Synthesis and Biological Activity of *trans*-(±)-*N*-Methyl-2-(3-pyridyl)-2-tetrahydrothiopyrancarbothioamide 1-Oxide (RP 49356) and Analogues: A New Class of Potassium Channel Opener

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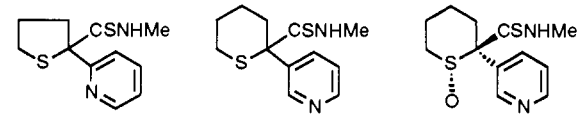
The synthesis and biological activity of *trans*-(±)-*N*-methyl-2-(3-pyridyl)-2-tetrahydrothiopyrancarbothioamide 1-oxide (**8a**, RP 49356) and analogues is reported. These compounds constitute a new structural class of K^+-channel opener. The effects of changes in the pyridyl group, thioamide, and thiane ring on in vitro K^+-channel opening activity are discussed. A 3-pyridyl or 3-quinolyl group, a small *N*-alkyl thioamide function, and a thiane oxide ring, in which the sulfoxide is in a trans relationship to the thioamide, are preferred for activity. Selected compounds were tested intravenously in the normotensive anaesthetized rat for hypotensive effects, and the activities reflect their in vitro K^+-channel opening activity. This led to further evaluation of compound **8a** and the selection of the (−)-enantiomer **8b** (RP 52891) for development as an antihypertensive and antianginal agent.

Recently several compounds have been identified that open K^+ channels, principally in smooth muscle, resulting in membrane hyperpolarization and reduced tissue reactivity. These agents, termed potassium channel openers,[1] have possible clinical applications in the treatment of, for example, hypertension, irritable bladder, coronary artery and peripheral vascular disease, and obstructive airway disease.[2] Several classes of compounds which are capable of opening K^+ channels are now known. Pinacidil[3] is a peripheral vasodilator, nicorandil[4] is an antianginal agent, and cromakalim[5] is a highly potent antihypertensive agent. To date most of the newer compounds have been designed from the benzopyran structure of cromakalim.[6a-f]

We now report the synthesis and biological activity of a new class of potassium channel opener, the lead compound being *trans*-(±)-*N*-methyl-2-(3-pyridyl)-2-tetrahydrothiopyrancarbothioamide 1-oxide (**8a**).[7a-d] The discovery of compound **8a** arose from the study of a series of 2-(2-pyridyl)tetrahydrothiophene-2-carbothioamides[8] which had antisecretory and antiulcer activity, possibly resulting from inhibition of K^+/H^+ ATP-ase and which led to the selection of picartamide[8] for further evaluation. As part of this work a number of structural modifications were carried out including the synthesis of the 2-(3-pyridyl)tetrahydrothiopyran **28**. In general screening,



Picartamide 28 8a

compound **28** was shown to have antihypertensive activity in the spontaneously hypertensive rat (SHR) screen. The onset of the antihypertensive effect was slow and the activity was found to be due to the sulfoxide metabolite **8a**. Studies have shown that the sulfoxide **8a** is a potent hypotensive agent, which acts as an opener of the ATP-sensitive K^+ channel.[9,10a,b] The sulfide **28** is inactive in vitro as a K^+ channel opener.

Chemistry

The tetrahydrothiopyran 1-oxide carbothioamides **8d-u**, in which the 3-pyridyl group of **8a** has been replaced

† Centre de Recherches de Vitry-Alfortville.

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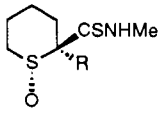
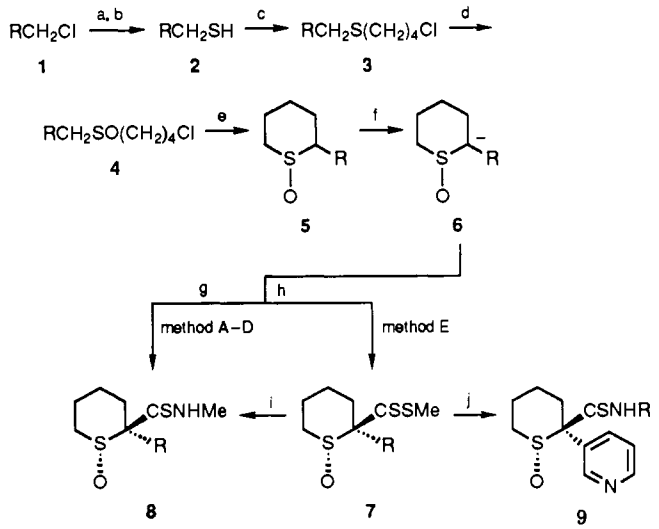
Table I. Aryl and Heterocyclyl Carbothioamides



compd	R	synthesis method	yield, %[a]	mp, °C	recrystn[b] solvent	formula[c]	analysis[d]	relaxn of rat aorta 20 mmol K^+ IC_{90}, μM[j]
8a	3-pyridyl	A,E	61	228	A	$C_{12}H_{16}N_2OS_2$	C,H,N,S	0.7 ± 0.09 (5)
8b	3-pyridyl (−)	*e*		216		$C_{12}H_{16}N_2OS_2$	C,H,N,S	0.4 ± 0.12 (4)
8c	3-pyridyl (+)	*e*		215		$C_{12}H_{16}N_2OS_2$	C,H,N,S	>30 (3)
8d	6-Cl-pyrid-3-yl	E	49	218–220	B	$C_{12}H_{15}ClN_2OS_2$	C[f],H,N	0.3 ± 0.02 (3)
8e	2-pyridyl	B	26	209–211	B	$C_{12}H_{16}N_2OS_2$	C,H,N,S	>30 (3)
8f	4-pyridyl	B	81	219–221	C	$C_{12}H_{16}N_2OS_2$	C,H,N,S	25 ± 1.1 (3)
8g	3-quinolyl	E	17	280	D	$C_{16}H_{18}N_2OS_2$	C,H,N,S,	0.06 ± 0.02 (6)
8h	2-Ph-thiazol-5-yl	C	6	168–170	B	$C_{16}H_{18}N_2OS_3$	C,H,N,S	4 ± 0.6 (5)
8i	5-isothiazolyl	C	25	195–196	B	$C_{10}H_{14}N_2OS_3$	C,H,N,S	7 ± 1.0 (4)
8j	2-benthiazolyl	C	22	194–196	B	$C_{14}H_{16}N_2OS_3$	C,H,N,S	29 ± 3.7 (3)
8k	3,4-diCl-phenyl	C	23	239–240	E	$C_{13}H_{15}Cl_2NOS_2$	C,H,N,[g]Cl,S	0.3 ± 0.05 (4)
8l	3,5-diCl-phenyl	C	26	235–237	F	$C_{13}H_{15}Cl_2NOS_2$	C,H,N,Cl,S	0.4 ± 0.08 (5)
8m	3-CF_3-phenyl	C	29	161–163	G	$C_{14}H_{16}F_3NOS_2$	C,H,N	0.8 ± 0.14 (3)
8n	3-CN-phenyl	C	34	227–228	H	$C_{14}H_{16}N_2OS_2$	C,H,N	1.6 ± 0.14 (5)
8o	3-F-phenyl	C	16	228	I	$C_{13}H_{16}FNOS_2$	C,H,N,F,S	7 ± 1.3 (4)
8p	4-Cl-phenyl	C	17	238–239	E	$C_{13}H_{16}ClNOS_2$	C,H,N,Cl,S	2.8 ± 0.5 (4)
8q	phenyl	D	27	241–243	F	$C_{13}H_{17}NOS_2$	C,H,N	9.5 ± 2.6 (4)
8r	2-naphthyl	C	18	240–242	E	$C_{17}H_{19}NOS_2$	C,H,N	2.0 ± 1.2 (4)
8s	4-Ph-phenyl	C	11	235–236	J	$C_{19}H_{21}NOS_2$	C,H,N	12 ± 2.7 (3)
8t	3-$CONH_2$-phenyl	Ex[h]		225–226		$C_{14}H_{18}N_2O_2S_2$	C,H,N,S	12 ± 3.2 (4)
8u	3-COOH-phenyl	Ex		237–238	D	$C_{14}H_{17}NO_3S_2$	C,H,N[i]	>30 (4)

[a] Yield in thioacylation step. [b] A, CH_3CN; B, purified on a silica column (EtOAc/MeOH), C, EtOAc; D, MeOH; E, triturated with toluene, F, EtOH, g, triturated with 60/80 petroleum ether; H, iPrOH; I, triturated with acetone; J, DMF/EtOH. [c] ^1H NMR spectra were consistent with the assigned structures. [d] Unless indicated all values were within 0.4%. [e] See ref 10. [f] C: calcd 47.6; found 47.1. [g] N: calcd 4.16; found 3.7. [h] Ex = experimental procedure described. [i] N: calcd 4.5; found 5.2. [j] Mean EC_{90} ± standard error of the mean (SEM) with the number of experiments given in parentheses.

