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

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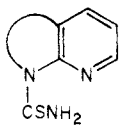
A series of thioureas derived from 5,6,7,8-tetrahydroquinoline, 1,5-, 1,6-, and 1,8-naphthyridines, pyrido[2,3-*b*]azepine, and 7-azaindoline has been prepared and tested for antisecretory activity in the pylorus-ligated rat and protective activity against gastric erosions caused by cold-restraint stress. 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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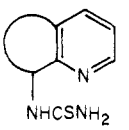

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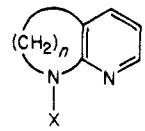
thioureas have been prepared by reactions of the parent heterocycle or amino derivatives with isothiocyanates and have been tested for antiulcer activity (activity against gastric erosions caused by cold-restraint stress) and for antisecretory activity (inhibition of secretion in pylorus-ligated rats) 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

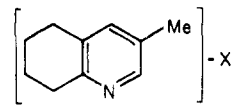
Table I. 1,2,3,4-Tetrahydro[1,8]naphthyridines and Five- and Seven-Membered Ring Analogues



No.	n	X	Mp, °C	Recrystn solvent	Formula[a]	Anti-ulcer act.[b]	Anti-secretory act.[b]
3[c]	2	CSNHCOPh	195	MeCN	$C_{15}H_{13}N_3OS$	±	±
4[c]	2	CSNH-*n*-Bu	116	IPA[d]-Et_2O	$C_{12}H_{17}N_3S\cdot HCl\cdot 0.5H_2O$	±	±
27[c]	2	$CSNH_2$	174	H_2O	$C_8H_9N_3S$	*e*	+++
28[f]	2	CSNHMe	109	EtOH	$C_9H_{11}N_3S$	++	+
29[f]	3	CSNHMe	78	IPA[d]	$C_{10}H_{13}N_3S$	++	+
30[c]	4	$CSNH_2$	121	IPA[d]	$C_{10}H_{13}N_3S$	±	+
31[c]	4	CSNHMe	192	IPA[d]	$C_{11}H_{15}N_3S\cdot HCl$	±	+++
				Miscellaneous Analogues			
5[c]	*N*-Methyl-1-[6-(5,6,7,8-tetrahydro-3-methyl-1,6 naphthyridine)] thiocarboxamide	179	IPA[d]	$C_{11}H_{15}N_3S$	+	±	
6[c]	*N*-Methyl-1-[5-(5,6,7,8-tetrahydro-1,5-naphthyridine)] thiocarboxamide	120	IPA[d]	$C_{10}H_{13}N_3S$	++	+	
7	3,4-Dihydro-1*H*-pyrido-[2,3-*d*]pyrimidine-2-thione	230	EtOH-H_2O	$C_7H_7N_3S\cdot 0.25H_2O$	±	±	

[a] All compounds had analyses within 0.4% for C, H, and N except 4 (C: calcd, 51.3; found, 51.8), 6 (C: calcd, 57.95; found, 58.4), and 29 (C: calcd, 57.9; found, 58.4). [b] Activity is assessed as in ref 1. [c] Prepared using method 2, Experimental Section. [d] Propan-2-ol. [e] Experiment abandoned due to deaths in test group. [f] Prepared using method 1, Experimental Section.

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



No.	X	Mp, °C	Recrystn solvent	Formula[a]	Anti-ulcer act.[b]	Anti-secretory act.[b]
8[c]	8-$NHCSNH_2$	114	EtOH	$C_{11}H_{15}N_3S\cdot H_2O$	+	+
9[f]	8-NHCSNHMe	113	MeCN	$C_{12}H_{17}N_3S$	+	+++
10	8-NHC(NHMe)=NCN	143	IPA[d]-DIPE[g]	$C_{13}H_{17}N_5$	±	±
11	8-NHC(NHMe)=$NCONH_2$	175	EtOH-H_2O	$C_{13}H_{19}N_5O\cdot 2HBr\cdot 1.5H_2O$	±	±
12	8-NHC(NMe)=$NCSNH_2$	157	IPA[d]	$C_{13}H_{19}N_5S$	+	±
13[f]	8-CH(CH_3)NHCSNHMe	172	IPA[d]-Et_2O	$C_{14}H_{21}N_3S\cdot HCl$	±	±
25	8-NHC(SMe)=NCN	157	IPA[d]-hexane	$C_{13}H_{16}N_4S$	±	
32[c]	5-$NHCSNH_2$	206	EtOH	$C_{11}H_{15}N_3S$	±	
33[f]	5-NHCSNHMe	142	MeCN	$C_{12}H_{17}N_3S$	±	±
34[f]	5-NHCSNHPh	184	EtOH	$C_{17}H_{19}N_3S$	±	+
35[f]	5-NHCSNHCOPh	187	EtOH	$C_{18}H_{19}N_3OS$	*e*	±
36[f]	8-NHCSNHCOPh	168	EtOH-Et_2O	$C_{18}H_{19}N_3OS$	±	±

