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5,6,7,8-Tetrahydroquinolines. 4.[1] Antiulcer and Antisecretory Activity of 5,6,7,8-Tetrahydroquinolinenitriles and -thioamides

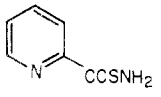
Doreen E. Beattie, Roger Crossley,* Adrian C. W. Curran, Geoffrey T. Dixon, David G. Hill, Anne E. Lawrence, and Robin G. Shepherd

Institute of Medical Research, Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire, SL6 OPH, England. *Received July 9, 1976*

A number of 5,6,7,8-tetrahydroquinoline-8-nitriles and -8-thioamides and related compounds have been found to be potent inhibitors of basal gastric secretion in the pylorus-ligated rat and to afford protection against gastric erosions induced in rats by cold-restraint stress. Molecular manipulation has proved useful in determining factors necessary for such activity and structure–activity relationships are discussed. It has been shown that the most necessary requirements for activity are a pyridine nitrogen with its available lone pair and a primary or secondary thioamide. Also desirable is a six-membered carbocyclic ring with relative freedom from steric hinderance around the 8 position.

Although the etiology of peptic ulceration is not fully understood, it is thought to be multifactorial, and present therapy is largely concerned with the neutralization or inhibition of gastric acid secretion by use of antacids and anticholinergic agents. The main disadvantage of antacid therapy is that these agents have a very short duration of action[2] and it is well known that anticholinergic drugs have limited therapeutic value in depressing gastric secretion in peptic ulcer patients, because the doses effective in the inhibition of acid secretion cause unpleasant side actions associated with blockade of parasympathetic stimulation.[3] In recent years, a number of nonanticholinergic antisecretory agents have been reported. Among the most notable of these are pyridyl-2-thioacetamide (CMN 131),[4] 2-methoxy-*N*-methyl-2-(2-pyridyl)thioacetamide (SKF 59377),[5] 2-phenyl-2-(2-pyridyl)thioacetamide (SC 15396),[4] and the histamine H_2-receptor antagonists burimamide,[4] metiamide,[4] and cimetidine.[6]

We decided to explore a system 1 which by virtue of its shape would bear some resemblance to pyridyl-2-thioacetamide and at the same time provide a substrate for molecular manipulation in order to define more closely requirements for activity. The 5,6,7,8-tetrahydroquinoline (THQ) ring system is one such system and 5,6,7,8-tetrahydroquinoline-8-thiocarboxamide (2) showed a high level



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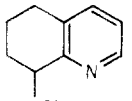

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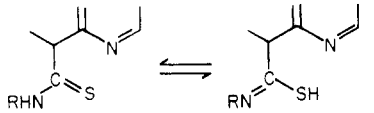
of antiulcer activity (erosion prevention in the cold-restraint rat) and antisecretory activity (pylorus-ligated rat) as shown in Table I.

There are many ways of investigating potential antiulcer activity. Acute gastric erosions can be induced in rats by imposing a stress situation, usually involving an element of immobilization,[7] or by a variety of chemical agents.[8] Various techniques are available for studying basal and chemically stimulated gastric acid secretion in both conscious and anesthetized animals.[9] The two tests described in this paper were considered the most suitable for primary screening purposes, in view of their wide acceptance and also because their nature is such that potential complications due to drug interactions are not involved. The doses used have been derived through experience, and because of the inherently more sensitive method for determining antisecretory activity these doses are one-third those used for the antiulcer test. Introduction of substituents into 2 and variation of carbocyclic ring size have enabled a series of analogues, Tables I and II, to be generated and these have been evaluated in the above two tests enabling structure–activity requirements to be delineated.

The tests used in this study may reflect different effects but they are so interrelated that separation of the effects is not possible; it may be that two independent actions of tetrahydroquinoline-8-thioamides are responsible for activity in the two screens *or* antiulcer activity may be a consequence of antisecretory activity. It is felt, however, that it is valid to consider the structure–activity relationship from the standpoint of the system having combined antiulcer–antisecretory activity especially as consideration of either one of the tests would lead to the same overall structure–activity relationships.

Replacement of sulfur by oxygen, e.g., 3 and 4, results in a loss of activity, a feature which has been noted before[10] and which is not perhaps too surprising considering the different chemical nature of amides and thioamides.