Scheme I [a]



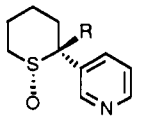
[a] Reagents: (a) NH_2CSNH_2, EtOH; (b) aqueous NaOH; (c) $Br(CH_2)_4Cl$ (d) MCPBA, CH_2Cl_2; (e) KOtBu, THF; (f) requisite base; (g) MeNCS; (h) CS_2, MeI; (i) $MeNH_2$, EtOH; (j) requisite amine, EtOH.

by other heterocyclic and aryl groups, are listed in Table I. The compounds **8a**, **8d–s** were synthesized as outlined in Scheme I starting from the appropriate chloromethyl compounds **1**. In order to limit the formation of disulfide, the intermediate mercaptan **2** was not isolated, but reacted in situ with 1-bromo-4-chlorobutane to give the chloride **3**, which upon oxidation afforded the sulfoxide **4**. Cyclization of the sulfoxide **4** to a cis/trans mixture of the key intermediate tetrahydrothiopyran 1-oxide **5** was accomplished using potassium *tert*-butoxide as base; in the case of sulfoxide **5** (R = 3-pyridyl) the isomers were separable by chromatography. The efficiency of the conversion of sulfoxide **5** into its carbanion **6** and subsequent thioacylation is dependent upon the choice of base and reaction conditions. The carbanion **6** can be converted to the thioamide **8** either directly using methyl isothiocyanate (methods A–D) or indirectly via the dithioester **7** (method E) and subsequent reaction with methylamine. The yields in the thioacylation step are very variable and usually modest (Table I). The amination of the dithioester **7** to thioamide **8** proceeds in high yield. In all cases only the isomer **8**, in which the thioamide is trans to the sulfoxide, is formed. The benzamide **8t** was synthesized by hydrolysis of the nitrile **8n** with methanolic KOH. Subsequent hydrolysis of the benzamide **8t** with aqueous KOH afforded the acid **8u**.

Table II lists a series of 3-pyridyltetrahydrothiopyran 1-oxides in which the *N*-methylcarbothioamide function has been replaced by other groups. The thioamides **9a–f** and thiohydrazide **9g** were synthesized by methods used in Scheme I. The dithioester **7** (R = 3-pyridyl) was aminated with the requisite amine to afford the thioamides **9a–f**, or hydrazine to give the thiohydrazide **9g**. Yields were generally low in the amination step. Although yields were not optimized, it was noticed that in some reactions the liberated methanethiol reduced the sulfoxide group. The acid **9h** was obtained by the alkaline hydrolysis of the ester **9f**. The nitrile **15**, alcohol **16**, and thiol **18** analogues were synthesized as shown in Scheme II. 3-Pyridylacetonitrile was alkylated with 4-chlorobutyl thiocyanic ester and cyclized under the phase transfer conditions of Makoska[11] to the 2-cyanothiane **10** which served as an

(11) Fedorynski, M.; Makosza, M. Reactions of Organic Anions. LII. Reactions of Organic Thiocyanates with Carbanions in Aqueous Medium. *Synthesis* 1974, 274–276.

Table II. 2-(3-Pyridyl)thiopyran-2-carbothioamide Sulfoxide Analogues



compd	R	synthesis method	yield, %[a]	mp, °C	recrystn[b] solvent	formula[c]	analysis[d]	relaxn of rat aorta 20 mmol K^+ IC_{90}, μM[h]
8a	CSNHMe	E	40	228	A	$C_{12}H_{18}N_2OS_2$	C,H,N,S	0.7 ± 0.09 (5)
5	H (trans)	Ex[e]	*f*	130	B	$C_{10}H_{13}NOS$	C,H,N,S	>30 (3)
9a	CSNHEt	E	20	169	C	$C_{13}H_{18}N_2OS_2$	C,H,N,S	0.3 ± 0.02 (3)
9b	CSNHPr	E	47	184	D	$C_{14}H_{20}N_2OS_2$	C,H,N,S	0.6 ± 0.12 (3)
9c	CSNH*i*Pr	E	8	209	E	$C_{14}H_{20}N_2OS_2$	C,H,N,S	10 ± 1.5 (3)
9d	CSNHBu	E	17	158	C	$C_{15}H_{22}N_2OS_2$	C,H,N,S	8 ± 2.4 (4)
9e	CSNHPh	E	20	182	F	$C_{17}H_{18}N_2OS_2$	C,H,N,S	>30 (2)
9f	$CSNH(CH_2)_2COOMe$	E	44	119–121	F	$C_{15}H_{20}N_2O_3S_2$	C,[g]H,N	>30 (2)
9g	$CSNHNH_2$	E	21	203	G	$C_{11}H_{15}N_3OS_2$	C,H,N	>30 (3)
9h	$CSNH(CH_2)_2COOH$	Ex	*f*	175–177		$C_{14}H_{18}N_2O_3S_2$	C,H,N	>30 (3)
15	CN	Ex	*f*	131–132	F	$C_{11}H_{12}N_2OS$	C,H,N,S	>30 (2)
16	CH_2OH	Ex	*f*	101–102	B	$C_{11}H_{15}NO_8$	C,H,N	>30 (4)
18	CH_2SH	Ex	*f*	120–122	F	$C_{11}H_{15}NOS_2$	C,H,N,S	>30 (3)
21	CONHMe	Ex	*f*	212–213	F	$C_{12}H_{16}N_2O_2S$	C,H,N,S	>30 (3)
22	C(=NH)OMe	Ex	*f*	oil	F	$C_{12}H_{16}N_2O_2S$	C,H,N,S	>30 (3)
23	C(=NMe)SMe	Ex	*f*	105–107	F	$C_{13}H_{18}N_2OS_2$	C,H,N,S	>30 (2)

[a] Yield in amination step. [b] A, CH_3CN; B, purified on a silica column (CH_2Cl_2/MeOH); C, MEK/iPr_2O; D, EtOH/iPr_2O, E, EtOH; F, purified on a silica column (EtOAc/MeOH); G triturated with CH_2Cl_2/Et_2O. [c] ^1H NMR spectra were consistent with the assigned structures. [d] Unless indicated all values were within 0.4%. [e] Ex = experimental procedure described. [f] Yields given in experimental procedure. [g] C:calcd 49.0; 48.5. [h] Mean ± SEM with the number of experiments in parentheses.

intermediate for the synthesis of the derivatives **15**, **16**, and **18**. Reaction of the nitrile **10** with DIBAL gave the aldehyde **11** which upon oxidation with MCPBA gave a mixture of *cis*-**12** and the more polar *trans*-**13** sulfoxides. The mixture was separated by chromatography and the *trans*-sulfoxide **13** was reduced to the alcohol **16** with sodium borohydride. The *cis*-sulfoxide **12** upon reduction gave the *cis*-alcohol **16a**. The *cis*-alcohol **16a** was obtained exclusively by the oxidation of the alcohol **11a** (obtained by the reduction of aldehyde **11**) with MCPBA. This result can be explained by the known complexation of alcohols[12] with MCPBA followed by cis delivery of oxygen to sulfur. A Mitsunobu-type reaction on the alcohol **16** with mercaptoacetic acid gave the *S*-acetyl compound **17** which was hydrolyzed to thiol **18**. Oxidation of the nitrile **10** with MCPBA gave a mixture of *cis*-**14** and *trans*-**15** cyano sulfoxides which were separated by flash chromatography. The amide **21** was synthesized from the thioamide **8a** by treatment with nitronium tetrafluoroborate. The imino ether **22** was synthesized by treating the nitrile **15** with sodium methoxide. Reaction of the thioamide **8a** with iodomethane in the presence of *n*-BuLi gave the *S*-methyl compound **23**.

3-Pyridyl carbothioamides in which changes to the tetrahydrothiopyran 1-oxide ring of the thioamide **8a** have been made are collected into Table III. The corresponding cis-isomer **26** of the thioamide **8a** was synthesized as shown in Scheme III. Deoxygenation of the dithioester **7** (R = 3-pyridyl) with P_2S_5 to thiane **24** followed by oxidation with MCPBA gave a mixture of *cis*- and *trans*-dithioester sulfoxides which were separated by chromatography. The less polar *cis*-sulfoxide **25** was aminated with methylamine to give *cis*-thioamide **26**. The sulfone **27** was synthesized by a route similar to that used for the thioamide **8a** (Scheme I). Oxidation of the chloride **3** with excess MCPBA gave the corresponding chloro sulfone which was cyclized using KO*t*-Bu and thioacylated (method E). The thiane **28** was obtained from nitrile **10** as shown in Scheme II via the acid **19** and amide **20**.[13] The dithiane **31** and oxathiane **32** were synthesized according to Scheme IV starting from pyridine-3-carbaldehyde. Reaction with the appropriate thiol gave thiane **29** and oxathiane **30** which were then subjected to thioacylation with methyl isothiocyanate. The corresponding tetrahydrothiophene **35**, tetrahydrofuran **36**, cyclohexyl **39**, and cyclopentyl **40** analogues were synthesized as shown in Scheme V. For compounds **35**, **36**, and **40** the initial step involved a phase transfer alkylation of 3-pyridylacetonitrile similar to that used for nitrile **10**. For the tetrahydrothiophene analogue **35**, alkylation was effected with 3-bromopropyl thiocyanate followed by spontaneous cyclization to the nitrile **33**. For the tetrahydrofuran analogue **36**, alkylation with the THP-ether of 3-bromopropanol was followed by acid hydrolysis of the THP group. A phase transfer chlorination[14] reaction with CCl_4 followed by cyclization gave the nitrile **34**. For the cyclopentyl analogue **40**, the initial step was phase transfer alkylation of 3-pyridylacetonitrile with 1,4-dibromobutane. For the cyclohexyl analogue **39**, the initial step was alkylation of ethyl 3-pyridylacetate with 1,5-dibromopentane in the presence of base to give ester **37**. Hydrolysis of the nitriles **33**, **34**, and **38** and ester **37** gave the corresponding acids **41a–d**, which were converted to the amides **42a–d** by standard methodology. Reaction with P_2S_5 afforded thioamides **35**, **36**, **39**, and **40**.