[a] All compounds had analyses within 0.4% except 12 (C: calcd, 56.3; found, 56.8). [b-f] See corresponding footnotes in Table I. [g] Diisopropyl ether.

evident, therefore, that whatever the position of the thiourea group it should be capable of free rotation. It is also probable that the thiourea group confers some degree of antiulcer–antisecretory activity per se but that this effect is increased by the proximity of the pyridine nitrogen.

The 5,6,7,8-tetrahydroquinoline-5- and -8-thioureas present a different picture. Here, moving the thiourea from the 8 to the 5 position results in loss of activity; even more noticeable is the increase in activity of going from $CSNH_2$ (**8**) to CSNHMe (**9**). It has been suggested recently, based on physicochemical considerations, that the NCN group makes an acceptable substitute for the sulfur atom in a thiourea and this change has been used effectively in a series of H_2-receptor antagonists.[3] That such

a change is not universally applicable is demonstrated in this series where the cyanoguanidine **10** was inactive. A similar loss of activity was noticed in the corresponding amide **11**; yet the corresponding thioamide **12** had weak antiulcer activity, probably reflecting the variation in pyridine nitrogen–$CSNH_2$ geometry. Such a variation in geometry was explored with the thiourea **13** showing expected loss of activity, thereby drawing parallels with the thioamide series where there is similar steric crowding around the 8 position.

The differences between thioamides and thioureas are of a subtle nature as would be expected from the differences in their chemical behavior. In the main, the thioureas appear more tolerant of their molecular environment but nevertheless probably produce their antiulcer–antisecretory effects in the same way as the thioamides.

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. Routine IR and NMR spectra are consistent with the structure indicated.

Pharmacology. The antiulcer and antisecretory tests used are the same as were described in paper 4.[1]

Chemistry. The thioureas used in this study were prepared by the reactions described below (methods 1 and 2) from the corresponding amines which were prepared as described or according to the references cited: 7-azaindoline,[4] 6,7,8,9-tetrahydro-5*H*-pyrido[2,3-*b*]azepine,[5] 1,2,3,4-tetrahydro-1,8-naphthyridine,[5] 1,2,3,4-tetrahydro-1,5-naphthyridine.[6]

Method 1. Preparation of Thioureas by Reaction of Amines with Isothiocyanates. A solution of the amine (0.01 mol) in MeCN (15–50 mL) was treated dropwise with a solution of the isothiocyanate (0.01 mol) in MeCN (15–50 mL), and the mixture was heated at reflux for 1–3 h. The solvent was removed by evaporation and the residue was recrystallized or converted into the hydrochloride.

Method 2. Hydrolysis of *N*-Benzoylthioureas. The *N*-benzoylthiourea (0.01 mol) in 10% NaOH solution (25 mL) was refluxed for 10 min–1 h. The resulting suspension was cooled and the resulting solid was removed by filtration and washed with H_2O until the washings were neutral. Recrystallization gave the corresponding thiourea.

5-Amino-5,6,7,8-tetrahydro-3-methylquinoline (14). 7,8-Dihydro-3-methylquinolin-5(6*H*)-one[7] (16.1 g, 0.1 mol), hydroxylamine hydrochloride (7.5 g, 0.11 mol), and NaOH (4.7 g, 0.12 mol) in an EtOH (87 mL)–H_2O (35 mL) solution were heated under reflux for 2 h, filtered, and allowed to cool. The resulting crystals were removed by filtration, washed with H_2O, and dried to give **5,6,7,8-tetrahydro-5-hydroxyimino-3-methylquinoline (15)** (15 g, 85%), mp 181 °C. Anal. ($C_{10}H_{12}N_2O$) C, H, N.

