3.00 (3 H, s, CH_3S^+), 3.30–3.58 (4 H, m, CCH_2S, NCH_2C), 4.25 (2 H, q, J = 7 Hz, CCH_2CO), 8.00 (1 H, s, Ar H); MS (M^+, $C_{13}H_{21}N_2S_2O_3$), calcd, 317.0994; found, 317.1001.

5c (29%): viscous oil; ^1H NMR (D_2O, pD 5.6) δ 2.13–2.25 (2 H, m, CCH_2C), 2.72 (3 H, s, Ar CH_3), 3.00 (3 H, s, CH_3S^+), 3.40–3.61 (2 H, m, CCH_2S), 3.59 (2 H, t, J = 6.4 Hz, NCH_2C), 4.41–4.52 (2 H, AB, J_{AB} = 15.7 Hz, SCH_2CO), 8.04 (1 H, s, Ar H); MS (M^+, $C_{11}H_{18}N_3S_2O_2$), calcd, 288.0840; found, 288.0803.

5d (52%): viscous liquid; ^1H NMR (D_2O, pD 4.9) δ 1.09–1.16 (6 H, m, $(CH_3)_2C$), 2.10–2.25 (2 H, m, CCH_2C), 2.73 (3 H, s, Ar CH_3), 3.00 (3 H, s, CH_3S^+), 3.40–3.60 (2 H, m, CCH_2S), 3.59 (2 H, t, J = 6.3 Hz, NCH_2C), 3.85–4.00 (1 H, m, NCH(C)), 8.05 (1 H, s, Ar H); MS (M^+, $C_{14}H_{24}N_3S_2O_2$), calcd, 330.1310; found, 330.1320.

5e (80%): viscous liquid; ^1H NMR (D_2O, pD 6.6) δ 0.50–0.60 and 0.75–0.84 (2 × 2 H, m, CHCH), 2.10–2.25 (2 H, m, CCH_2C), 2.58–2.70 (1 H, m, NCH(C)), 2.74 (3 H, s, Ar CH_3), 3.01 (3 H, s, CH_3S^+), 3.40–3.60 (2 H, m, CCH_2S), 3.61 (2 H, t, J = 6.4 Hz, NCH_2C), 8.07 (1 H, s, Ar H); MS (M^+, $C_{14}H_{22}N_3S_2O_2$), calcd, 328.1153; found, 328.1132.

5f (48%): viscous liquid; ^1H NMR (D_2O, pD 5.2) δ 1.80–2.00 (4 H, m, CCH_2CH_2C), 2.10–2.27 (2 H, m, CCH_2C), 2.71 (3 H, s, Ar CH_3), 2.98 (3 H, s, CH_3S^+), 3.30–3.61 (8 H, m, CCH_2S, NCH_2C, NCH_2CCCH_2N), 8.04 (1 H, s, Ar H); MS (M^+, $C_{15}H_{24}N_3S_2O_2$), calcd, 342.1310; found, 342.1330.

5g (55%): viscous liquid; ^1H NMR (D_2O, pD 2.9) δ 2.10–2.28 (2 H, m, CCH_2C), 2.72 (3 H, s, Ar CH_3), 2.98 (3 H, s, CH_3S^+), 3.30–3.90 (12 H, m, CCH_2S, NCH_2C, NCH_2CH_2O), 8.05 (1 H, s, Ar H); MS (M^+, $C_{15}H_{24}N_3S_2O_3$), calcd, 358.1259; found, 358.1240.

5h: hygroscopic solid (71%): mp 78–81 °C; IR (KBr) 3000–3500 (salt bands), 1630–1680 (amide I), 1550 (amide II), 1600, 1500 (aromatic); ^1H NMR (D_2O, pD 4.3) δ 2.10–2.30 (2 H, m, CCH_2C), 2.64 (3 H, s, Ar CH_3), 3.04 (3 H, s, CH_3S^+), 3.45–3.61 (4 H, m, CCH_2S, NCH_2C), 7.20–7.30 (1 H, m, C_4-H), 7.34–7.42 (4 H, m, C_2-H, C_3-H, C_5-H, C_6-H), 7.95 (1 H, s, Ar H); MS (M^+, $C_{17}H_{22}N_3S_2O_2$), calcd, 364.1153; found, 364.1138; Anal. ($C_{17}H_{22}N_3S_2O_2Cl\cdot H_2O$) C, H, N.

5i (80%): hygroscopic white powder; mp 76–79 °C; IR (KBr) 3000–3500 (salt bands), 1640–1670 (amide I), 1545 (amide II), 1510 (aromatic); ^1H NMR (D_2O, pD 6.7) δ 2.10–2.30 (2 H, m, CCH_2C), 2.62 (3 H, s, Ar CH_3), 3.05 (3 H, s, CH_3S^+), 3.45–3.61 (4 H, m, CCH_2S, NCH_2C), 3.80 (3 H, s, CH_3O), 6.90 (2 H, AB, J_{AB} = 9.0 Hz, C_3-H, C_5-H), 7.28 (2 H, AB, J_{AB} = 9.0 Hz, C_2-H, C_6-H), 7.91 (1 H, s, Ar H); MS (M^+, $C_{18}H_{24}N_3S_2O_3$), calcd, 394.1259; found, 394.1245. Anal. ($C_{18}H_{24}N_3S_2O_3Cl\cdot H_2O$) C, H, N.