The enantiomers (−)-**8b** and (+)-**8c** of racemate **8a** were obtained either by separation of the diastereoisomeric amides of acid **19** (prepared as shown in Scheme II) formed with the *tert*-butyl ester of L-proline[10] or by chiral phase HPLC on the racemate **8a**. An X-ray determination of the enantiomer **8b** (Figure 1) indeed shows a trans

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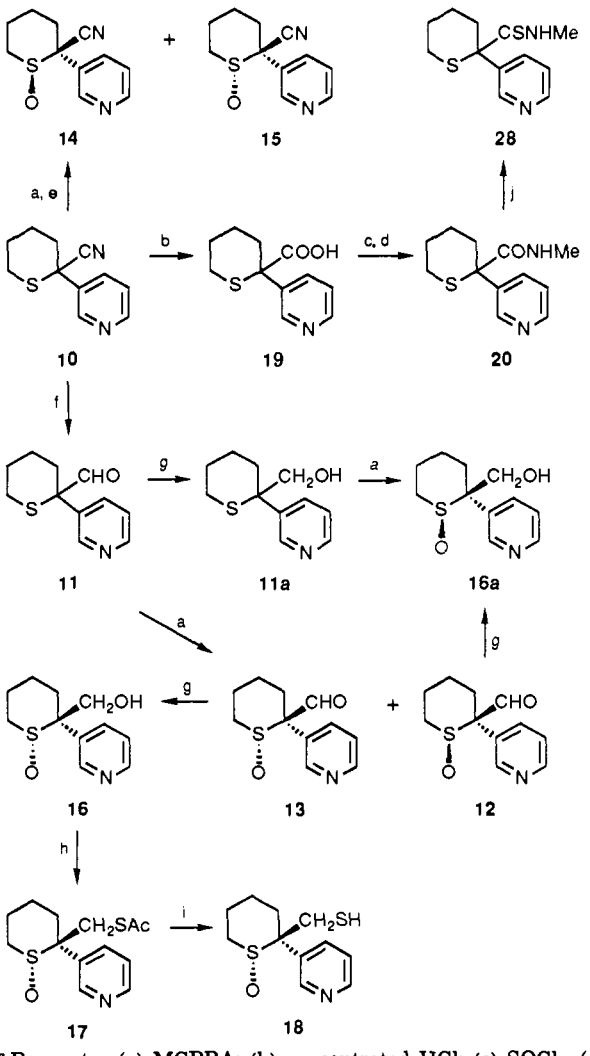
(13) Rhone-Poulenc Sante, 1981, EP A 0073704.

(14) Jonczyk, A.; Kwast, A.; Makoska, M. Reactions of Carbon Tetrachloride with Carbon Acids in a Catalytic Two Phase System. *J. Org. Chem.* **1979**, *44*, 1192–1194.

Scheme II [a]



[a] Reagents: (a) MCPBA; (b) concentrated HCl; (c) $SOCl_2$; (d) $MeNH_2$; (e) chromatography; (f) DIBAL; (g) $NaBH_4$; (h) Ph_3P, AcSH, DIAD; (i) NH_4OH; (j) Lawesson's reagent.

relationship between the thioamide and sulfoxide and a *R* configuration at the chiral carbon and sulfur atoms.

Structure–Activity Relationships

For purposes of discussion of structure–activity relationships in this novel series, the structural changes are classified into three types: namely variation of (i) the aromatic heterocycle, (ii) the thioamide, and (iii) the saturated heterocycle. An examination of the variation of K^+ channel opening activity in vitro in response to these types of structural change was first undertaken. The screen is based upon the characteristic ability of K^+-channel openers to relax rat aorta toned with 20 mmol but not 60 mmol KCl. A compound was considered to be active if it possessed an IC_{90} less than 30 μM. Since smooth muscle relaxants acting by other mechanisms may also relax only 20 mmol KCl induced tone, the activity of a compound was attributed to K^+ channel opening only if it was reversed by glibenclamide, an agent known to block ATP-regulated K^+ channels.[15]

The effect upon activity of variation of the aromatic heterocycle is shown in Table I. The pyridine ring must be linked at the 3-position as in the thioamide **8a** rather than the 2- or 4-positions (**8e–f**). The (–) enantiomer **8b** was twice as active as the racemate **8a**, whereas the (+) enantiomer **8c** was inactive. Activity was retained when a 6-chloro substituent was introduced into the pyridine ring (as in **8d**). The 3-quinolyl analogue **8g** showed a 10-fold increase in activity over the 3-pyridyl analogue **8a**. Other heterocyclic replacements **8h–j** showed modest activity. In the aryl series the enhancement of activity by the presence of an electron withdrawing group in the meta position is demonstrated in analogues **8k–o** when compared to the unsubstituted compound **8q**. This activity is reinforced by the presence of a *p*-chloro substituent as in **8k,p**. The naphthyl analogue **8r** is more active than the unsubstituted compound **8q**. Activity is reduced by meta-substituted polar groups as in **8t,u**.

Table II lists analogues of the thioamide **8a** in which the *N*-methylcarbothioamide group has been modified. In the simple alkyl thioamide analogues **9a–d**, activity is optimal in the ethyl compound **9a**. The substituted alkyl analogues **9f,h** and the phenyl analogue **9e** are inactive. The thiohydrazide **9g**, nitrile **15**, imidate **22**, alcohol **16**, and thiol **18** were all inactive. The requirement for an alkylthioamide seems crucial for good activity; this is reinforced by the inactivity of the amide **21** and the *S*-methyl analogue **23**.

The activities of compounds with a modified thiopyran 1-oxide ring are collected into Table III. The requirement for a trans relationship of the thioamide to the sulfoxide is indicated by the inactivity of the cis-isomer **26**. Furthermore the requirement for a sulfoxide group is indicated by the loss in activity of the sulfone **27**, thiane **28**, 1,3-dithiane **31**, 1,3-oxathiane **32**, tetrahydrothiophene **35**, and tetrahydrofuran **36**. The cyclopentyl analogue **40** and the cyclohexyl analogue **39** show modest activity.

Molecular Modeling

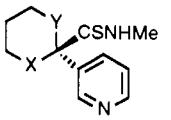
Conformational analysis of the (–) enantiomer **8b** with further full geometry optimization, using the semiempirical molecular orbital program MOPAC and the AM1 Hamiltonian, of all the low-energy structures showed that several distinct conformations of **8b** could exist within a 2 kcal/mol energy band of the lowest energy structure. The global minimum energy conformation calculated by this method has the thioamide group and the sulfoxide oxygen trans diaxial, and indeed corresponds to that determined by X-ray crystallography (Figure 1). The energy difference between this type of conformation with an axial thioamide group and alternative conformations with an equatorial thioamide group is small (ΔE 1.7 kcal/mol), some stabilization coming from an internal "hydrogen bond" (S→O···H–N), as shown in Figure 2. The relative stabilities of the axial and equatorial thioamide forms were found to be sensitive to changes in the ring structure.[16]

Similar conformational studies on the cis-isomer of the sulfoxide **26** (inactive in vitro) showed that the lowest energy conformation of the molecule has the thioamide group axial, but twisted almost 180° relative to the trans-isomer **8b** (Figure 3) so as to form an internal hydrogen bond to the now equatorial sulfoxide oxygen (S→O···H–N 2.1 Å from MOPAC/AM1 calculations); conformations with

(15) Bernardi, H.; Bidard, J. N.; Fosset, M.; Hugues, M.; Mourre, C.; Rehm, H.; Romey, G.; Schmidt-Antomarchi, H.; Schweitz, H.; de Weille, J. R.; Lazdunski, M. Molecular Properties of Potassium Channels. *Arzneim.-Forsch.* **1989**, *39*, 159–163.

(16) Mason, J. S. Personal communication.

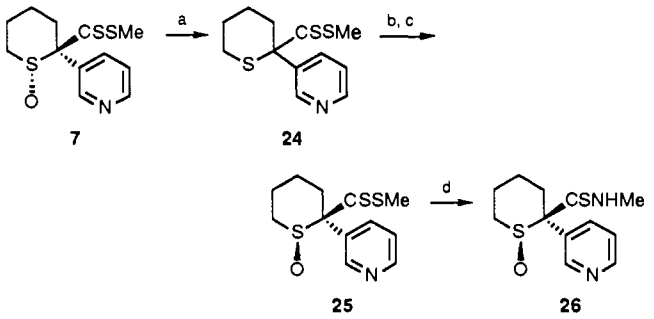
Table III. 2-(3-Pyridyl)thiopyran-2-carbothioamide Analogues



compd	X	Y	mp, °C	recrystn[a] solvent	formula[b]	analysis[c]	relaxn of rat aorta 20 mmol K^+ IC_{90}, μM[f]
8a	SO (trans)[d]	CH_2	228	A	$C_{12}H_{16}N_2OS_2$	C,H,N,S	0.7 ± 0.09 (5)
26	SO (cis)	CH_2	154	B	$C_{12}H_{16}N_2OS_2$	C,H,N,S	>30 (4)
27	SO_2	CH_2	206	C	$C_{12}H_{16}N_2O_2S_2$	C,H,N,S	>30 (4)
28	S	CH_2	122	D	$C_{12}H_{16}N_2S_2$	C,H,N,S	>30 (3)
31	S	S	158	A	$C_{11}H_{14}N_2S_3$	C,H,N,S	>30 (3)
32	S	O	194	A	$C_{11}H_{14}N_2OS_2$	C,H,N,S	>30 (2)
35	S	db[e]	133	D	$C_{11}H_{14}N_2S_2$	C,H,N,S	>30 (4)
36	O	db	128	E	$C_{11}H_{14}N_2OS$	C,H,N,S	>30 (2)
39	CH_2	CH_2	163–164	C	$C_{13}H_{18}N_2S$	C,H,N,S	3 (2)
40	CH_2	db	169	D	$C_{12}H_{16}N_2S$	C,H,N,S	30 ± 1.9 (4)

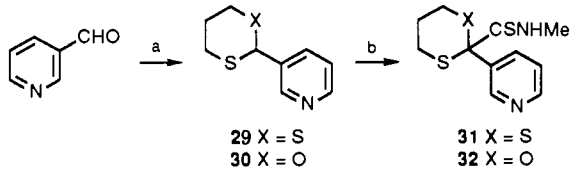
[a] A, CH_3CN; B, purified on a silica column (CH_2Cl_2/EtOAc 4:1), C, EtOAc; D, EtOH; E, iPr_2O/EtOH. [b] ^1H NMR spectra were consistent with the assigned structure. [c] Unless indicated, all values were within 0.4 %. [d] trans to the thioamide. [e] db = Direct bond. [f] Mean ± SEM with number of experiments in parentheses.