A solution of **15** (5 g, 0.3 mol) and 2 N NaOH (100 mL, 0.2 mol) in EtOH (100 mL) was stirred vigorously and Ni–Al alloy (7.5 g) was added portionwise over 30 min. The mixture was stirred for 2 h and filtered through Kieselghur and to the filtrate was added H_2O (100 mL). The solution was evaporated to low volume and extracted with chloroform to give **14** (4.6 g, 100%). An aliquot was converted into the **dihydrochloride** with ethereal HCl in ether and recrystallized from MeOH–Et_2O, mp >300 °C. Anal. ($C_{10}H_{14}N_2$·2HCl·0.25H_2O) C, H, N.

8-Amino-5,6,7,8-tetrahydro-3-methylquinoline (16). A mixture of 5,6,7,8-tetrahydro-3-methylquinoline[7] (100 g, 0.68 mol), $MeCO_2H$ (380 mL), and 30% H_2O_2 (100 mL, 0.94 mol) was heated with stirring at 80 °C for 6 h. A further 50 mL (0.47 mol) of H_2O_2 was added and the heating was continued for 16 h and evaporated. The residue was dissolved in H_2O and basified with NH_4OH (sp gr 0.88) and the aqueous solution was washed with *n*-hexane and extracted into $CHCl_3$. The $CHCl_3$ solution was washed with H_2O, dried ($MgSO_4$), and evaporated to give crude **5,6,7,8-tetrahydro-3-methylquinoline 1-oxide** which was dissolved in acetic anhydride (200 mL) and added slowly to refluxing acetic anhydride (200 mL). The resulting solution was evaporated to give crude **8-acetoxy-5,6,7,8-tetrahydro-3-methylquinoline** which was heated at 80 °C with 10% aqueous HCl (1 L, 2.8 mol) for 2 h. The cooled solution was basified with aqueous NaOH and extracted with Et_2O and the extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was distilled to give **5,6,7,8-tetrahydro-8-hydroxy-3-methylquinoline (17)**, bp 90–100 °C (0.1 mm Hg), which was recrystallized from *n*-hexane (62 g, 56%), mp 58 °C. Anal. ($C_{10}H_{13}NO$) C, H, N.

A solution of **17** (20 g, 0.12 mol) in CH_2Cl_2 (1 L) was treated with MnO_2 (200 g, 2.3 mol) and the suspension was stirred at ambient temperature for 16 h, filtered, and evaporated and the residue was distilled to give **5,6-dihydro-3-methylquinolin-8(7*H*)-one (18)** (15 g, 71%), bp 132–134 °C (0.3 mmHg). The **hydrochloride** gave mp 215 °C dec. Anal. ($C_{10}H_{11}NO$·HCl·0.5H_2O) C, H, N.

By the method used to prepare **15**, **18** was converted in 43% yield into **5,6,7,8-tetrahydro-8-hydroxyimino-3-methylquinoline (19)** [mp 188 °C (from EtOH). Anal. ($C_{10}H_{12}N_2O$) C, H, N] and **19** was converted by the method used to prepare **14** into **16** dihydrochloride (35%) [mp 210 °C. Anal. ($C_{10}H_{14}N_2$·2HCl·0.25H_2O) C, H, N].

8-(1-Aminoethyl)-5,6,7,8-tetrahydro-3-methylquinoline (20). A 9% w/v solution of *n*-BuLi in hexane (741 mL, 1.04 mol) was added slowly with stirring to a solution of 5,6,7,8-tetrahydro-3-methylquinoline (147 g, 1.0 mol) in toluene (250 mL) at −20 °C and was followed by the addition of EtOAc (100 mL, 1.02 mol). The reaction mixture was allowed to warm to ambient temperature over 1.5 h and H_2O (200 mL) was added followed by 2 N HCl to acidify. The aqueous layer was separated, washed with EtOAc, basified with K_2CO_3, and extracted with $CHCl_3$ and the extracts were washed with H_2O, dried ($MgSO_4$), and evaporated. The residue was distilled to give **8-acetyl-5,6,7,8-tetrahydro-3-methylquinoline (21)**, bp 130–132 °C (0.6 mmHg). The **hydrochloride** was prepared in Et_2O using ethereal HCl (25 g, 11%), mp 159 °C (from MeOH–Et_2O). Anal. ($C_{12}H_{15}NO$·HCl) C, H, N.