2-Methyl-4-[[[3-(methylthio)propyl]amino]carbonyl]-thiazole[23] **(6)**: pale yellow viscous liquid; bp 160 °C (0.01 mmHg) (Kugelrohr); IR ($CHCl_3$) 3400 (NH), 2980, 2910 (CH), 1650 (amide I), 1540 (amide II) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.82–1.93 (2 H, m, CCH_2C), 2.07 (3 H, s, CH_3S), 2.54 (2 H, t, J = 7 Hz, CH_2S), 2.66 (3 H, s, Ar CH_3), 3.46–3.54 (2 H, m, CCH_2N), 7.40 (1 H, br, NH), 7.89 (1 H, s, Ar H); MS (M^+, $C_9H_{14}N_2S_2O$), calcd, 230.0547; found, 230.0532. Anal. ($C_9H_{14}N_2S_2O$) N: calcd, 12.16; found, 11.73.

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Registry No. **2a**, 79-08-3; **2b**, 105-36-2; **2c**, 683-57-8; **2d**, 75726-96-4; **2d**·HCl, 104240-92-8; **2e**, 77600-79-4; **2e**·HCl, 104240-93-9; **2f**, 90892-09-4; **2f**·HCl, 104240-94-0; **2g**, 40299-87-4; **2g**·HCl, 104240-95-1; **2h**, 5326-87-4; **2h**·HCl, 104240-96-2; **2i**, 29182-87-4; **2i**·HCl, 104240-97-3; **2j**, 3598-91-2; **2j**·HCl, 104240-98-4; **2k**, 22344-79-2; **2k**·HCl, 104240-99-5; **3a**, 104320-74-3; **3b**, 104321-40-6; **3c**, 104320-75-4; **3d**, 104241-10-3; **3e**, 104320-76-5; **3f**, 104241-12-5; **3g**, 104320-77-6; **3h**, 104241-14-7; **3i**, 104241-16-9; **3j**, 104241-18-1; **3k**, 104241-20-5; **5a**, 104241-00-1; **5b**, 104241-01-2; **5c**, 104241-02-3; **5d**, 104241-03-4; **5e**, 104241-04-5; **5f**, 104241-05-6; **5g**, 104241-06-7; **5h**, 104241-07-8; **5i**, 104241-08-9; **6**, 104266-58-2; α-bromoacetyl chloride, 22118-09-8; demethylbleomycin A2 (Cu(II) complex), 71801-39-3; 2-propanamine, 75-31-0; cyclopropanamine, 765-30-0; pyrrolidine, 123-75-1; morpholine, 110-91-8; benzenamine, 62-53-3; 4-methoxybenzenamine, 104-94-9; 4-nitrobenzenamine, 100-01-6; 2-naphthalenamine, 91-59-8.

Synthesis and Antisecretory and Antiulcer Activities of Derivatives and Analogues of 2-(2-Pyridyl)tetrahydrothiophene-2-carbothioamide

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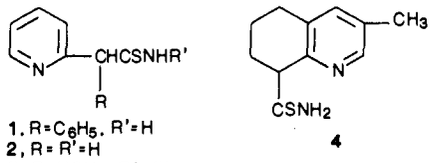
New thioamide derivatives of 2-(2-pyridyl)tetrahydrothiophene-2-carbothioamide (**29**) and related compounds (in which the tetrahydrothiophene ring was replaced by tetrahydrothiopyran, tetrahydrofuran, 1,3-dithiane, or 1,3-oxathiane and where the pyridine ring was replaced by other nitrogen heterocycles) were synthesized and tested for their antisecretory and antiulcer activities. These thioamides were prepared according to one of the following methods: (i) reaction of an isothiocyanate with the carbanion of the corresponding cyclic precursor (for secondary thioamides); (ii) reaction of ammonia or an amine with the dithio ester prepared from the same precursor (for primary, secondary, and tertiary thioamides). These thioamides were evaluated by the Shay method to measure their antisecretory activity and by the stress-induced-ulcer method to test their antiulcer activity. Structure–activity relationships are discussed. *N*-Methyl-2-(2-pyridyl)tetrahydrothiophene-2-carbothioamide (R.P. 40749, **30**) exhibited activities that were at least 10 times higher than those reported for cimetidine.

Thioacetamide derivatives bearing the pyridine nucleus (for example, 2-phenyl-2-(2-pyridyl)thioacetamide (**1**, SC 15396),[1] 2-(2-pyridyl)thioacetamide (**2**, CMN 131),[2] *N*-methyl-2-methoxy-2-(2-pyridyl)thioacetamide (**3**, SKF 59377),[3] and 3-methyl-5,6,7,8-tetrahydroquinoline-8-carbothioamide (**4**, Tiquinamide)[4]) are known to possess non-anticholinergic antisecretory properties.