Scheme III [a]



[a] Reagents: (a) P_2S_5, CH_2Cl_2, (b) MCPBA; (c) chromatography; (d) $MeNH_2$, EtOH.

Scheme IV [a]



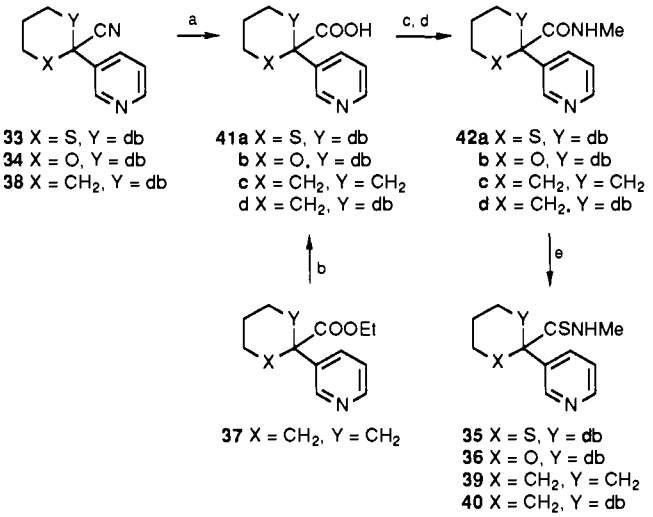
[a] Reagents: (a) $HS(CH_2)_3XH$; (b) base, MeNCS.

the orientation of the thioamide and pyridyl groups corresponding to those in the X-ray structure of (−) enantiomer **8b**, which could be considered as representing the "active" conformation, have an energy (MOPAC/AM1) greater than 5 kcal/mol above the lowest energy structure.

Biological Activity

The hypotensive activities of selected compounds were then determined and compared to the in vitro K^+-channel opening activity (Table IV). Blood pressure changes were monitored in the anaesthetized normotensive rat upon iv infusion. The activity of the quinolyl analogue **8g** is in the range expected when compared to the in vitro data. The substituted aryl analogues **8k,n** were correspondingly less active in vivo than the 3-pyridyl analogue **8a**, which could be explained by lower bioavailability. The *N*-ethylthioamide **9a** showed good in vivo activity, being equiactive with **8a**, despite its greater in vitro potency, while the *N*-butyl analogue **9d** was, as expected, much less active. Although the sulfide **28** was inactive as a K^+-channel opener, its modest in vivo activity can be explained by metabolic oxidation to the sulfoxide.

Scheme V [a]



[a] Reagents: (a) concentrated HCl; (b) NaOH, MeOH; (c) $SOCl_2$; (d) $MeNH_2$; (e) P_2S_5. db = direct bond.

The (−) enantiomer **8b** was twice as active as the racemate **8a** in the in vitro and the in vivo screens, the (+) enantiomer **8c** being inactive. Although the pyridyl analogue **8a** was less active than the quinolyl analogue **8g**, it was selected for further study upon synthetic considerations. An extensive preclinical evaluation of **8a** and its active enantiomer **8b** has been carried out.[17]

The thioamide **8a** is a potent blood pressure lowering agent in conscious and anaesthetized rats and dogs. This effect is due to vasodilation which in conscious animals is accompanied by an increase in heart rate. In several models of experimental hypertension, small oral doses of racemate **8a** produced marked decreases in blood pressure. For instance in the SHR screen 5–15 min after an oral dose of 0.25 mg/kg, there was a maximal reduction in blood pressure of −56 ± 7 mmHg (base line value 166 ± 3 mmHg, n = 6), this effect was still significant 5 h later (−20 ± 2 mmHg). Both racemate **8a** and (−) enantiomer **8b** induced marked increases in coronary blood flow at doses which are devoid of blood pressure effects. Furthermore very

(17) Auchampach, J. A.; Maruyama, M.; Cavero, I.; Gross, G. J. The Potassium Channel Agonist RP 52891 Reduces Infarct Size in the Anaesthetized Dog. *Pharmacologist* **1990**, *32*, 147 (Abstract 164).

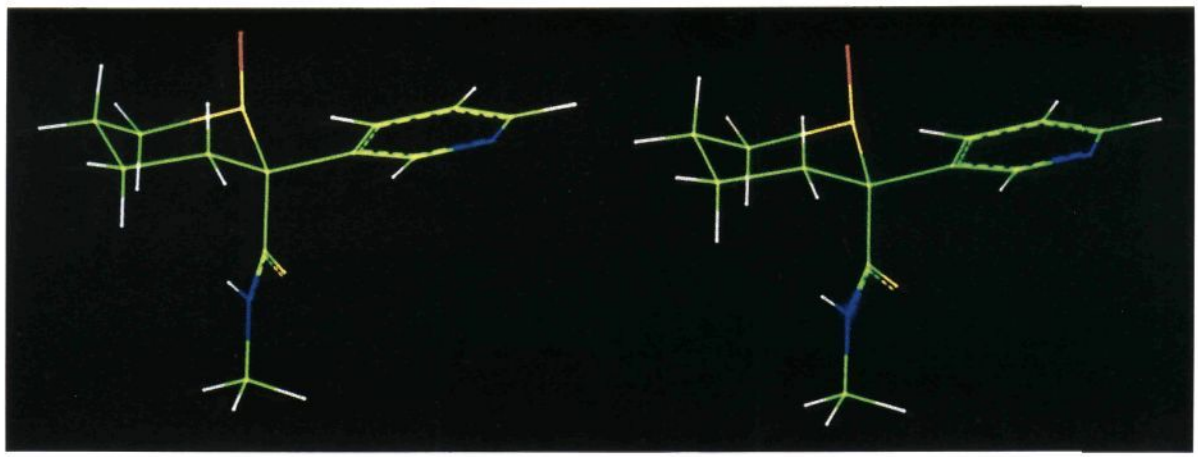


Figure 1. Stereoview of a solid-state conformation obtained from the X-ray analysis of the enantiomer **8b**.

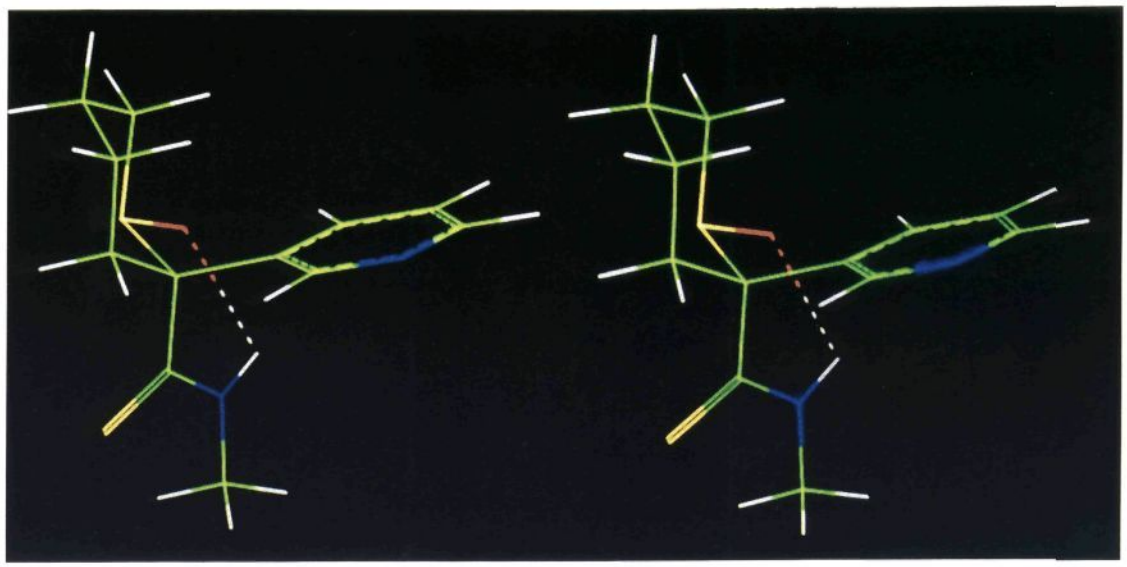


Figure 2. Stereoview of an AM 1 low-energy conformer of **8b** with equatorial thioamide and sulfoxide groups. The dashed line (orange/white) represents a possible hydrogen bond.