By the method used to prepare **15**, **21** was converted in 41% yield into **8-(1-hydroxyiminoethyl)-5,6,7,8-tetrahydro-3-methylquinoline (22)** [**hydrochloride** mp 190 °C (from propan-2-ol–Et_2O). Anal. ($C_{12}H_{16}N_2O$·HCl) C, H, N] and **22** was converted by the method used to prepare **14** into **20** dihydrochloride (40%) [mp 201 °C. Anal. ($C_{12}H_{18}N_2$·2HCl·0.5H_2O) C, H, N].

5,6,7,8-Tetrahydro-3-methyl-1,6-naphthyridine (23). A solution of *N*-benzyl-4-piperidone (142 g, 0.75 mol), 3-amino-2-methylacrolein[8] (42.5 g, 0.5 mol), pyridine (3.95 g, 0.05 mol), BF_3·Et_2O (7.1 g, 0.05 mol), and xylene (75 mL) was refluxed 16 h under a Dean-Stark water separator. The cooled reaction mixture was diluted with xylene and extracted with 2 N HCl. The extracts were washed with xylene, basified with Na_2CO_3, and extracted with $CHCl_3$ and the $CHCl_3$ solution was dried and evaporated. The residue was distilled to give **6-benzyl-5,6,7,8-tetrahydro-3-methyl-1,6-naphthyridine (24)** (27 g, 23%), bp 150 °C (0.05 mmHg) [**dihydrochloride** mp 249 °C (from propan-2-ol–diisopropyl ether). Anal. ($C_{16}H_{18}N_2$·2HCl·0.25H_2O) C, H, N].

A solution of **24** dihydrochloride (3.1 g, 0.01 mol) was dissolved in 90% MeOH–H_2O (50 mL) and hydrogenated over 5% Pd/C (0.5 g) at atmospheric pressure and ambient temperature until uptake was complete. The filtrate, after removal of the catalyst, was evaporated and the residue was basified with aqueous Na_2CO_3 and extracted into $CHCl_3$ and the extracts were dried ($MgSO_4$) and evaporated to give **23** (0.9 g, 61%) [**dihydrochloride** mp >300 °C (from MeOH). Anal. ($C_9H_{12}N_2$·2HCl) H, N; C: calcd, 48.8; found, 49.3].

***N*-Cyano-*N'*-(5,6,7,8-tetrahydro-3-methylquinolin-8-yl)-*S*-methylisothiourea (25).** **16** dihydrochloride (5 g, 0.02 mol) was dissolved in H_2O (20 mL) and the solution was basified with Na_2CO_3, saturated with NaCl, and extracted with $CHCl_3$ and the extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in a solution of dimethyl *N*-cyanoimidodithiocarbonate[9] (2.5 g, 0.017 mol) in EtOH (50 mL) and the solution was allowed to stand at ambient temperature for 16 h and heated at reflux for 24 h. The residue, after evaporation, was dissolved in 2 N HCl and the solution was washed with $CHCl_3$ and basified with K_2CO_3 and the precipitate after filtration and drying was re-

crystallized from *n*-hexane to give **25** (1.2 g, 22%).

***N*-Cyano-*N'*-(5,6,7,8-tetrahydro-3-methylquinolin-8-yl)-*N''*-methylguanidine (10).** **25** (2 g, 0.008 mol) was suspended in EtOH (5 mL), a 33% solution of $MeNH_2$ in EtOH (25 mL, 0.27 mol) was added, and the mixture was stirred 1 h at ambient temperature. The solvent was removed by evaporation and the residue was induced to crystallize by trituration with diisopropyl ether and recrystallized from propan-2-ol–diisopropyl ether to give **10** (1.6 g, 85.5%).

***N*-(5,6,7,8-Tetrahydro-3-methylquinolin-8-yl)-*N'*-methyl-*N''*-thiocarbamoylguanidine (12).** A mixture of pyridine (20 mL) and Et_3N (6 mL) was saturated with H_2S at 0 °C. **10** (1.5 g, 0.006 mol) was added and the solution was heated in a bomb at 70 °C for 20 h. The solvent was removed by evaporation and the residue was triturated with Et_2O to give a solid which was recrystallized from propan-2-ol to give **12** (1.1 g, 64%).