1, R = C_6H_5, R' = H
2, R = R' = H
3, R = OCH_3, R' = CH_3
4

A structural feature common to these compounds is the

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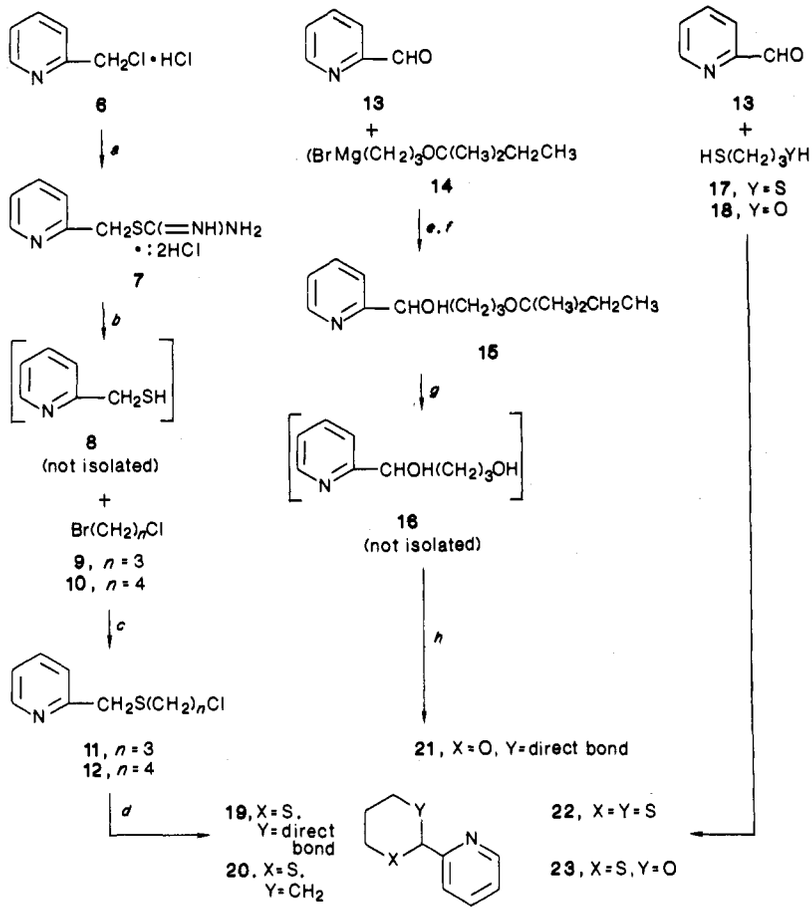
Scheme I



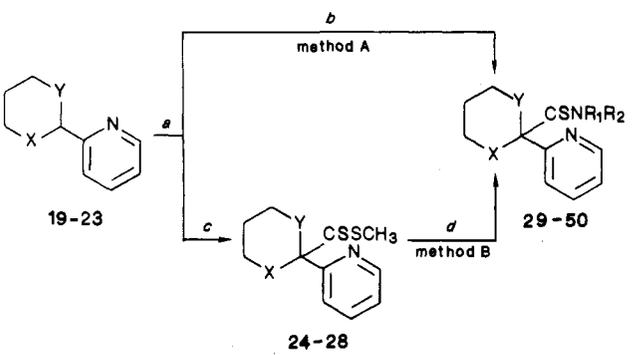
[a] H_2NCSNH_2/C_2H_5OH. [b] NaOH. [c] NaOH. [d] t-C_4H_9OK/HMPA–THF. [e] Ether. [f] H^+. [g] p-Toluenesulfonic acid/toluene. [h] Polyphosphoric acid. [i] p-Toluenesulfonic acid/$ClCH_2CH_2Cl$.

presence of two hydrogen atoms, one on the position α to the pyridine ring and the other on the nitrogen atom of the thioamide function. The latter appears to be important because a change from primary and secondary to tertiary thioamides is detrimental for activity, which probably means that the molecule is capable of existing in the thiol imine form.[5] However, there is the possibility that the molecule exists in the thioenol form. Thus it would be interesting to observe the effect on activity when there is no hydrogen atom α to the pyridine ring, i.e., by removing the possibility of the presence of this thioenol form. We decided therefore to prepare a series of novel thioamides **29–50** (Table I) in which the carbon atom in the position α to the pyridine ring was incorporated into a saturated heterocycle[6] (tetrahydrothiophene, tetrahydrofuran, 1,3-dithiane, or 1,3-oxathiane).

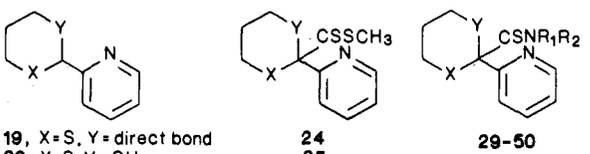
Chemistry

Compounds **19–23** are precursors of the thioamides **29–50** (Table I), and they possess a carbon atom that bears an acidic proton. They can be metalated by a strong base such as butyllithium or lithium dialkylamide (Scheme II). The carbanion can then react either with an isothiocyanate (method A) or with carbon disulfide, followed by alkylation with methyl iodide to yield the corresponding dithio esters **24–28**. Reaction with ammonia or an amine gave the expected thioamides (method B).

Scheme II



[a] n-C_4H_9Li, $(C_2H_5)_2NLi$, or $[(CH_3)_2CH]_2NLi$/HMPA–THF. [b] R_2NCS (R_1 = H). [c] CS_2 + ICH_3. [d] HNR_1R_2/C_2H_5OH.



