dissolved in EtOH and the solution was acidified with an ethereal HCl solution. There was obtained 0.06 g (28%) of product. The analytical sample was obtained from aqueous EtOH,

(14) Black, J. W.; Duncan, W. A. M.; Durant, C. J.; Ganellin, C. R.; Parsons, E. M. *Nature (London)* **1972**, *236*, 385.
(15) Martin-Smith, M.; Price, B. J.; Clitherow, J. W.; Bradshaw, J. British Patent 1 604 675, 1981.
(16) Gilman, D. J.; Wardleworth, J. M.; Yellin, T. O. U.S. Patent 4 165 378, 1979.

mp 256–259 °C. The IR spectrum of the product was identical with the IR spectrum of **6a**·HCl prepared from **5a** and **2a**. A mixture melting point of the products prepared by the two methods was undepressed.

3-[3-(Diethoxymethyl)phenoxy]propanamine (5d). To a solution of 15.3 g (0.43 mol) of 2-[3-[3-(1,3-dioxolan-2-yl)phenoxy]propyl]-1*H*-isoindole-1,3(2*H*)-dione[11] in 500 mL of EtOH was added 60 mL of hydrazine hydrate. The reaction mixture was stirred until a viscous precipitate was formed and was then allowed to stand overnight at room temperature. The reaction mixture was filtered under suction and evaporated to dryness in a rotary evaporator first by aspirator and then by vacuum pump. To the residue was added 100 mL of dry Et_2O. The Et_2O was then decanted from the undissolved portion of the residue. The residue was washed two more times, and the ether phases were combined, filtered, and taken to dryness in a rotary evaporator. The product amounted to 8.7 g (79%) and was used directly in the next step.

***N*-[3-[3-(Diethoxymethyl)phenoxy]propyl]thieno[3,4-*d*]isothiazol-3-amine 1,1-Dioxide (13).** A solution of 0.76 g (0.003 mol) of **5d** and 0.66 g (0.003 mol) of **2a** in 50 mL of EtOH was heated under reflux for 5 h. The EtOH was removed in a rotary evaporator. Trituration of the residue with ether gave 1.3 g (100%) of product. An analytical sample was obtained from EtOH, mp 130–133 °C. Anal. ($C_{19}H_{24}N_2O_5S_2$) H, N; C: calcd, 53.75; found, 53.17.

3-[3-(Thieno[3,4-*d*]isothiazol-3-ylamino)propoxy]benzaldehyde *S',S'*-Dioxide (6d). To 10 mL of H_2O was added 10 mL of concentrated HCl followed by 0.7 g (0.0016 mol) of **13**. The reaction mixture was stirred for 1 h at room temperature and was then filtered. There was obtained 0.5 g (89%) of product. An analytical sample was obtained from acetone–H_2O, mp 182–185 °C.

Preparation of 6a·HCl from 6d (Method 3). To 0.35 g (0.001 mol) of **6d** in 30 mL of EtOH was added 0.43 g (0.005 mol) of piperidine. The reaction mixture was heated for a few minutes until a clear solution was obtained and then was allowed to stand at room temperature overnight. To the solution was added 0.19 g (0.005 mol) of $NaBH_4$. The reaction mixture was allowed to stand overnight and the EtOH was removed in a rotary evaporator. H_2O (30 mL) was added to the residue followed by the dropwise addition of concentrated HCl to pH 2. A crystalline product formed, which amounted to 0.45 g (99%). The analytical sample was obtained from EtOH, mp 227–230 °C. Anal. ($C_{20}H_{25}N_3O_3S_2$·HCl) C, H, N.

A portion of the product was basified with concentrated NH_4OH and then recrystallized from EtOAC, giving the analytical product, mp 140–142 °C. The IR spectrum was identical with **6a** prepared by method 1.

4-(Aminosulfonyl)-*N*-[3-[3-(1-piperidinylmethyl)phenoxy]propyl]-3-thiophenecarboxamide Hydrochloride (12). Method A. A stirred mixture of 2.2 g (0.01 mol) of methyl 4-sulfamoylthiophene-3-carboxylate[4] and 2.4 g (0.01 mol) of **5a** was heated in an oil bath kept at 170 °C for 3 h. The mixture was cooled to 100 °C and 15 mL of EtOH was added. The resulting solution was diluted with 1 mL of H_2O and was acidified to pH 1 with concentrated HCl. The precipitate that formed was recrystallized twice from EtOH to afford 0.2 g (40%) of product, mp 195–197 °C. Recrystallization from H_2O gave the hydrate, mp 130–134 °C.

Method B. To 0.74 g (0.002 mol) of **11** in 25 mL of absolute EtOH was added 0.35 g (0.004 mol) of piperidine. After the reaction solution was warmed for a few minutes on a hot plate, the solution was allowed to stand overnight at room temperature. $NaBH_4$ (0.08 g, 0.002 mol) was then added. The reaction mixture was stirred for 3 days and the EtOH was removed in a rotary evaporator. H_2O (25 mL) was added to the residue, which was then warmed on a hot plate. The mixture was treated with charcoal and filtered. The filtrate was acidified to pH 2 with concentrated HCl. The crystalline product that was formed amounted to 0.27 g (28%). The analytical sample was obtained from H_2O, mp 126–129 °C. The IR spectrum was identical with that of hydrated **12** prepared by method A.