It is when a change to secondary and tertiary thioamides is made that information about the necessity of the thioamide group becomes available. Some secondary thioamides 5–7 still retain respectable levels of activity (although slightly reduced compared with primary thioamides) so a change of primary to secondary is not undesirable per se, but the size of the substituent evidently is of importance. A change from secondary to tertiary 8 is detrimental which probably means that the thioamides need to be capable of existing at least, in some part, in the thiolimine form either by electron delocalization (9) or by



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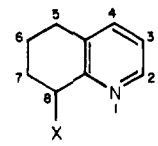
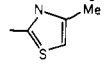
in vivo S-alkylation. Conversion of the thioamide into a thiazole 10 or imidazoline 11 or tetrahydropyrimidine 12, features which have been associated with other antiul-

Table I. 5,6,7,8-Tetrahydroquinoline Derivatives



No.	Substituents	X	Mp, °C	Recrystn solvent	Formula[a]	Anti-ulcer act.[b]	Anti-secretory act.[c]
2[d,e]		$CSNH_2$	263	MeOH-Et_2O	$C_{10}H_{12}N_2S\cdot HCl$	++++	+++
3[d,e]	3-Me	$CONH_2$	118	Hexane	$C_{11}H_{14}N_2O$	±	
4[d]	2-Ph	$CONH_2$	145	EtOAc	$C_{16}H_{16}N_2O$	±	
5[e]		CSNHMe	250	IPA[f]	$C_{11}H_{14}N_2S\cdot HCl$	++++	+++
6[d,e]	3-Me	CSNHMe	160	Benzene	$C_{12}H_{16}N_2S$	++	+
7[e]	2,3-[-$(CH_2)_4$-]	CSNHMe	265	IPA[f]	$C_{15}H_{16}N_2S\cdot HCl$		+
8[d]	3-Me	$CSNMe_2$	136	EtOAc	$C_{13}H_{18}N_2S$	±	±
10	3-Me		233	EtOH-Et_2O	$C_{14}H_{16}N_2S\cdot 2HCl$	±	±
11	3-Me		[g]	MeOH-EtOAc	$C_{13}H_{17}N_3\cdot 2HCl\cdot 2H_2O$	±	±
12	3-Me		165	MeOH-EtOAc	$C_{14}H_{19}N_3\cdot 2HCl\cdot 1.5H_2O$	±	±
16	3-Me,1-O	$CSNH_2$	186	IPA[f]	$C_{11}H_{14}N_2OS$	±	±
17	3-Me,1-O	CN	136	Benzene-PE[h]	$C_{11}H_{12}N_2O$	±	±
21[d]	2-Ph	$CSNH_2$	211	MeOH-Et_2O	$C_{16}H_{16}N_2S\cdot HCl$	++	±
22[e]	2-*n*-Bu	$CSNH_2$	56	Hexane	$C_{14}H_{20}N_2S$	+	+
23[d]	2-*t*-Bu	$CSNH_2$	126	Hexane	$C_{14}H_{20}N_2S$	++	±
24[d]	2,3-[-$(CH_2)_4$-]	$CSNH_2$	[i]	DIPE[j]	$C_{14}H_{18}N_2S$	±	+
25[k]	3,4-[-$(CH_2)_4$-]	$CSNH_2$	162	Benzene	$C_{14}H_{18}N_2S$	++	+
26	3,8-Me_2	$CSNH_2$	277	IPA[f]	$C_{12}H_{16}N_2S\cdot HCl$	+	±
27[e]	3,7,7-Me_3	$CSNH_2$	162	IPA[f]	$C_{13}H_{18}N_2S\cdot HCl\cdot 0.25H_2O$	+	±
28	3-Me,8-MeO	CSNHMe	104	Hexane	$C_{13}H_{18}N_2OS$		±
29	3-Me	CN	189	IPA[f]	$C_{11}H_{12}N_2\cdot HCl$	+	+
31	3,5-Me_2	$CSNH_2$	226	IPA[f]-DIPE[j]	$C_{12}H_{16}N_2S\cdot HCl$	++	+++
34	3,6-Me_2	$CSNH_2$	237	EtOH	$C_{12}H_{16}N_2S\cdot HCl$	+++	++
41[l]	8-OAc,3-Me	$CSNH_2$	118	IPA[f]	$C_{13}H_{16}N_2OS\cdot 0.25H_2O$		±
42[d,e]	3-Me	$CSNH_2$	219	IPA[f]-Et_2O	$C_{11}H_{14}N_2S\cdot HCl$	+++	+++
43[l]		CN	185	EtOH-Et_2O	$C_{10}H_{10}N_2\cdot HCl\cdot 0.25H_2O$	*m*	+
44[d]	2-Me	$CSNH_2$	98	Hexane	$C_{11}H_{14}N_2S$	+++	+++
45[d]	2-CH_2CSNH_2	H	142	IPA[f]	$C_{11}H_{14}N_2S$	++	±
46[e]	4-Me	$CSNH_2$	213	EtOH-Et_2O	$C_{11}H_{14}N_2S\cdot HCl$	++	+++
47[e]	2-Et	$CSNH_2$	75	Hexane	$C_{12}H_{16}N_2S$		+
48[e]	2,4-Me_2	$CSNH_2$	84	Hexane	$C_{12}H_{16}N_2S$		+
49[e]	3,4-Me_2	$CSNH_2$	165	EtOAc	$C_{12}H_{16}N_2S$		++
50[k]	2,3-[-$(CH_2)_3$-]	$CSNH_2$	118	IPA[f]	$C_{13}H_{16}N_2S\cdot HCl\cdot H_2O$	+	+
51[e]	8-CSNHMe	CSNHMe	217	IPA[f]	$C_{13}H_{17}N_3S_2\cdot HCl\cdot 0.25H_2O$	±	±
53[d]	2,3-[-$(CH)_4$-]	$CSNH_2$	239	H_2O	$C_{14}H_{14}N_2S\cdot HCl\cdot 0.5H_2O$	++	±
54[k]	2,3-[-$(CH_2)_5$-]	$CSNH_2$	112	Hexane	$C_{15}H_{20}N_2S$	++	+
55[k]	3,4-[-$(CH_2)_4$-]	CSNHMe	113	IPA[f]-Et_2O	$C_{15}H_{20}N_2S\cdot 0.25H_2O$	±	±
56[e]	3-Me	CSNH-*n*-Bu	195	IPA[f]	$C_{15}H_{22}N_2S\cdot HCl$	+	+
57[d]	2-Ph	CN	100	Et_2O	$C_{16}H_{14}N_2$	+	±
59[e]	2-Me,4-Ph	$CSNH_2$	175	EtOAc	$C_{17}H_{18}N_2S$		±
60[e]	3-Me	CSNHPh	140	IPA[f]	$C_{17}H_{18}N_2S$	±	±
61[e]	3-Me	$CSNHCH_2Ph$	230	EtOH	$C_{18}H_{20}N_2S\cdot HCl$	+	±
62[e]	3-Me	$CSNH(CH_2)_3Ph$	238	IPA[f]	$C_{20}H_{24}N_2S\cdot HCl$	±	±