19, X = S, Y = direct bond
20. X = S, Y = CH_2
21. X = O, Y = direct bond
22, X = Y = S
23, X = S, Y = O

24
25
26
27
28

29–50

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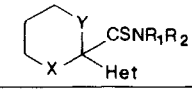
(6) Rhône-Poulenc U.S. Patents 4 272 534 and 4 379 154.

Table I



no.	Het	X	Y	R_1	R_2	yield,[a] %	method	mp, °C	recrystn solvent[b]	formula[e]	antisecretory act.[f] (po) % inhibn at 30 mg/kg	antisecretory act.[f] (po) ED_{50}, mg/kg	antiulcer act. (po) dose, mg/kg	antiulcer act. (po) % protected rats
29	2-pyridyl	S	db[g]	H	H	26	B	192	AC	$C_{10}H_{12}N_2S_2$		3.2 (0.5–22.3)	100	100
30	2-pyridyl	S	db	H	CH_3	28	A	131	E	$C_{11}H_{14}N_2S_2$		0.4 (0.1–1.3)	4.5	50
						34	B	131	E					
31	2-pyridyl	S	db	H	C_2H_5	20	A	96	E	$C_{12}H_{16}N_2S_2$		1.6 (1–2.6)	10	50
32	2-pyridyl	S	db	H	$(CH_2)_3CH_3$	10	A	*c*		$C_{14}H_{20}N_2S_2$		5.5 (2.5–12.1)	30	100
33	2-pyridyl	S	db	H	$(CH_2)_6CH_3$	24	B	*d*		$C_{17}H_{26}N_2S_2$	0 NS	>30	100	33
34	2-pyridyl	S	db	H	$(CH_2)_{11}CH_3$	29	B	60	E	$C_{22}H_{36}N_2S_2$	0 NS	>30	100	0
35	2-pyridyl	S	db	H	C_6H_5	42	A	95	E	$C_{16}H_{16}N_2S_2$	0 NS	>30		
36	2-pyridyl	S	db	H	$CH_2C_6H_5$	28	B	71	E	$C_{17}H_{18}N_2S_2$	58	≤30	100	100
37	2-pyridyl	S	db	H	CH_2CH_2OH	36	B	132	E	$C_{12}H_{16}N_2OS_2$	25 NS	>30	100	16
38	2-pyridyl	S	db	H	$CH_2CH{=}CH_2$	28	B	75	E	$C_{13}H_{16}N_2S_2$	20 NS	>30	100	0
39	2-pyridyl	S	db	H	$(CH_2)_2N(CH_3)_2$	21	B	138	E	$C_{14}H_{21}N_3S_2 \cdot CH_3SO_3H$	0 NS	>30	100	16
40	2-pyridyl	S	db	H	$(CH_2)_3N(CH_3)_2$	50	A	*d*		$C_{15}H_{23}N_3S_2$	0 NS	>30	100	0
41	2-pyridyl	S	db	H	NH_2	34	B	172	M	$C_{10}H_{13}N_3S_2$	0 NS	>30	100	0
42	2-pyridyl	S	db	CH_3	CH_3	27	B	100	E	$C_{12}H_{16}N_2S_2$	74	<30	100	83
43	2-pyridyl	S	db		$(CH_2)_5$	10	B	90	I	$C_{15}H_{20}N_2S_2$	30 NS	>0	100	83
44	2-pyridyl	S	db		$(CH_2)_2O(CH_2)_2$	25	B	139	E	$C_{14}H_{18}N_2OS_2$	54	≤30	100	83
45	2-pyridyl	S	db		$(CH_2)_2N(CH_3)(CH_2)_2$	9	B	124	E	$C_{15}H_{21}N_3S_2$	8 NS	>30	100	0
46	2-pyridyl	S	CH_2	H	CH_3	13	B	153	E	$C_{12}H_{16}N_2S_2$		2.6 (1.0–6.5)	10	100
47	2-pyridyl	O	db	H	CH_3	25	A	115	E	$C_{11}H_{14}N_2OS$		0.5 (0.1–2.2)	4.5	66
48	2-pyridyl	S	S	H	H	13	B	214	AC	$C_{10}H_{12}N_2S_3$		2.8 (0.6–12.7)	100	100
49	2-pyridyl	S	S	H	CH_3	21	A	159	E	$C_{11}H_{14}N_2S_3$		5.7 (3.2–10.1)	10	50
50	2-pyridyl	S	O	H	CH_3	25	B	157	E	$C_{11}H_{14}N_2OS_2$		1.6 (0.5–4.9)	5	50
51	4-CH_3-2-pyridyl	S	db	H	CH_3	19	A	181	E–AC	$C_{12}H_{16}N_2S_2$		1 (0.5–2)	10	83
52	5-CH_3-2-pyridyl	S	db	H	CH_3	17	A	134	E	$C_{12}H_{16}N_2S_2$		5.7 (2.7–12.3)	10	60
53	6-CH_3-2-pyridyl	S	db	H	H	27	B	171	E	$C_{11}H_{14}N_2S_2$	71	<30	100	100
54	6-CH_3-2-pyridyl	S	db	H	CH_3	24	A	121	DCE–EE	$C_{12}H_{16}N_2S_2$		1.5 (0.8–2.8)	10	50
55	4-[$CH_3(CH_2)_3$]-2-pyridyl	S	db	H	CH_3	22	A	102	IE	$C_{15}H_{22}N_2S_2$	78	<30	100	100
56	3-pyridyl	S	db	H	CH_3	18	B	133	E	$C_{11}H_{14}N_2S_2$	49	≥30	100	100
57	4-pyridyl	S	db	H	CH_3	16	B	178	AC	$C_{11}H_{14}N_2S_2$	53	≤30	100	83
58	2-quinolyl	S	db	H	CH_3	26	B	124	E	$C_{15}H_{16}N_2S_2$		3.0 (1.3–7.1)	100	100
59	3-pyridazinyl	S	db	H	CH_3	6	A	199	E	$C_{10}H_{13}N_3S_2$			100	100
60	pyrazinyl	S	db	H	CH_3	18	A	127	P–IE	$C_{10}H_{13}N_3S_2$	38	>30	100	100
1												5.5 (1.7–17.4)		
4												1.6 (0.6–3.8)		
5	cimetidine											30 (7.4–118)	100	50