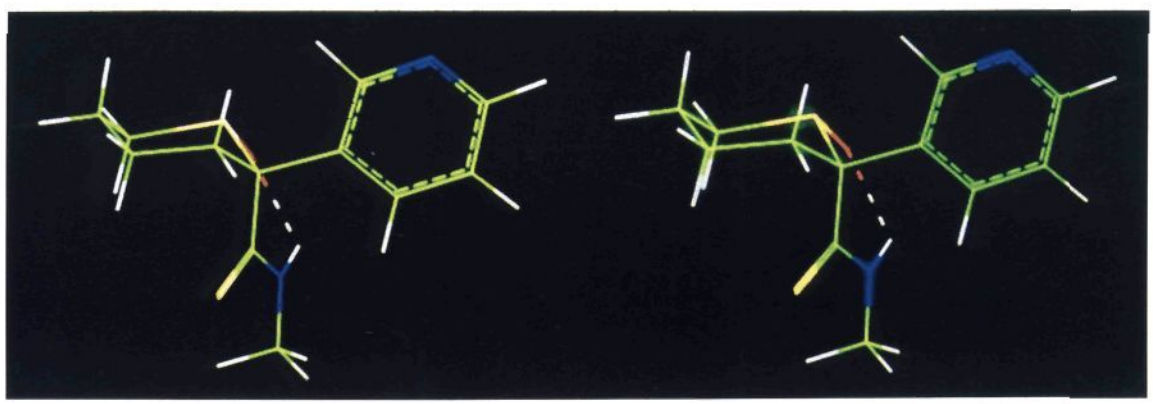
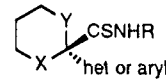


Figure 3. Stereoview of the AM1 lowest energy conformer of the cis-isomer **26**. The dashed line (orange/white) indicates a possible hydrogen bond between the equatorial sulfoxide group and the axial thioamide group, now twisted 180° relative to the AM1 lowest energy conformer of **8b**.

small doses of enantiomer **8b** (10 μg/kg iv bolus + 0.1 μg/kg/min throughout the experimental procedure) in anaesthetized dogs reduced by 34% the size of infarct produced by a 90-min ligation of the left descending coronary artery followed by 5-h reperfusion.[17] All the cardiovascular effects of racemate **8a** and enantiomer **8b** can be antagonized by the hypoglycemic sulfonylurea glibenclamide which blocks ATP-modulated K^+ channels. For example glibenclamide antagonizes not only the vasorelaxant activity of racemate **8a** in the KCl-precontracted isolated aorta but also coronary vasodilatation in dogs and the cardioprotective effects of racemate **8b** in globally ischemic rat hearts. These results suggest that **8a** and **8b** activate a cardiovascular K^+ channel.

Table IV. Comparative Hypotensive Effects of Selected Compounds



compd	het or aryl	X[a]	Y	R	relaxn of rat aorta 20 mmol K^+ IC_{90}, μM[b]	iv anaes rat ED_{30} mmHg, $\mu g/kg$[c]
8a	3-pyridyl	SO	CH_2	Me	0.7 ± 0.09 (5)	0.12 [0.09, 0.14] (16)
8b	3-pyridyl (−)	SO	CH_2	Me	0.4 ± 0.12 (4)	0.05 [0.03, 0.07] (14)
8c	3-pyridyl (+)	SO	CH_2	Me	>30 (3)	>0.75 (3)
8g	3-quinolyl	SO	CH_2	Me	0.06 ± 0.02 (6)	0.04 [0.02, 0.06] (13)
8k	3,4-diCl-phenyl	SO	CH_2	Me	0.3 ± 0.05 (4)	1.28 [0.9, >1.5] (11)
8n	3-CN-phenyl	SO	CH_2	Me	1.6 ± 0.4 (5)	0.63 [0.4, 0.84] (12)
9a	3-pyridyl	SO	CH_2	Et	0.3 ± 0.02 (3)	0.15 [<0.09, >0.18] (4)
9d	3-pyridyl	SO	CH_2	Bu	8 ± 2.4 (4)	1.5 (2)
28	3-pyridyl	S	CH_2	Me	>30 (3)	1.5 [1.2, >1.5] (7)
cromakalim					0.2 ± 0.08 (6)	0.06 [0.04, 0.11] (23)

[a] SO trans. [b] Mean ± SEM with the number of experiments in parenthesis. [c] Mean and 95% confidence in brackets and number of rats examined in parentheses.

Summary

The chemical syntheses and structure–activity relationships of a series of novel tetrahydrothiopyran thioamides are described. Optimal biological activity requires a 3-substituted pyridyl or quinolyl group and a thioamide attached to the C-2 atom of a thiopyran 1-oxide. A trans stereochemistry of the thioamide and sulfoxide groups is preferred. This family of compounds possesses K^+ channel opening activity which under in vivo conditions is associated with blood pressure lowering effects, coronary vasodilatation, and myocardial tissue protection.[17] The (−) enantiomer **8b** (Aprikalim) is undergoing development as an antihypertensive and antianginal agent.[18]

Experimental Section

Melting points were determined using an Electrothermal or a Reichert-Kofler apparatus and are uncorrected. Spectroscopic data for all compounds were recorded on a Pye-Unicam SP3-200 and a Nicolet 205 XB FT (IR), VG 7070E (MS), and Varian XL-200 and VXR 400 (NMR) instruments and were consistent with assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within 0.4% of the theoretical values. NMR data are reported in ppm downfield relative to external TMS (0 ppm) as standard. Concentration refers to evaporation under aspirator vacuum using a Buchi rotary evaporator. Precoated silica gel 60 F_{254} plates with a layer thickness of 0.25 mm from E. Merck, Darmstadt were used for thin-layer chromatography. Preparative column chromatography was performed using medium pressure "flash" chromatography. The stationary phase used was "Sorbsil" (Crosfield) silica gel, mesh size 40–60 μm supplied by Rhone Poulenc. All organic solutions were dried over magnesium sulfate. Yields are not optimized.

Crystallographic Studies. Suitable single crystals of the (−) enantiomer **8b** were grown from water. The cell parameters were obtained from a least-squares fit to 25 reflections with $20° < \theta < 40°$: a = 7.562 (6) Å, b = 13.097 (9) Å, c = 12.815 (9) Å, β = 106.77 (4)°, V = 645 (1) Å^3, monoclinic, $P2_1$, Z = 2, ρ = 1.382 g cm^{-3}, F (000) = 284, T = 293 K. 2628 reflections were collected on a Philips PW1100 diffractometer in a range $12° < 2\theta < 135°$ using Cu Kα radiation (λ = 1.54184 Å). The structure was solved with the use of MULTAN 80;[19] 1027 reflections ($0.089 < \sin\theta/\lambda < 0.571$) were employed in a least-squares refinement for 102 variables, using hydrogen atom positions generated by standard geometric considerations and not refined. The refinements lead to a final R = 0.047 ($R\omega$ = 0.065); final electron density maps did not show any significant feature. The refinement taking into account the X-ray anomalous dispersion led to 1*R*,2*R* configuration for the molecule. The crystal packing shows a hydrogen bond between the NH of the thioamide and the nitrogen of the pyridine group of another molecule. Tables of fractional coordinates, anisotropic thermal factors, bond lengths, valence angles, and torsional angles have been deposited as supplementary material.

Molecular Modeling. Graphical display and manipulation was performed using the Chem-X suite of programs[20] running on a VAX 3500 and an Evans and Sutherland PS 390 graphics station. Conformational analysis was initially carried out using the default Chem-X force field; the structures were constructed from fragments whose geometry had been fully optimized by MOPAC/AM1 (QCPE 455, version 5.0)[21] calculations and MOPAC/AM1 derived charges were used. All potential low-energy structures were further minimized using MOPAC/AM1 using the criteria for terminating the optimization defined by the PRECISE keyword; further systematic conformational analysis was then performed on these structures using Chem-X in order to identify any further potential minima. Selective optimizations (torsional angle fixed) were performed with MOPAC/AM1 in order to evaluate the energy of conformations of particular interest. The AM1 parameters used for sulfur in the MOPAC calculations were identical to those in AMPAC version 2.1 (QCPE 506).[20]

4-Chlorobutyl 3-Pyridylmethyl Sulfide (3). A solution of 3-(chloromethyl)pyridine hydrochloride (200 g, 1.2 mol) in EtOH (480 mL) at 50 °C was added dropwise to a refluxing solution of thiourea (101 g, 1.4 mol) in EtOH (480 mL). The mixture was heated at reflux for 3 h and cooled, and the precipitate was collected in a yield of 274 g (95%), mp 215 °C. To a solution of the isothiourea dihydrochloride (150 g, 0.62 mol) in water (275 mL) under a nitrogen atmosphere was added dropwise a 10 N solution of NaOH (200 mL) at 5 °C and then heated at 70 °C for 20 min to give in situ the thiol **2** (R = 3-pyridyl). The thiol was immediately cooled to room temperature, triethylbenzylammonium chloride (6.2 g, 27 mmol) and 4-bromo-1-chlorobutane (107 g, 0.62 mol) in CH_2Cl_2 (165 mL) were added, and the mixture was stirred overnight at room temperature. Extraction with CH_2Cl_2 followed by washing the organic layer with water (200 mL) and drying gave a clear solution, which was passed down a silica gel column to remove polar products. The filtrate contained 0.42 mol (68%) of **3** (R = 3-pyridyl) according to the titration with perchloric acid and was used directly in the next step, IR ($CHCl_3$) cm^{-1} 1590, 1570, 1475, 2950, 2860, 1425.