[a] All new compounds had analyses within 0.4% for C, H, and N except 16 (H: calcd, 6.3; found, 6.8), 11 (N: calcd, 13.0; found, 12.4), and 54 (N: calcd, 10.8; found, 10.3). [b] Statistically significant activity ($p < 0.05$) is assessed on the following scale: ±, marginal or nonsignificant inhibition at 100 mg/kg; +, inhibition at 100 mg/kg; ++, inhibition at 30 mg/kg; +++, inhibition at 10 mg/kg; ++++ inhibition at 3 mg/kg. For comparison purposes: atropine sulfate ++++, SC 15 396 ++, gefarnate ±. [c] Statistically significant activity ($p < 0.05$) is assessed on the following scale: ±, marginal or nonsignificant inhibition at 30 mg/kg; +, <70% inhibition at 30 mg/kg; ++, >70% inhibition at 30 mg/kg; +++, inhibition at 10 mg/kg. For comparison purposes: atropine sulfate inhibition at 3 mg/kg, SC 15 396 +++, metiamide +. [d] Reference 12. [e] Reference 1. [f] Propan-2-ol. [g] Melts at 133 °C, solidifies and remelts at 240 °C. [h] Petroleum ether, bp 40-60 °C. [i] Melts at 106 °C, solidifies and remelts at 150 °C. [j] Diisopropyl ether. [k] Prepared from known starting materials by methods in paper 3.[1] [l] Prepared from known materials by methods in paper 2.[12] [m] Experiment abandoned due to death(s) in test group.

cer–antisecretory drugs, results in loss of activity and again points to the desirability of maintaining an intact thioamide.

Perhaps one of the most unexpected substitutions which can be made is that of cyano for the thioamide group. This substitution leads to compounds which retain activity, albeit diminished.[11] This activity could be fortuitous but the ready interconversion chemically between nitriles and thioamides[12] raises the possibility either that they are both metabolized to the same active compound or that because of the chemical similarity between the two groups they may both interact similarly with a potential receptor.