***N*-Carbamyl-*N'*-(5,6,7,8-tetrahydro-3-methylquinolin-8-yl)-*N''*-methylguanidine Dihydrobromide (11).** **10** (1.0 g, 0.004 mol) was dissolved in concentrated HBr (50 mL) and evaporated. A 50% EtOH–concentrated HBr solution (50 mL) was added and evaporated and EtOH (50 mL) was added and evaporated. The residue was triturated with propan-2-ol and recrystallized from EtOH to give **11** (0.8 g, 46%).

3,4-Dihydro-1*H*-pyrido[2,3-*d*]pyrimidine-2-thione (7). A solution of 2-aminonicotinonitrile[10] (1.2 g, 0.01 mol) in EtOH (50 mL) previously saturated with NH_3 was hydrogenated at 50 psi and ambient temperature over 5% $Rh–Al_2O_3$ (0.2 g) until uptake ceased. The solution after filtration was evaporated and the residue was dissolved in Et_2O and filtered. The filtrate was acidified with ethereal HCl and the solid removed by filtration and triturated with hot EtOH to give **2-amino-3-aminomethylpyridine dihydrochloride (26)** (0.6 g, 31%), mp 250 °C. Anal. ($C_6H_9N_3·2HCl$) C, H, N.

A solution of **26** (3.5 g, 0.028 mol) in 50% EtOH–H_2O (20 mL) at 40 °C was treated with CS_2 (2.1 g, 0.028 mol). The mixture was heated at 60 °C for 1 h and at reflux for 2 h. 12 N HCl (0.5 mL) was then added and reflux was continued for 16 h. After cooling the resulting crystals were removed by filtration and washed with 50% EtOH–H_2O to give **7** (2.5 g, 53%).

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Attempted Inhibition of Histidine Decarboxylase with β-Alkyl Analogues of Histidine

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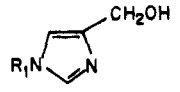
The synthesis of β-methyl- (**10b**), β-ethyl- (**10c**), and β-*n*-hexylhistidine (**10d**) in five steps from 4-(*N*-triphenylmethyl)imidazolecarboxaldehyde (**4**) is described. Neither of the amino acids nor the methyl esters of **10b** or **10c** were inhibitors of the histidine decarboxylase from rat stomach.

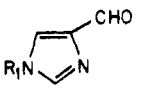
As a continuation of our work on inhibition of histidine decarboxylase, we were interested in analogues of histidine containing an alkyl substituent in the β position. We had previously reported that the methyl ester of L-histidine was a potent inhibitor of this enzyme.[1] When an alkyl group was substituted on the α position of the methyl ester, the resultant compound was a very weak enzyme inhibitor. We therefore wanted to test compounds where the alkyl substituent was at the β position since this change might lead to compounds in which the inhibitory potency of the methyl ester of L-histidine was maintained or even increased.

As a synthetic entry to the β-alkylhistidines we chose to modify Albertson's classic synthesis of histidine[2] by use of the appropriate 1-(4-imidazolyl)alkyl chloride (**7**) (Chart I) in reaction with diethyl acetamidomalonate. Use of the *N*-triphenylmethyl blocked aldehyde **4**[3] as a viable intermediate to **7b–d** was attractive in view of the excellent results in protection and subsequent deblocking of an imidazole reported by Burger and co-workers in their synthesis of some β-substituted analogues of histamine.[3,4] Although the blocked aldehyde **4** was available from **3** in reasonable yield by a modification of Burger's[3] method,

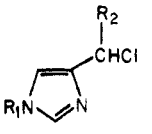
Chart I



1, R_1 = H
2, R_1 = $C(C_6H_5)_3$



3, R_1 = H
4, R_1 = $C(C_6H_5)_3$



7a, R_1 = H; R_2 = H
b, R_1 = H; R_2 = CH_3
c, R_1 = H; R_2 = CH_2CH_3
d, R_1 = H; R_2 = $(CH_2)_5CH_3$
8a, R_1 = $C(C_6H_5)_3$; R_2 = H
b, R_1 = $C(C_6H_5)_3$; R_2 = CH_3

we found that it was more expedient to simply react 4-imidazolylmethanol (**1**)[5] with triphenylmethyl chloride in dimethylformamide to give **2**. Oxidation of **2** with activated manganese dioxide in hot dioxane gave **4** in 80% yield for the two steps. That the triphenylmethyl group in **4** was correctly assigned to the nitrogen atom across the