2-(3-Pyridyl)tetrahydrothiopyran 1-Oxide (5, R = 3-pyridyl). To a solution of the sulfide **3** (R = 3-pyridyl, 0.24 mol) in CH_2Cl_2 (1450 mL) at room temperature was added dropwise

(18) Richer, C.; Pratz, J.; Mulder, P.; Mondot, S.; Giudicelli, J. F.; Cavero, I. Cardiovascular and Biological effects of K^+ Channel Openers, a Class of Drugs with Vasorelaxant and Cardioprotective Properties. *Life Sci.* **1990**, *47*, 1693–1705.

(19) Main, P. Department of Physics, University of York, York, England.

(20) Developed and distributed by Chemical Design Ltd., Oxford, England.

(21) Available from QCPE, Department of Chemistry, Indiana University, Bloomington, IN 47405.

a solution of 82% MCPBA (50.5 g, 0.24 mol) in CH_2Cl_2 (300 mL), and the solution was stirred overnight. The mixture was neutralized with aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2 (2 × 300 mL). The organic layers were combined, washed with water (2 × 200 mL), dried, and concentrated to give quantitatively crude* sulfoxide 4 (R = 3-pyridyl) as an orange unstable oil, which was immediately dissolved in THF for the next step. IR ($CHCl_3$) cm^{-1} 1050 (S→O) (*titrating 81% with 0.1 N $HClO_4$). A solution of sulfoxide 4 (R = 3-pyridyl, 81% pure, 58.7 g, 0.2 mol) in dry THF (120 mL) was added dropwise over 1 h under N_2 to a solution of KO*t*-Bu (46 g, 0.41 mol) in dry THF (250 mL) at 0 °C. After stirring overnight at room temperature, the solution was acidified with glacial AcOH (20 mL) and filtered. Washing with CH_2Cl_2 (30 mL) and concentration gave a residue, which was subjected to flash chromatography eluting with CH_2Cl_2/MeOH (90:10) to give sulfoxide 5 as a trans/cis mixture (60:40), yield 25 g (62%). The diastereoisomers were separated by flash chromatography eluting with EtOAc/MeOH (80:20) to give firstly (1*RS*,2*RS*) *trans*-5: mp 130 °C; NMR ($CDCl_3$) 1.6–2.0 (m, 3 H), 2.15 (m, 1 H), 2.5 (m, 1 H), 2.66 (m, 2 H), 3.15 (bddd, 1 H), 3.52 (dd, 1 H), 7.28 (bdd, 1 H), 7.7 (ddd, 1 H), 8.53 (bd, 1 H), 8.56 (bdd, 1 H). Anal. ($C_{10}H_{13}NOS$) C, H, N, S. Then the more polar (1*RS*,2*SR*) *cis*-5 followed: mp 120 °C; NMR ($CDCl_3$) 1.6–2.2 (m, 6 H), 2.75 (ddd, 1 H), 3.5 (ddd, 1 H), 3.6 (dd, 1 H), 7.3 (bdd, 1 H), 7.65 (ddd, 1 H), 8.6 (m, 2 H). Anal. ($C_{10}H_{13}NOS$) C, H, N, S.

General Procedures for Thioacylations of 5 (Methods A–E). Method A. *trans*-*N*-Methyl-2-(3-pyridyl)-2-tetrahydrothiopyrancarbothioamide 1-Oxide (8a). Sodium amide was prepared from Na (0.7 g, 30 mmol), $Fe(NO_3)_3 \cdot 9H_2O$ (0.07 g, 0.2 mmol), and liquid NH_3 (10 mL).[22] A solution of 5 (R = 3-pyridyl, 2.93 g, 15 mmol) in THF (35 mL) was added dropwise over 2 min at −35 °C and after stirring for 2 min a solution of MeNCS (1.6 g, 22 mmol) in THF (4 mL) was quickly added. The mixture was stirred for 5 min at −35 °C and then allowed to warm to 20 °C after the addition of NH_4Cl (1.8 g, 34 mmol). The precipitate was filtered and washed with THF and CH_2Cl_2, and the filtrate and washings were concentrated. The residue was recrystallized from EtOAc. **8a**: yield 2 g (50%); mp 228 °C; NMR ($CDCl_3$) 1.6–1.8 (m, 3 H), 2.1–2.35 (m, 2 H), 2.87 (ddd, 1 H), 3.07 (bddd, 1 H), 3.15 (d, 3 H), 3.8 (ddd, 1 H), 7.37 (dd, 1 H), 8.2 (ddd, 1 H), 8.55 (bdd, 2 H), 8.65 (bd, 1 H). Anal. ($C_{12}H_{16}N_2OS_2$) C, H, N, S.

Method B. *trans*-*N*-Methyl-2-(4-pyridyl)-2-tetrahydrothiopyrancarbothioamide 1-Oxide (8f). A suspension of 5 (R = 4-pyridyl, 0.6 g, 3.1 mmol) in dry THF (25 mL) was cooled to −20 °C with stirring, and a 1.0 M solution of lithium bis(trimethylsilyl)amide (4.0 mL, 4 mmol) was added dropwise and the mixture stirred at −20 °C for 1 h. A solution of MeNCS (0.3 g, 4.1 mmol) in dry THF (2 mL) was added and the mixture stirred at −15 °C for 1 h. The mixture was poured into saturated NaCl solution (100 mL) and extracted with CH_2Cl_2 (2 × 50 mL). The combined organic extracts were washed with water (20 mL), dried, and concentrated. The residue was crystallized from EtOAc to give 8f: yield 0.65 g (81%); mp 219–221 °C; NMR (DMSO-d_6) 1.2–2.1 (m, 5 H), 2.5–2.7 (m, 1 H), 2.9–3.0 (m, 1 H), 2.98 (s, 3 H), 3.61 (dt, 1 H), 7.57 (dd, 2 H), 8.58 (dd, 2 H), 10.0 (bs, 1 H). Anal. ($C_{12}H_{16}N_2OS_2$) C, H, N, S.

Method C. *trans*-*N*-Methyl-2-(3-cyanophenyl)-2-tetrahydrothiopyrancarbothioamide 1-Oxide (8n). To a stirred solution of 5 (R = 3-cyanophenyl, 2 g, 9.12 mmol) in dry THF (60 mL) and HMPA (20 mL) under argon at −75 °C was added dropwise a solution of 1.6 mol *n*-BuLi in THF (7.32 mL, 12.4 mmol). The resultant red-brown solution was stirred for a further 1 h at −75 °C before the dropwise addition of methyl isothiocyanate (0.8 mL, 11.5 mmol) in dry THF (20 mL) at −60 °C. The mixture was then allowed to warm to room temperature slowly and stirred for a further 18 h. The solution was poured into saturated saline solution and extracted with EtOAc (100 mL). The organic layer was washed with water (50 mL), dried, and evaporated to give a dark brown oil. The residue was chromatographed on silica eluting with EtOAc/MeOH (95:5). Recrystallization from *i*-PrOH gave 8n: yield 0.9 g (34%); mp 227–228 °C; NMR (DMSO-d_6) 1.0–2.0 (m, 4 H), 2.4–2.75 (m, 2 H), 2.95–3.0 (m, 1 H), 3.36 (d, 3 H), 3.68 (dt, 1 H), 7.62 (t, 1 H), 7.8–8.0 (m, 3 H), 9.96 (bs, 1 H). Anal. ($C_{14}H_{16}N_2OS_2$) C, H, N.

Method D. *trans*-*N*-Methyl-2-phenyl-2-tetrahydrothiopyrancarbothioamide 1-Oxide (8q). A stirred solution of $(i\text{-Pr})_2NH$ (2.15 g, 21.1 mmol) in dry THF (50 mL) under argon was cooled to −60 °C and treated with a 1.6 M solution of *n*-BuLi in hexane (13.8 mL, 22.1 mmol). The solution was allowed to warm to 20 °C, stirred for 10 min, and then cooled to −60 °C. The solution was treated dropwise during 5 min with a solution of 5 (R = phenyl, 3.36 g, 17.3 mmol) in THF (35 mL), and stirring was continued for 15 min at −60 °C. The resulting yellow solution was treated at −60 °C with a solution of methyl isothiocyanate (1.62 g, 22.2 mmol) in THF (25 mL) over 5 min and stirred for 2 h at this temperature. The reaction mixture was treated with water (45 mL) and EtOAc (45 mL), allowed to warm to 0 °C, and stored for 18 h at this temperature while a colorless solid crystallized. This was collected and recrystallized from EtOH to give 8q: yield 1.25 g (27%); mp 241–243 °C; NMR (DMSO-d_6) 1.2–1.82 (m, 3 H), 1.98 (qt, 1 H), 2.42–2.76 (m, 2 H), 2.88 (m, 1 H), 2.96 (d, 3 H), 3.68 (td, 1 H), 7.28 (m, 3 H), 7.6 (m, 2 H), 9.88 (d, 1 H). Anal. ($C_{13}H_{17}NOS_2$) C, H, N.