The remaining variations which have been effected have involved the THQ ring and have served to identify

Table II. Miscellaneous Thiocarboxamides

No.		Mp, °C	Recrystn solvent	Formula[a]	Anti-ulcer act.[b]	Anti-secretory act.[c]
13[n]	Quinoline-8-thiocarboxamide	210	MeOH-Et_2O	$C_{10}H_8N_2S$·HCl	*m*	+++
14[l]	1,2,3,4-Tetrahydroquinoline-8-thiocarboxamide	139	DIPE[j]	$C_{10}H_{12}N_2S$	*m*	±
15	Decahydro-3-methylquinoline-8-thiocarboxamide	203	IPA[f]	$C_{11}H_{20}N_2S$		±
18[l]	3-Methylcyclopenteno[*b*]pyridine-7-thiocarboxamide	202	Et_2O	$C_{10}H_{12}N_2S$·HCl·0.25H_2O	++	±
19[l]	1,2,3,5,6,7-Hexahydrodicyclopenta-[*b*,*e*]pyridine-3-thiocarboxamide	229	MeOH-Et_2O	$C_{12}H_{14}N_2S$·HCl	±	+
20[l]	1,2,3,4,5,7,8,9,10,11-Decahydro-dicyclohepta[*b*,*e*]pyridine-5-thiocarboxamide	80	Et_2O	$C_{16}H_{22}N_2S$·HCl·0.5H_2O	±	±
52[k]	3-Methylcyclopenteno[*b*]pyridine-7,7-di(*N*-methylthiocarboxamide)	188	IPA[f]	$C_{13}H_{17}N_3S_2$	±	±
58[k]	2,3-Dihydro-1*H*-cyclopenta[*b*]-quinoline-3,3-di(*N*-methylthio-carboxamide)	171	Benzene	$C_{16}H_{17}N_3S_2$·HCl	±	±

[a-m] See corresponding footnotes in Table I. [n] H. Coates, A. H. Cook, I. M. Heilbron, D. H. Hey, A. Lambert, and F. B. Lewis, *J. Chem. Soc.*, 401 (1943).

structurally sensitive areas. In order to test how necessary was a 5,6,7,8-tetrahydroquinoline ring, quinoline-8-thiocarboxamide (**13**), 1,2,3,4-tetrahydroquinoline-8-thiocarboxamide (**14**) and 3-methyldecahydroquinoline-8-thiocarboxamide (**15**) were prepared. Antisecretory activity was only associated with the quinoline emphasizing the need for the pyridine ring to remain intact with its available lone pair, a point reinforced by the lack of activity of the 1-oxides **16** and **17**.

Variation in size of the carbocyclic ring (**18–20**) seems to indicate that a six-membered ring is preferred and suggests that because of the concurrent alteration in geometry at the "8" position the molecule probably interacts with a receptor site.

In order to consider the steric requirements around such a proposed receptor the substituents on the THQ ring have been varied. The 2 position is essentially noncritical as substitution here by groups as large as phenyl (**21**) and *n*- and *tert*-butyl (**22**, **23**), although reducing, do not totally destroy activity. Similarly, construction of bridges at the 2 and 3 positions (e.g., **24**) and 3 and 4 positions (**25**) indicates the relatively noncritical nature of all the positions on the pyridine ring. Methyl group substitution on the molecule indicates the noncritical nature of the 2, 3, 4, 5, and 6 positions.

The most sensitive area appears to be around the thioamide group and substitution here (e.g., **26–28**) with small groups greatly reduces the activity.

It is possible, therefore, to draw up a ranking of positions with regard to sensitivity, i.e., $8 > 7 > 4 \equiv 2 > 3 \equiv 5 \equiv 6$.

It is considered that the THQ-8-$CSNH_2$ type of structure probably has its effect by binding to a receptor and not by in vivo release of H_2S with resulting interference with cell respiration and that the pyridine nitrogen and the thioamide sulfur and nitrogen play a part in the binding to such a receptor.

Experimental Section

The melting points were taken on a Townson and Mercer or a Mettler FP1 melting point apparatus and are uncorrected. Where analyses are indicated by symbols of the elements, analytical results obtained were within ±0.4% of the theoretical values.