4-(Aminosulfonyl)-*N*-[3-(3-formylphenoxy)propyl]-3-thiophenecarboxamide (11). A mixture of 2.53 g (0.01 mol) of **5d** and 2.21 g (0.01 mol) of methyl 4-sulfamoylthiophene-3-carboxylate was heated on a steam bath for 1 h. A vacuum pump was used to remove the MeOH that had formed. To the residue were then added 25 mL of H_2O and 2 mL of concentrated HCl. After the mixture was allowed to stand overnight, a crystalline product was deposited, which amounted to 1.59 g (43%). The analytical sample (mp 132–134 °C) was obtained from EtOH.

Preparation of 6a·HCl from 12 (Method 4). To a suspension of 1.3 g (0.003 mol) of **12** in 50 mL of dry xylene was added 0.9 g (0.006 mol) of $POCl_3$. The mixture was heated under reflux for 2 h. The xylene was decanted from the residue and 20 mL of EtOH was added. The mixture was heated on a hot plate. The addition of a small quantity of H_2O to the ethanolic mixture resulted in a clear solution. On cooling the solution in ice there was obtained 0.8 g (67%) of product, mp 255–258 °C.

The infrared spectrum of this material was identical with that of 6a·HCl prepared by method 1.

Thieno[3,4-*d*]isothiazol-3-amine 1,1-Dioxide (14). To 1 mL of concentrated NH_4OH was added 0.1 g (0.000 45 mol) of **2a**. A few drops of EtOH was added and the reaction mixture was heated to boiling for a few minutes. The reaction mixture was allowed to stand overnight at room temperature. The crystalline product amounted to 0.08 g (94%), mp 297–300 °C. Anal. ($C_5H_4N_2S_2O_2$) C, H, N.

1-[[3-(3-Bromopropoxy)phenyl]methyl]piperidine (15). To a suspension of 0.4 g (0.01 mol) of 60% NaH in 20 mL of dry DMF was added dropwise over 5 min a solution of 1.9 g (0.01 mol) of 3-(1-piperidinylmethyl)phenol[5] in 20 mL of dry DMF. To the stirred mixture was added 6.0 g (0.03 mol) of 1,3-dibromopropane. After 2 h the mixture was diluted with 150 mL of H_2O and extracted with 100 mL of $CHCl_3$. The $CHCl_3$ layer was washed with 50 mL of 10% NaOH solution and then with H_2O. The $CHCl_3$ layer was dried over $MgSO_4$, filtered, and evaporated in a rotary evaporator. The residue was dissolved in 100 mL of Et_2O and the solution was extracted with 100 mL of H_2O. The Et_2O layer was dried over $MgSO_4$, filtered, and acidified with an ethereal HCl solution. The mixture was then extracted with H_2O and the H_2O layer was basified with aqueous Na_2CO_3 solution and then was extracted with Et_2O. The Et_2O solution was dried over $MgSO_4$, filtered, and evaporated to dryness, giving 0.53 g (17%) of product. The hydrochloride salt prepared from ethereal HCl solution was recrystallized from EtOAC, affording an analytical sample, mp 133–135 °C. Anal. ($C_{15}H_{22}BrNO$·HCl) Cl.

Preparation of 6a from 14 (Method 5). To a suspension of 0.65 g (0.0017 mol) of 60% NaH in 10 mL of dry DMF was added dropwise over 5 min a solution of 0.32 g (0.0017 mol) of **14** in 10 mL of dry DMF. The mixture was stirred at room temperature for 5 min and then 0.53 g (0.0017 mol) of **15** was added. The mixture was stirred at room temperature for 1 h and was then poured into 150 mL of water. The mixture was extracted with 75 mL of $CHCl_3$ and the $CHCl_3$ solution was washed with H_2O. The $CHCl_3$ layer was dried over $MgSO_4$, filtered, and evaporated in a rotary evaporator. The residue was dissolved in Et_2O, which was then washed with H_2O. The Et_2O was dried over $MgSO_4$ and filtered, and the filtrate was acidified with an ethanolic HCl solution. The resulting precipitate amounted to 0.4 g (52%). An analytical sample (mp 256–259 °C) was obtained from aqueous EtOH. The IR spectrum was identical with that of **6a**·HCl prepared by method 1.

Preparation of 6a from 6c (Method 6). A mixture of 0.2 g (0.0005 mol) of **6c** and 0.3 g (0.001 mol) of PtO_2 was shaken in an atmosphere of H_2 in a Parr apparatus until no further uptake of H_2 was observed. The reaction mixture was filtered and evaporated to dryness, giving 0.29 g (100%) of residue. The IR spectrum of the residue was identical with that of **6a**.

Acknowledgment. We are indebted to M. Politowski and staff for microanalyses and IR spectra, B. Hofmann for the NMR spectra, P. Dove, A. Sandor, G. Palumbo, and C. Buonato for biological assays, and M. E. Fiala and J. McKay for preparing the manuscript. We further thank R. L. Vogel for technical assistance.