Method E. *trans*-*N*-Methyl-2-(3-pyridyl)-2-tetrahydrothiopyrancarbothioamide 1-Oxide (8a). A solution of thiopyran 5 (R = 3-pyridyl, 30.6 g, 0.157 mol) in dry THF (500 mL) was added dropwise over 25 min at 20 °C under N_2 to a solution of KO*t*-Bu (51.8 g, 0.46 mol) in dry THF (220 mL). After stirring for 1 h at this temperature, the solution was cooled to −5 °C and then solutions of CS_2 (71.5 g, 0.94 mol) in THF (60 mL) and MeI (133.5 g, 0.94 mol) in THF (60 mL) were successively added. When the additions were complete, the mixture was stirred for 1 h and the temperature allowed to rise to 20 °C. The precipitate was removed and the solution concentrated. The residue was treated with oxalic acid in EtOH, and the crystals were isolated and washed with Et_2O/EtOH (80:20) to give the oxalate of 7: yield 38.6 g (65.5%); mp 160 °C. After treatment of the aqueous solution of this salt with aqueous $NaHCO_3$ solution and extraction into CH_2Cl_2 (2 × 100 mL), the organic phase was collected, dried, and evaporated to give the carbodithioate 1-oxide 7 (R = 3-pyridyl): yield 27.3 g (61%); mp 152 °C; NMR ($CDCl_3$) 1.5–1.8 (m, 2 H), 1.9 (m, 1 H), 2.25 (m, 1 H), 2.61 (s, 3 H), 2.85–3.05 (m, 3 H), 3.35 (m, 1 H), 7.3 (dd, 1 H), 8.0 (ddd, 1 H), 8.6 (dd, 1 H), 8.8 (bd, 1 H).

A 33% w/v solution of $MeNH_2$ in EtOH (35 mL, 0.37 mol) was added dropwise at 25 °C to a solution of 7 (R = 3-pyridyl, 26.6 g, 93.3 mmol) in EtOH (270 mL) and the mixture stirred for 2 h and concentrated. The residue was recrystallized from MeCN to give 8a: yield 15.9 g (40%); mp 228 °C; (spectral data similar to that obtained in method A).

(1*R*,2*R*)-*N*-Methyl-2-(3-pyridyl)tetrahydrothiopyran-2-carbothioamide 1-oxide (8b) was prepared from acid 19 by separation of the diastereoisomeric amides formed with the *tert*-butylprolyl esters[10] and by chiral HPLC: mp 216 °C; $[\alpha]^{20}_D$ −220° ($CHCl_3$, 1.05 g/mL). Anal. ($C_{12}H_{16}N_2OS_2$) C, H, N, S.

(1*S*,2*S*)-*N*-Methyl-2-(3-pyridyl)tetrahydrothiopyran-2-carbothioamide 1-oxide (8c) was similarly prepared from 19: mp 215 °C; $[\alpha]^{20}_D$ +221° ($CHCl_3$, 1.33 g/mL). Anal. ($C_{12}H_{16}N_2OS_2$) C, H, N, S.

***trans*-*N*-Methyl-2-(3-carbamoylphenyl)-2-tetrahydrothiopyrancarbothioamide 1-Oxide (8t).** A suspension of nitrile 8n (1.0 g, 3.4 mmol) in 1 N NaOH (4 mL, 4 mmol) was stirred overnight at 80 °C. The reaction mixture was cooled, neutralized with 2 N HCl and the white solid collected as 8t: yield 0.8 g (76%); mp 225–226 °C; NMR (DMSO-d_6) 1.2–2.1 (m, 4 H) 2.4–2.9 (m, 3 H), 2.94 (d, 3 H), 3.4 (bs, 2 H), 3.68 (dt, 1 H), 7.41 (d, 1 H), 7.8 (d, 2 H), 8.04 (s, 1 H), 9.95 (d, 1 H). Anal. ($C_{14}H_{18}N_2O_2S_2$) C, H, N, S.

***trans*-*N*-Methyl-2-(3-carboxyphenyl)-2-tetrahydrothiopyrancarbothioamide 1-Oxide (8u).** To a solution of KOH (4 g, 7.12 mmol) in EtOH (75 mL) was added amide 8t (4 g, 12.8 mmol), and the mixture was heated at reflux overnight. After cooling, the solution was filtered and evaporated, and the residue was acidified with 2 N HCl. The white precipitate was collected, dried, and recrystallized from MeOH to give 8u: yield 2.7 g (68%); mp 237–238 °C; NMR (DMSO-d_6) 1.2–2.1 (m, 4 H), 2.4–2.95 (m, 3 H), 2.96 (d, 3 H), 3.68 (dt, 1 H), 7.5 (q, 1 H), 7.88 (dd, 2 H), 8.1

(22) Fieser and Fieser. *Reagents for Organic Synthesis*; John Wiley & Sons: New York, 1967; Vol. 1, p 1034.

(s, 1 H), 9.94 (d, 1 H), 11.8 (bs, 1 H). Anal. ($C_{14}H_{17}NO_3S_2$) C, H, N: calcd 4.5, found 5.2.

***trans*-N-(2-Carboxyethyl)-2-(3-pyridyl)-2-tetrahydrothiopyrancarbothioamide 1-Oxide (9h).** A solution of **9f** (2.63 g, 7.73 mmol) in 1 N NaOH (11.6 mL, 11.6 mmol) and water (11.6 mL) was kept at 25 °C for 24 h. The solution was brought to pH 4 with 1 N HCl (11.6 mL) giving a copious precipitate which was collected and washed with water to give **9h** as colorless crystals in a yield of 2.25 g (89%): mp 175–177 °C dec; NMR (DMSO-d_6) 1.28–1.78 (m, 3 H), 1.98 (m, 1 H), 2.43–2.78 (m, 4 H), 2.92 (m, 1 H), 3.5–3.96 (m, 3 H), 7.4 (m, 1 H), 7.95 (dt, 1 H), 8.51 (dd, 1 H), 8.69 (d, 1 H), 10.02 (bs, 1 H), 12.34 (bs, 1 H). Anal. ($C_{14}H_{18}N_2O_3S_2$) C, H, N.

2-Cyano-2-(3-pyridyl)tetrahydrothiopyran (10). To a solution of NaOH (40 g, 1 mol) in water (40 mL) and TEBA (1.7 g, 7.6 mmol) at 25 °C was added dropwise with stirring a solution of pyridine-3-acetonitrile (15 g, 0.127 mol) and 4-chlorobutyl thiocyanic ester (19.5 g, 0.13 mol) in toluene (100 mL) and the mixture stirred at 55–60 °C for 1 h. Water (200 mL) was added and the mixture filtered. The organic layer was collected and the aqueous phase extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried and concentrated to give a dark oil which was subjected to flash chromatography eluting with EtOAc/MeOH (95:5) to give **10**: yield 14 g (54%); mp 80 °C; NMR ($CDCl_3$) 1.75 (m, 2 H), 1.9 (m, 4 H), 2.85 (bddd, 1 H), 3.1 (ddd, 1 H), 7.4 (dd, 1 H), 7.95 (bddd, 1 H), 8.65 (bdd, 1 H), 8.96 (bd, 1 H). Anal. ($C_{11}H_{12}N_2S$) C, H, N, S.

***cis*- and *trans*-2-Cyano-2-(3-pyridyl)tetrahydrothiopyran 1-Oxide (14) and (15).** The cyanothiopyran **10** (9 g, 44 mmol) was dissolved in CH_2Cl_2 (50 mL) and treated dropwise at room temperature with 85% MCPBA (8.9 g, 50 mmol) in CH_2Cl_2 (20 mL). The solution was stirred for 5 h at room temperature: filtered, and concentrated. The residue was subjected to flash chromatography eluting with EtOAc/MeOH (95:5) to give firstly the less polar *cis*-**14**: yield 3.9 g (40%); mp 108–110 °C; NMR (DMSO-d_6) 1.7–2.3 (m, 4 H), 2.7 (dt, 1 H), 3.1–3.4 (m, 3 H), 7.58 (m, 1 H), 7.95 (d, 1 H), 8.65 (m, 2 H). Anal. ($C_{11}H_{12}N_2OS$) C: calcd 60.0, found, 59.5; H, N; S: calcd 14.5, found 14.0; then *trans*-**15**: yield 2.8 g (29%); mp 131–132 °C; NMR (DMSO-d_6) 1.6–1.96 (m, 3 H), 2.1 (m, 1 H), 2.46 (m, 2 H), 2.9 (dt, 1 H), 3.7 (dd, 1 H), 7.58 (m, 1 H), 8.0 (dd, 1 H), 8.7 (d, 1 H), 8.8 (s, 1 H). Anal. ($C_{11}H_{12}N_2OS$) C, H, N, S.

2-(3-Pyridyl)-2-tetrahydrothiopyrancarboxaldehyde (11). A solution of **10** (10.3 g, 50 mmol) in toluene (100 mL) was treated with a 1 M solution in toluene of DIBAL (75.6 mL, 75 mmol) at 0 °C and kept at that temperature for 36 h. The reaction mixture was added to 2 M AcOH (500 mL) and extracted with toluene (2 × 200 mL). The extracts were combined, dried, and concentrated to give a residue which was purified by flash chromatography eluting with EtOAc to give **11**: yield 6.12 g (59%); orange oil; NMR ($CDCl_3$) 1.56–2.04 (m, 5 H), 2.52–2.68 (m, 3 H), 7.32 (m, 1 H), 7.74 (m, 1 H), 8.56 (dd, 1 H), 8.64 (d, 1 H), 9.34 (s, 1 H). Anal. ($C_{11}H_{13}NOS$) C, H, N.