[a] Yield calculated from **19–23**. [b] AC, acetonitrile; M, methanol; E, ethanol; P, propanol; I, 2-propanol; EE, diethyl ether; IE, diisopropyl ether; DCE, 1,2-dichloroethane. [c] Bp 178–185 °C (0.6 mmHg). [d] Yellow oil, purified by chromatography. [e] All compounds were analyzed for CHNOS, and the results were within 0.4% of theory. [f] Statistically significant activity $p < 0.05$ (Student's *t* test). NS = no statistically significant activity. [g] db = direct bond.

Compounds **19–23** were prepared (Scheme I) by analogy to the methods previously described[9-11] in which we have replaced the benzene ring by a pyridine moiety. The tetrahydrothiophene **19** was obtained by starting from the reaction of the chloride **6** with thiourea in ethanol to yield the isothiourea dihydrochloride **7**. Alkaline hydrolysis gave the mercaptan **8** (which was not isolated, thus limiting the formation of disulfide). It was reacted in situ with **9** to give **11**. Cyclization to **19** was achieved by using potassium *tert*-butoxide as the base. Compound **20** was obtained in the same way by using **10** instead of **9**.

The tetrahydrofuran **21** was prepared by the following method. Reaction of the Grignard reagent[10] **14** with the aldehyde **13** yielded the carbinol **15**. After deprotection the diol **16** was cyclized in acidic medium to give **21**.

Derivatives **22** and **23** were obtained by condensing the aldehyde **13** with propane-1,3-dithiol **17** and 3-mercaptopropan-1-ol **18**, respectively.

Compounds **51–55** (substituted in the pyridine ring), **56–57** (modification of the position of substitution of the pyridine moiety), and **58–60** (replacement of the pyridine ring by other nitrogen heterocycles) were prepared in a similar manner to that described for compounds **29–50** by starting from the corresponding analogues[12,14-18] of **6**.

Biological Activity and Discussion

Emphasis was centered on the study of the antisecretory activity of the compounds. The antiulcer effect was not studied as extensively. The antisecretory activity was examined initially at a dose of 30 mg/kg po, and when the inhibition was found to be greater than 80%, lower doses were examined in order to determine the ED_{50} value. The antiulcer activity was generally determined at doses of 100 and/or 10 mg/kg po. A careful examination of the results (see Table I) in terms of each of the three substructures (thioamides, nitrogen-containing aromatic heterocycle, saturated heterocycle) allowed some observations with regard to structure–activity relationship.

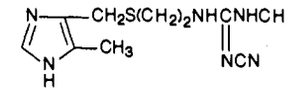
The activity was poor with tertiary thioamides (**42–45**) but increased with primary thioamides (**29, 48, 53**) and was particularly high with secondary thioamides, especially when the nitrogen substituent was a lower alkyl group such as methyl, ethyl, or butyl (**30–32, 46, 47, 49–52, 54, 55, 58**). It appears from these results that the thioenol form is not necessary for activity but the presence of a thiol imine form is probably an important contributing factor.[5] In the case of secondary thioamides, an increase in the length of the chain (**33, 34**) or the introduction of unsaturation (**35, 36, 38**) or of functional groups (**37, 39–41**) resulted in a decrease of activity.

As in the case of known pyridine thioacetamides **1–4**, the pyridine ring must be linked in the 2-position (**30**) rather than in the 3- (**56**) or 4-position (**57**). A good level of activity was preserved when substituents were introduced into the pyridine ring (**51–55**) or when it was replaced by another nitrogen heterocycle, provided that the heterocycle was linked in the α-position of the nitrogen atom (**58–60**).

Lastly, the activity remained high for each of the saturated heterocycles containing sulfur and/or oxygen (**47–50**).

These compounds were found to be non-anticholinergic agents against acetylcholine-induced spasm of isolated rabbit jejunum (technique of Magnus[19]) and were not histamine H_2 receptor antagonists against histamine inhibition of electrically induced spasm of isolated rat uterus (technique of Black[20]).