Pharmacology. (a) **Cold-Restraint Induced Gastric Erosions.** Stress erosions were induced in rats by a method similar to that described by Senay and Levine.[13] Male Sprague–Dawley rats (from the Charles River Laboratories), weighing 80–100 g, were fasted overnight but allowed water ad libitum and divided into groups of six. The rats were dosed orally with either 0.3% carboxymethylcellulose (CMC) in 0.9% saline, or with the test drug, in the same vehicle, in a volume of 10 mL/kg. A 3-h period of combined cold and restraint immediately followed dosing and afterward the rats were sacrificed and the severity of gastric mucosal erosions was assessed on a 0–6 scale as follows. Score 0, no visible erosions or blood; 1, blood in stomach or single pinpoint erosion; 2, several pinpoint erosions or one intermediate erosion; 3, several intermediate erosions or one large erosion; 4–6, progressively greater severity of mucosal erosions.

The results were analyzed using Student's *t* test, and the percentage inhibition of gastric erosions in the drug-treated group was calculated as

$$\frac{\text{mean score of control groups} - \text{mean score of drug-treated group}}{\text{mean score of control group}} \times 100$$

(b) **Four-Hour Pylorus-Ligated (Shay) Rats.** The method used was similar to that described by Shay et al.[14] Groups of six male Sprague–Dawley rats, weighing 150–200 g, were fasted for 18 h in separate cages with raised wide-mesh grids to prevent coprophagy but allowed water ad libitum. Each rat was anesthetized with halothane in oxygen, a small midline incision was made, and the pylorus was ligated. Each rat in the test group received the test compound introduodenally in 0.2 mL of CMC–saline; rats in the control group received the vehicle alone. Four hours later the animals were sacrificed and the gastric contents collected and measured. The gastric juice was titrated against 1 N NaOH, using a Metrohm potentiographic autotitrator, to determine the concentration of free acid (at pH 3.0). The hourly outputs of free acid were calculated and the results for the drug-treated group expressed as a percentage of the values for the control group. The statistical significance of the difference between the volumes from the control and drug-treated group was calculated using Student's *t* test.

Chemistry. Most of the compounds have been described previously or were prepared by analogous methods from known starting materials (details are given in footnotes to Tables I and II). Routine IR and NMR spectra are consistent with the structures indicated.

5,6,7,8-Tetrahydro-3,8-dimethylquinoline-8-thiocarboxamide (26). A solution of 8-cyano-5,6,7,8-tetrahydro-3-methylquinoline (**29**) (1.7 g, 0.01 mol) in Et_2O (6 mL) was added to a 9% w/v solution of BuLi (10 mL, 0.014 mol) in hexane with stirring. A solution of MeI (4.25 g, 0.03 mol) in Et_2O (4 mL) was then added and the mixture was stirred at 40 °C for 1 h. H_2O was added to dilute and the mixture was extracted with 2 N HCl solution and the resulting aqueous extracts were basified with

Na_2CO_3 and extracted with Et_2O. The extracts were dried ($MgSO_4$) and evaporated to give **8-cyano-5,6,7,8-tetrahydro-3,8-dimethylquinoline** (1.6 g, 86%), pure by TLC and GC, which was converted into **26** using H_2S in pyridine–Et_3N solution.[12]

Decahydro-3-methylquinoline-8-thiocarboxamide (15). A solution of 5,6,7,8-tetrahydro-3-methylquinoline-8-carboxamide hydrochloride (**3 hydrochloride**) (4.53 g, 0.02 mol) in EtOH (150 mL) and water (50 mL) was hydrogenated over Pt (from 0.5 g of PtO_2) at ambient temperature and 50 psi until the theoretical uptake had occurred (24 h). The catalyst was removed by filtration and the residue, after evaporation of the filtrate, was recrystallized from propan-2-ol to give **decahydro-3-methylquinoline-8-carboxamide hydrochloride (30)** (3.9 g, 84%), mp 199 °C. Anal. ($C_{11}H_{20}N_2O$·HCl) C, H, N. **30** was dissolved in H_2O (25 mL) and the pH was adjusted to 9 with aqueous NaOH. The resulting solid was removed by filtration, washed with H_2O, and air-dried to give the free base (3.3 g), which was converted into **15** with P_2S_5 in pyridine.[12]