N-Methyl-2-(2-pyridyl)tetrahydrothiophene-2-carbothioamide (**30**, R.P. 40 749) exhibits antisecretory (ED_{50} = 0.4 mg/kg po) and antiulcer (ED_{50} = 5.9 mg/kg po) activity levels that are at least 10 times higher than those we found for cimetidine[21] (**5**).



5

Clinical studies have shown that this product inhibits gastric secretion in man.[22-24]

In conclusion, this novel family of thioamides has interesting antisecretory and antiulcer activity, and a comparison with known thioamides can be made. It was confirmed that replacement of the primary or secondary thioamide group by a tertiary thioamide group led to a loss of activity. Replacement of all the protons in the position α to the pyridine ring led us to interesting products. As can be seen, the level of activities observed was high and, for certain compounds, much superior to reference compounds.

Experimental Section

Reactions were monitored by TLC with the following system: 1:1 (v/v) cyclohexane/ethyl acetate (silica plates, Merck F 254). The products were purified by column chromatography with Merck silica (0.063–0.200 mm). The melting points were taken on a Kofler apparatus. Products were analyzed by using the following techniques: (i) titration by perchloric acid, 0.1 N in acetic acid; (ii) structural analysis including infrared spectroscopy (Perkin-Elmer type 580 B spectrometer), nuclear magnetic resonance (Brüker WM 250 and/or VARIAN T 60 spectrometer), and mass spectroscopy (Finnigan 3 300 spectrometer). Microanalysis was performed for each thioamide (conformed to 0.4% of theory).

In order to illustrate the reactions in Schemes I and II, the preparation of the precursors **19–23** and of thioamide **30** starting from **19** is described according to the two procedures A and B of Scheme II.

2-(2-Pyridylmethyl)isothiourea Hydrochloride (7). A so-

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lution of 233 g (1.42 mol) of 2-(chloromethyl)pyridine hydrochloride[12] (6) and 135 g (1.78 mol) of thiourea in 1500 mL of EtOH was heated at reflux for 1.5 h. After cooling, the precipitate was filtered, washed with EtOH, and dried to give 320 g (97%) of 7: mp 220 °C; IR (KBr) 3240, 3070, 3720, 2530 ($C(=N^+H_2)NH_2$, $\equiv N^+H$ pyridine) cm^{-1}.

3-Chloropropyl 2-Pyridylmethyl Sulfide (11). A solution of 453 g (1.9 mol) of 7 and 151 g (3.8 mol) of NaOH in 1180 mL of water was heated at 70 °C for 20 min. After cooling, a solution of 92.5 g (2.3 mol) of NaOH in 210 mL of water and then 303 g of 9 (1.9 mol) were added. The mixture was stirred overnight and was extracted with CH_2Cl_2. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and filtered through a silica gel column in order to eliminate polar impurities. The filtrate was evaporated under reduced pressure to give 330 g (86%) of 11 as a yellow oil: IR (CCl_4) 1270 (CH_2Cl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.01 (quintuplet, 2 H, J = 6.5 Hz, $CH_2CH_2CH_2$), 2.64 (t, 2 H, J = 6.5 Hz, SCH_2CH_2), 3.60 (t, 2 H, J = 6.5 Hz, CH_2Cl), 3.83 (s, 2 H, Ar CH_2S), 7.17–8.53 (m, 4 H, Ar H).

2-(2-Pyridyl)tetrahydrothiophene (19). To a solution of 283 g (2.5 mol) of t-BuOK in 2400 mL of a mixture of THF–HMPA (85:15, w/w) was added dropwise a solution of 330 g (1.64 mol) of 11 in 400 mL of THF. The mixture was stirred at room temperature for 1 h, diluted with water, and extracted with ether. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give 189 g (70%) of 19 as a brown oil: ^1H NMR ($CDCl_3$) δ 1.98–3.23 (m, 6 H, $SCH_2CH_2CH_2C$), 4.64 (t, 1 H, J = 7 Hz, SCH-CH_2), 7.13–8.54 (m, 4 H, Ar H).

4-Chlorobutyl 2-Pyridylmethyl Sulfide (12). The same method as described for the synthesis of 11 was followed with use of 10. The sulfide 12 was obtained as a yellow oil with a yield of 76%: IR (CCl_4) 1285 (CH_2Cl) cm^{-1}.

2-(2-Pyridyl)tetrahydrothiopyran (20). This was prepared similarly to compound 19, starting from 12, with a yield of 79%.

4-(1,1-Dimethylpropoxy)-1-(2-pyridyl)-1-butanol (15). A solution of 14 was prepared in 600 mL of ether from 24.3 g of Mg and 209 g (1 mol) of 1-bromo-3-(1,1-dimethylpropoxy)propane.[10] A solution of 85.7 g (0.8 mol) of 13 in 200 mL of ether was then added dropwise at 10–20 °C. The mixture was heated at reflux for 1 h, cooled, and hydrolyzed with 450 mL of 2.2 N HCl. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue was distilled to give 123.5 g (65%) of 15: bp 124 °C (1 mm); IR ($CHCl_3$) 3330 (OH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, J = 7 Hz, CH_2CH_3), 1.5–2.0 (m, 6 H, CH_2CH_3 and $CHCH_2CH_2CH_2$), 3.40 (t, 2 H, J = 7 Hz, CH_2CH_2O), 4.85 (m, 2 H, CHOH and CHOH), 7.10–8.50 (m, 4 H, Ar H).