5,6,7,8-Tetrahydro-3,5-dimethylquinoline-8-thiocarboxamide (31). A solution of 7,8-dihydro-3-methylquinolin-5(6*H*)-one[15] (25 g, 0.155 mol) in Et_2O (100 mL) was added with stirring to a solution of MeMgI in Et_2O [from magnesium (3.8 g, 0.156 mol), MeI (25 g, 0.176 mol), and Et_2O (20 mL)] at 0 °C. The reaction mixture was refluxed for 1.5 h, cooled in an ice bath, treated with an excess of saturated NH_4Cl solution, and separated and the aqueous layer was extracted three times with Et_2O. The combined extracts were dried ($MgSO_4$) and evaporated and the residue was recrystallized from diisopropyl ether to give **5,6,7,8-tetrahydro-5-hydroxy-3,5-dimethylquinoline (32)** (12 g, 44%), mp 123 °C. Anal. ($C_{11}H_{15}NO$) C, H, N.

32 (6 g) was added portionwise to polyphosphoric acid (100 g) at 85 °C with stirring. The reaction mixture was then heated at 180 °C for 3 h, cooled, and poured into H_2O (300 mL). The resulting solution was basified with 20% KOH solution and extracted three times with $CHCl_3$ and the extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was dissolved in Et_2O and the solution was treated with ethereal HCl giving an oil. The Et_2O was decanted and the oil was dissolved in $MeCO_2H$ (150 mL) and hydrogenated at 50 psi and ambient temperature over Pt [from PtO_2 (0.5 g)] until uptake of H_2 ceased. The catalyst was removed by filtration and the residue, after evaporation of the filtrate, was dissolved in H_2O. The aqueous solution was basified with NaOH solution and extracted with $CHCl_3$ and the extracts were dried ($MgSO_4$) and evaporated. The residue was distilled to give **5,6,7,8-tetrahydro-3,5-dimethylquinoline (33)** (4.7 g, 71%), bp 122–126 °C (15 mmHg). An aliquot was converted into the **hydrochloride** with ethereal HCl in Et_2O and recrystallized from MeCN–Et_2O, mp 172 °C. Anal. ($C_{11}H_{15}N$·HCl) C, H, N.

33 was converted into **31** with BuLi and trimethylsilyl isothiocyanate.[1]

5,6,7,8-Tetrahydro-3,6-dimethylquinoline-8-thiocarboxamide (34). A solution of 3,6-dimethylquinoline[16] hydrochloride (56 g, 0.28 mol) in CH_3CO_2H (200 mL) and H_2O (10 mL) was hydrogenated at 50 psi and ambient temperature over Pt [from PtO_2 (0.5 g)] until the theoretical uptake occurred. The catalyst was removed by filtration and the residue, after evaporation of the filtrate, was dissolved in H_2O. The solution was basified (Na_2CO_3) and extracted with $CHCl_3$ and the extracts were dried ($MgSO_4$) and evaporated and the residue was distilled to give **5,6,7,8-tetrahydro-3,6-dimethylquinoline (35)** (11 g, 25%), bp 120–124 °C (15 mmHg). An aliquot was converted into the hydrochloride with ethereal HCl in ether, mp 189 °C. Anal. ($C_{11}H_{15}N$·HCl) H, N; C: calcd, 66.8; found, 66.2.

35 was converted into **34** using BuLi and trimethylsilyl isothiocyanate.[1]

5,6,7,8-Tetrahydro-8-methoxy-3-methylquinoline-8-(*N*-methyl)thiocarboxamide (28). A stirred solution of **3** (19 g, 0.1 mol) in CH_2Cl_2 (100 mL) was treated dropwise with a solution of *m*-chloroperoxybenzoic acid (17.25 g, 0.1 mol) in CH_2Cl_2 (150 mL) and the mixture was stirred overnight at ambient temperature. The resulting solution was extracted with aqueous Na_2CO_3 solution and the extracts were acidified with 2 N HCl, filtered, adjusted to pH 9.0 with Na_2CO_3, acidified with CH_3COOH, and continuously extracted with $CHCl_3$ over 24 h. The extracts were dried ($MgSO_4$) and evaporated and the residue was recrystallized from benzene to give **5,6,7,8-tetrahydro-3-methylquinoline-8-carboxamide 1-oxide (36)** (8 g, 39%), mp 208 °C. Anal. ($C_{11}H_{14}N_2O_2$) C, H, N.

36 (2.6 g, 0.013 mol) was added portionwise to acetic anhydride (13 mL) at 90 °C. The reaction mixture was heated at 120 °C for 0.5 h, cooled to 0 °C, and filtered and the resulting solid was washed with dry ether and recrystallized from MeOH to give **8-acetoxy-5,6,7,8-tetrahydro-3-methylquinoline-8-carboxamide (37)** (2.0 g, 64%), mp 205 °C. Anal. ($C_{13}H_{16}N_2O_3$) C, H, N.