2-(2-Pyridyl)tetrahydrofuran (21). A solution of 122 g (0.51 mol) of 15 and 107 g (0.55 mol) of p-toluenesulfonic acid monohydrate in 1 L of toluene was heated at reflux for 28 h. After cooling, the mixture was neutralized with an aqueous solution of $NaHCO_3$. The aqueous layer was extracted with ethyl acetate, and the organic layers were washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give 26 g (34%) of 21 as a yellow oil: IR (CCl_4) 1065 (CH_2OCH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.98–4.03 (m, 6 H, $OCH_2CH_2CH_2C$), 5.03 (t, 1 H, J = 6.3 Hz, $OCHCH_2$), 7.17–8.55 (m, 4 H, Ar H).

2-(2-Pyridyl)-1,3-dithiane (22). A solution of 26.7 g (0.25 mol) of 13, 94.4 g (0.87 mol) of 17, and 3.7 g (0.02 mol) of p-toluenesulfonic acid monohydrate in 2500 mL of 1,2-dichloroethane was refluxed for 20 h with a Dean–Stark trap to collect the azeotroped water. After cooling, the mixture was washed with 540 mL of 7 N KOH and with water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give 41.9 g (85%) of 22 as a brown oil: ^1H NMR ($CDCl_3$) δ 2.00–3.00 (m, 6 H, $SCH_2CH_2CH_2S$), 5.35 (s, 1 H, SCHS), 7.21–8.57 (m, 4 H, Ar H).

2-(2-Pyridyl)-1,3-oxathiane (23). The same method as described for the synthesis of 22 was followed with use of 3-mercaptopropane-1-ol[13] (18). The oxathiane 23 was obtained as a brown oil with a yield of 80%: ^1H NMR ($CDCl_3$) δ 1.8–4.2 (m, 6 H, $SCH_2CH_2CH_2O$), 5.90 (s, 1 H, SCHO), 7.10–8.50 (m, 4 H, Ar H).

***N*-Methyl-2-(2-pyridyl)tetrahydrothiophene-2-carbothioamide (30). (a) Method A.** To a stirred solution of 142 mL (0.23 mol) of 1.6 M butyllithium solution in hexane at −60 °C under nitrogen was added dropwise a solution (25%, w/w) of 22.5 g (0.22 mol) of diisopropylamine in a mixture of THF–HMPA (50:50 w/w) followed, in the same solvent at the same concentration, by 30 g (0.18 mol) of 19 and then 16.8 g (0.23 mol) of methyl isothiocyanate. After the mixture was stirred for 1 h at −60 °C, the cold bath was removed and water was added followed by ethyl acetate. The organic layer was washed with water, dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residual crude product was recrystallized from ethanol to give 10.8 g (25%) of 30: mp 131 °C; IR (KBr) 3200 (NH), 1536, 1340 (NC=S) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.7–3.51 (m, 6 H, $CH_2CH_2CH_2S$), 3.23 (d, 3 H, $CSNCH_3$), 7.15–8.46 (m, 4 H, Ar H), 9.97 (s, 1 H, NHCS).

(b) Method B. In a similar experiment using 785 mL (1.25 mol) of 1.6 M butyllithium in hexane, 120 g (0.73 mol) of 19 and 97 g (1.25 mol) of carbon disulfide were added followed by 180 g (1.25 mol) of methyl iodide. After workup, the resulting crude oil was chromatographed on silica with a mixture of cyclohexane and ethyl acetate (90:10, v/v) as eluant. Recrystallization of the crude product from diisopropyl ether afforded 80 g (43%) of 24: mp 63 °C; IR (CCl_4) 1590, 1570, 1470, 1430 (2-pyridyl), 1410, 1090, 970 ($CSSCH_3$) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.15–3.13 (m, 6 H, $SCH_2CH_2CH_2C$), 2.56 (s, 3 H, $CSSCH_3$), 7.15–8.53 (m, 4 H, Ar H).

To a stirred solution of 10 g (0.04 mol) of 24 in 32.5 mL of ethanol was added 2.5 g of a solution (33%, w/w) of methylamine in the same solvent. After the mixture was stirred for 30 min at room temperature, 30 crystallized. It was collected, dried, and recrystallized from ethanol to give 7.4 g (79%) of 30, mp 131 °C.

Pharmacology. (a) Gastric Antisecretory Activity. Gastric antisecretory activity was evaluated against histamine-stimulated gastric acid secretion in Shay rats.[25,26]

Groups of six female rats (OFA, IFFA-CREDO) weighing 150–175 g were fasted for 24 h prior to the test in cages with wire-mesh floors to prevent coprophagy, but the rats were allowed water ad libitum. Then, animals were submitted to the following procedures spaced 30 min apart: promethazine hydrochloride injection (10 mg/kg intraperitoneally), histamine hydrochloride injection (100 mg/kg subcutaneously), and, under chloral hydrate anesthesia (200 mg/kg intraperitoneally), small midline incision and pylorus ligation. Two hours after the abdomen was closed, the rats were sacrificed, the stomach was removed, and the gastric juice was titrated against 0.1 N sodium hydroxide. The statistical significance of the difference between the gastric acid outputs of the control and drug-treated group was calculated by using the Student's t test, and on the more potent antisecretory compounds, an ED_{50} value was calculated from the regression line.

The test compounds, suspended in 10% gum arabic solution, were administered orally in volumes of 5 mL/kg, 1 h before histamine injection.

(b) Antiulcer Activity. Antiulcer activity was evaluated against restraint-induced gastric erosions in rats, by using the technique of Rossi.[27] Groups of six female rats (OFA, IFFA-CREDO) weighing 150–175 g and fasted for 24 h were subjected to restraint in suitable cages of wire netting. Twenty-four hours later, the rats were sacrificed and the severity of gastric mucosal erosions was assessed. A rat was said to be protected when no gastric mucosal erosion was observed.

The test compounds, suspended in 10% gum arabic solution, were administered orally in volumes of 5 mL/kg, 1 h before restraint.

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Registry No. 6, 6959-47-3; 7, 1822-49-7; 9, 109-70-6; 10, 6940-78-9; 11, 76732-77-9; 12, 82081-46-7; 13, 1121-60-4; 15, 82081-58-1; 17, 109-80-8; 18, 504-63-2; 19, 76732-76-8; 20, 82081-45-6; 21, 82081-57-0; 22, 80085-67-2; 23, 82081-51-4; 24, 76743-15-2; 29, 76732-75-7; 31, 76743-12-9; 32, 76743-11-8; 33,

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Phenylpiperazine-Based Radiopharmaceuticals for Brain Imaging. 3. Synthesis and Evaluation of Radioiodinated 1-Alkyl-4-phenylpiperazines

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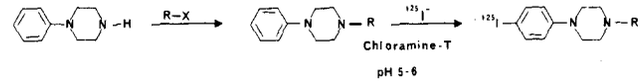
As part of our program in radiopharmaceutical chemistry we have prepared and evaluated a series of radioiodinated 1-alkyl-4-phenylpiperazines as potential brain-imaging agents. The compounds were chosen on the basis of their synthetic versatility, activation toward electrophilic substitution, and ease of purification. The intermediates **1–6** were readily obtained and converted to the corresponding radioiodinated products **7–12** in 76–91% isolated radiochemical yields. The tissue distribution in rats indicated that the 1-*N*-butyl derivative **9** possesses the best combination of brain uptake (0.28–0.35% ID·kg/g), retention, and selectivity (brain/blood > 20) over the 4-h evaluation period. A subsequent imaging and tissue distribution study in the dog using ^{131}I-labeled **9** supported the results observed in the rat and suggested the potential of this agent as a brain-imaging agent.

The development of single-photon emission computed tomographic (SPECT) instrumentation with sensitivity and resolution approaching that of the positron emission tomographic (PET) devices has stimulated the search for X-ray-emitting compounds capable of crossing the intact blood–brain barrier (BBB) and providing information regarding local cerebral perfusion.[1,2] Many types of brain pathology present themselves as alterations of blood flow and/or metabolic status prior to changes in brain morphology or density that can be detected by conventional radiologic methods. PET scanning has been particularly valuable in identifying many of these disorders, including early stroke, epilepsy, Huntington's chorea, Alzheimer's disease, and others.[3-6] This modality requires an on-site cyclotron, synthetic capability, and a PET scanner to prepare and use the short-lived radiopharmaceuticals. Widespread application of the brain scanning techniques may require the use of radionuclides that are available from generator sources or are sufficiently long-lived to be incorporated into an agent and shipped to the site of use.

Although ^{99m}Tc is the radionuclide of choice in clinical nuclear medicine, the difficulty in preparing a suitable chelate that will bind reduced ^{99m}Tc, readily cross the BBB, and be retained without redistribution long enough to provide useful scintigraphic images slowed its general acceptance.[7-11] Only recently, however, the derivatives of

Scheme I



	R		R
2	C_2H_5	8	C_2H_5
3	n-C_3H_9	9	n-C_4H_9
4	c-C_4H_9	10	c-C_4H_9
5	n-C_6H_{13}	11	n-C_6H_{13}
6	c-C_6H_{11}	12	c-C_6H_{11}

technetium-99m propyleneamine oxime (^{99m}TcPnAO) have been introduced into clinical nuclear medicine[12,13] and demonstrate significant potential. Organic radiopharmaceuticals, however, labeled with iodine radionuclides have been much more successful. The more promising of these radiopharmaceuticals are ^{123}I-labeled *N*-isopropyl-1-(4-iodophenyl)-2-aminopropane (*N*-isopropyl-*p*-iodoamphetamine, IMP)[14,15] and *N,N,N'*-trimethyl-*N'*-(2-hydroxy-3-methyl-5-iodobenzyl)-1,3-propanediamine (HIPDM).[16,17] The utility of IMP as an indicator of cerebral perfusion has been demonstrated in several clinical studies.[18-20] A comparison of HIPDM and IMP in-

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