37 (0.8 g, 0.003 mol) was added to a solution of NH_3 in MeOH (150 mL) at 0 °C and the suspension was stirred at ambient temperature for 18 h. The solution was evaporated and the residue was dissolved in 2 N HCl and washed with EtOAc, the pH was adjusted to 9.0 with Na_2CO_3, and the solution was extracted with EtOAc and $CHCl_3$. The combined extracts were dried ($MgSO_4$) and evaporated and the residue was recrystallized from EtOAc to give **5,6,7,8-tetrahydro-8-hydroxy-3-methylquinoline-8-carboxamide hemihydrate (38)** (0.46 g, 69%), mp 118 °C. Anal. ($C_{11}H_{14}N_2O_2$·$0.5H_2O$) C, H, N.

A solution of **38** (2.6 g, 0.011 mol) in dimethoxyethane (20 mL) was treated portionwise with cooling with 60% NaH suspension in oil (0.5 g, 0.017 mol) and the mixture was treated dropwise with a solution of MeI (3.9 g, 0.0275 mol) in dimethoxyethane (4 mL) and stirred at ambient temperature for 1.5 h. The reaction mixture was diluted with H_2O, acidified with 2 N HCl and washed with EtOAc, basified with Na_2CO_3, and extracted with $CHCl_3$. The extracts were washed with brine, dried ($MgSO_4$), and evaporated to give **5,6,7,8-tetrahydro-8-methoxy-3-methylquinoline-8-(*N*-methyl)carboxamide (39)** (2.98 g, 100%). An aliquot was converted into the **hydrochloride**, using ethereal HCl in propan-2-ol, which was recrystallized from propan-2-ol–diisopropyl ether, mp 124 °C. Anal. ($C_{13}H_{18}N_2O_2$·HCl·$1.25H_2O$) C, H, N.

Thionyl chloride (0.9 mL, 0.007 mol) was added dropwise to a solution of **39** (1.6 g, 0.007 mol) in pyridine (7.5 mL) at 0 °C with stirring. After 4 h at 0 °C the mixture was treated with H_2S gas over 5 min and allowed to stand 3 days at ambient temperature. The solvent was removed by evaporation and the residue was diluted with H_2O, basified with Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried ($MgSO_4$) and the residue, after evaporation, was purified by chromatography on a silica column eluting with EtOAc to give **28** (0.15 g, 9%).

8-Cyano-5,6,7,8-tetrahydro-3-methylquinoline 1-Oxide (17) and 5,6,7,8-Tetrahydro-3-methylquinoline-8-thiocarboxamide 1-Oxide (16). A stirred solution of **29** (17.2 g, 0.1 mol) in CH_2Cl_2 (100 mL) was treated dropwise with a solution of 85% *m*-chloroperoxybenzoic acid (20.3 g, 0.1 mol) in CH_2Cl_2 (150 mL) and the mixture was stirred at ambient temperature overnight. The solution was washed with aqueous Na_2CO_3 and brine, dried ($MgSO_4$), and evaporated. The residue was triturated with benzene and recrystallized from benzene–petroleum ether (bp 40–60 °C) to give **17** (15 g, 80%).

17 was converted into **16** using H_2S in pyridine–Et_3N solution.[12]

8-Acetoxy-8-cyano-5,6,7,8-tetrahydro-3-methylquinoline (40) [mp 84 °C from propan-2-ol–Et_2O. Anal. ($C_{13}H_{14}N_2O_2$·HCl·$0.25H_2O$) C, H, N] was prepared from **17** in an analogous manner to the preparation of **37**, and **40** was converted into **8-acetoxy-5,6,7,8-tetrahydro-3-methylquinoline-8-thiocarboxamide (41)** by reaction with H_2S in pyridine–Et_3N solution.[12]

3,4,5,6-Tetrahydro-2-(5,6,7,8-tetrahydro-3-methylquinolin-8-yl)pyrimidine Dihydrochloride (12) and 4,5-Dihydro-2-(5,6,7,8-tetrahydro-3-methylquinolin-8-yl)imidazole Dihydrochloride (11). A mixture of **29** (3.4 g, 0.02 mol) and 1,3-diaminopropane (5 mL) was treated with CS_2 (30 drops) and heated at 115–120 °C for 1 h, cooled, and dissolved in H_2O. The aqueous solution was washed with Et_2O and extracted with $CHCl_3$; the extracts were washed with H_2O, dried ($MgSO_4$), and evaporated; the residues were dissolved in propan-2-ol and treated with ethereal HCl; and the solid was twice recrystallized from MeOH–EtOAc to give **12** (1.2 g, 20%).

11 was similarly prepared from **29** using 1,2-diaminoethane.

2-(5,6,7,8-Tetrahydro-3-methylquinolin-8-yl)-4-methylthiazole Dihydrochloride (10). 5,6,7,8-Tetrahydro-3-methylquinoline-8-thiocarboxamide (**42**) (2.0 g, 0.01 mol) was

dissolved in methanol (40 mL) with slight warming and chloroacetone (2.1 mL, 0.01 mol) was added and the mixture was allowed to stand 3 days. The solution was evaporated and the residue was dissolved in 2 N HCl solution, washed with Et_2O, basified with Na_2CO_3, and extracted with $CHCl_3$. The extracts were dried ($MgSO_4$), and evaporated and the residue was extracted with hot hexane. The cooled hexane solution was filtered and evaporated and the residue was dissolved in a little EtOH and ethereal HCl was added precipitating **10** (1.6 g, 50%).

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Notes

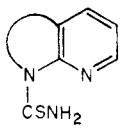
5,6,7,8-Tetrahydroquinolines. 5.[1] Antiulcer and Antisecretory Activity of 5,6,7,8-Tetrahydroquinolinethioureas and Related Heterocycles

Doreen E. Beattie, Roger Crossley,* Adrian C. W. Curran, David G. Hill, and Anne E. Lawrence

Institute of Medical Research, Wyeth Laboratories, Huntercombe Lane South, Taplow, Maidenhead, Berkshire, SL6 OPH, England. *Received July 9, 1976*

A series of thioureas derived from 5,6,7,8-tetrahydroquinoline, 1,5-, 1,6-, and 1,8-naphthyridines, pyrido[2,3-*b*]azepine, and 7-azaindoline has been prepared and tested for antisecretory activity in the pylorus-ligated rat and protective activity against gastric erosions caused by cold-restraint stress. The thioureas exhibit different structure–activity relationships from the corresponding 5,6,7,8-tetrahydroquinoline-8-thiocarboxamides and these relationships are discussed. The activity of the thioureas is less affected by structural differences than the corresponding thioamides although they probably have the same mode of action.

Following definition of a series of 5,6,7,8-tetrahydroquinoline-8-thiocarboxamides with antiulcer and antisecretory activity,[1] it became of interest to consider related thioureas formed by replacing the ring carbon adjacent to the $CSNH_2$ group with nitrogen (**1**) as well as thioureas formed by replacing $CSNH_2$ by $NHCSNH_2$ (**2**). The



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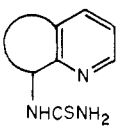

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thioureas have been prepared by reactions of the parent heterocycle or amino derivatives with isothiocyanates and have been tested for antiulcer activity (activity against gastric erosions caused by cold-restraint stress) and for antisecretory activity (inhibition of secretion in pylorus-ligated rats) as has been reported previously[1] for the tetrahydroquinolinethioamides. The thioureas show similar levels of activity to the thioamides (Tables I and II) but have different requirements for activity, being less influenced by steric constraints.

Considering first the thioureas formed by replacing the ring carbon by nitrogen (Table I), a difference between the two related series becomes apparent on changing the size of rings. The corresponding thioamides were found to be sensitive to this change whereas the thioureas are not so sensitive. The implication is, bearing in mind that as the activity of the thioamides was primarily affected by substituents on the adjacent carbon, the effect of replacing this carbon by nitrogen is to counteract the effect of changing ring size.

For this system the activity is, as in the case of the thioamides, apparently governed by the size of the CSNHR group, as large groups, e.g., benzoyl (**3**) or *n*-butyl (**4**) reduce the activity.

In order to determine the effect of repositioning the thiourea group on activity the 1,6- and 1,5-naphthyridine derivatives **5** and **6** were prepared and both were found to be active. This was a rather unexpected finding as it tended to upset previously conceived notions[2] that the relationship between the pyridine nitrogen and the $CSNH_2$ group must be fairly precise. To explore this situation further the pyrido[2,3-*d*]pyrimidine-2-thione (**7**) was prepared and found to have insignificant activity. It is