2-(3-Pyridyl)-2-tetrahydrothiopyranmethanol (11a). A solution of **11** (3.7 g, 17.8 mmol) in EtOH (185 mL) was treated with $NaBH_4$ (1.48 g, 39.2 mmol) at 0 °C and then stirred at 25 °C for 20 min. The reaction mixture was diluted with water (150 mL) and extracted into $CHCl_3$ (2 × 150 mL). The combined extracts were dried and concentrated to give a residue, which was purified by flash chromatography eluting with EtOAc/MeOH (99:1) to give **11a**: yield 2.98 g (80%); mp 86–89 °C; NMR ($CDCl_3$) 1.4–1.58 (m, 1 H), 1.68–1.9 (m, 3 H), 2.16–2.3 (m, 1 H), 2.38–2.56 (m, 2 H), 2.6–2.72 (m, 1 H), 3.24–3.54 (brs, 1 H), 3.8 (q, 2 H), 7.26 (m, 1 H), 8.0 (m, 1 H), 8.32 (dd, 1 H), 8.76 (d, 1 H). Anal. ($C_{11}H_{15}NOS$) C, H, N.

***cis*-2-(3-Pyridyl)-2-tetrahydrothiopyranmethanol 1-Oxide (16a).** A solution of **11a** (0.5 g, 2.4 mmol) in CH_2Cl_2 (17 mL) was treated with 85% MCPBA (0.49 g, 2.41 mmol) at 0 °C and stirred at this temperature for 1 h. The reaction mixture was washed with saturated $NaHCO_3$ solution and the aqueous layer extracted with CH_2Cl_2 (75 mL). The combined organic layers were dried and concentrated to give a residue which was purified by flash chromatography eluting with $CHCl_3$/MeOH (9:1), followed by trituration with pentane to give **16a**: yield 0.26 g (48%); mp 118–120 °C; NMR ($CDCl_3$) 1.55–1.92 (m, 4 H), 2.12–2.38 (m, 2 H), 2.72 (td, 1 H), 2.86–2.94 (m, 1 H), 3.92 (s, 2 H), 7.36 (m, 1 H), 7.8 (m, 1 H), 8.59 (dd, 1 H), 8.71 (d, 1 H). Anal. ($C_{11}H_{15}NO_2S$) C, H, N.

Compound **16a** was also synthesized by the following route: A solution of **12** (72 mg, 0.32 mmol) in EtOH (3 mL) was treated with $NaBH_4$ (18 mg, 0.48 mmol) at 0 °C and then stirred for 1 h at 25 °C. Dilution with water, extraction with CH_2Cl_2, and purification by flash chromatography gave **16a**, identical with the above product.

***cis*- and *trans*-2-(3-Pyridyl)-2-tetrahydrothiopyrancarboxaldehyde 1-Oxide (12 and 13).** A solution of **11** (1.0 g, 4.8 mmol) in CH_2Cl_2 (17 mL) was added to a solution of 85% MCPBA (0.98 g, 4.8 mmol) in CH_2Cl_2 (17 mL) at 0 °C during 20 min and kept at this temperature for a further 20 min. The mixture was washed with saturated $NaHCO_3$ solution (2 × 25 mL). The washings were extracted with CH_2Cl_2 (4 × 25 mL). The combined extracts were dried and concentrated to give a yellow oil which was subjected to flash chromatography eluting with EtOAc/MeOH (7:3) to give initially the less polar *cis*-**12**: yield 0.04 g (4%); mp 73–75 °C; NMR ($CDCl_3$) 1.62–1.98 (m, 3 H), 2.22–2.4 (m, 2 H), 2.62 (td, 1 H), 2.76–3.06 (m, 2 H), 7.44 (m, 1 H), 7.82 (m, 1 H), 8.65 (dd, 1 H), 8.74 (d, 1 H), 10.04 (s, 1 H). Anal. ($C_{11}H_{13}NO_2S$) C, H, N. *trans*-**13** eluted next: yield 0.26 g (23%); mp 98–99 °C; NMR ($CDCl_3$) 1.44–1.84 (m, 2 H), 1.98–2.12 (m, 1 H), 2.2–2.4 (m, 2 H), 2.86 (td, 1 H), 3.04–3.14 (m, 2 H), 7.42 (m, 1 H), 7.78 (m, 1 H), 8.66 (m, 2 H), 9.62 (s, 1 H). Anal. ($C_{11}H_{13}NO_2S$) C: calcd 59.2, found 58.6; H, N.

***trans*-2-(3-Pyridyl)-2-tetrahydrothiopyranmethanol 1-Oxide (16).** A solution of *trans*-**13** (0.45 g, 2 mmol) in EtOH (18 mL) was treated with $NaBH_4$ (0.11 g, 3 mmol) at 0 °C and stirred at 25 °C for 1 h. The reaction mixture was treated with water (11 mL) and extracted with $CHCl_3$ (50 mL). The extract was dried and concentrated and the residue purified by flash chromatography eluting with CH_2Cl_2/MeOH (85:15) to give **16**: yield 0.3 g (65%); mp 101–102 °C; NMR ($CDCl_3$) 1.68–1.92 (m, 3 H), 2.02–2.18 (m, 2 H), 2.54–2.68 (m, 1 H), 2.82–3.04 (m, 2 H), 3.62–3.9 (bs, 1 H), 4.0 (d, 1 H), 4.18 (d, 1 H), 7.3 (m, 1 H), 8.26 (dt, 1 H), 8.48 (dd, 1 H), 8.82 (d, 1 H). Anal. ($C_{11}H_{15}NO_2S$) C, H, N.

***trans*-2-(3-Pyridyl)tetrahydrothiopyran-*S*-acetylmethanethiol 1-Oxide (17).** A solution of diisopropyl azodicarboxylate (2.76 mL) in dry THF (17 mL) was added dropwise to a stirred solution of Ph_3P (3.56 g, 1.56 mmol) in dry THF (64 mL) at 0 °C, and the solution was stirred at this temperature for 1 h. A cream precipitate formed, a solution of **16** (1.53 g, 6.8 mmol) and thioacetic acid (0.97 mL) in THF (20 mL) was added dropwise, and the reaction mixture was stirred at 0 °C for 1 h and at room temperature for 2 h. The reaction mixture was concentrated and the residue diluted with ether (30 mL) and allowed to stand overnight at room temperature. The solid was filtered off and the filtrate concentrated to give an oil which was subjected to flash chromatography eluting with EtOAc/MeOH (9:1) to give a golden oil **17**: yield 1.38 g (71%); NMR ($CDCl_3$) 1.6–2.3 (m, 5 H), 2.3 (s, 3 H), 2.7 (m, 1 H), 3.0 (m, 2 H), 3.7 (q, 2 H), 7.34 (m, 1 H), 7.96 (dd, 1 H), 8.58 (d, 1 H), 8.7 (s, 1 H). Anal. ($C_{13}H_{17}NO_2S_2$) C; H: calcd 6.05, found 6.5; N.

***trans*-2-(3-Pyridyl)tetrahydrothiopyranmethanethiol 1-Oxide (18).** To a stirred solution of **17** (1.1 g, 3.9 mmol) in MeOH (30 mL) at room temperature was added NH_4OH solution (d = 0.88, 6.5 mL) and the solution stirred for 2 h. Concentration followed by flash chromatography with EtOAc/MeOH (4:1) as eluent gave **18**: yield 0.69 g (73%); mp 120–122 °C; NMR ($CDCl_3$) 1.1 (dd, 1 H), 1.6–2.0 (m, 4 H), 2.06–2.3 (m, 2 H), 2.66–2.84 (m, 1 H), 2.84 (q, 2 H), 3.0–3.36 (dq, 2 H), 7.4 (q, 1 H), 8.0 (d, 1 H), 8.6 (d, 1 H), 8.75 (s, 1 H). Anal. ($C_{11}H_{15}NOS_2$) C, H, N, S.

***trans*-N-Methyl-2-(3-pyridyl)-2-tetrahydrothiopyrancarboxamide 1-Oxide (21).** The thioamide **8a** (2.7 g, 10 mmol) was dissolved in CH_2Cl_2 (100 mL) and stirred at room temperature while a 0.5 M solution of nitronium tetrafluoroborate in sulfolane (25 mL) was added dropwise over 5 min and the solution stirred for 1 h. The solution was extracted with 2 M Na_2CO_3 soln (50 mL), dried, and evaporated. The residue was subjected to flash chromatography eluting with EtOAc/MeOH (4:1) to give **21**: yield 0.3 g (12%); mp 212–213 °C; NMR ($CDCl_3$) 1.56–2.38 (m, 6 H), 2.83 (d, 3 H), 2.94–3.11 (m, 1 H), 3.28–3.42 (m, 1 H), 5.63 (q, 1 H), 7.32–7.41 (m, 1 H), 7.81–7.88 (m, 1 H), 8.60 (dd, 1 H), 8.67 (dd, 1 H). Anal. ($C_{12}H_{16}N_2O_2S$) C, H, N, S.

trans-**Methyl 2-(3-Pyridyl)tetrahydrothiopyran-2-carboximidate 1-Oxide (22).** To a stirred solution of **15** (3 g, 13.6 mmol) in MeOH (30 mL) was added Na metal (0.03 g, 1.3 mmol) and the solution stirred at room temperature for 6 h. The solution was concentrated and the residue subjected to flash chromatography eluting with EtOAc/MeOH (95:5) to give **22** as a clear oil: yield 0.7 g (20%); NMR ($CDCl_3$) 1.52–2.16 (m, 5 H), 2.6–2.8 (m, 2 H), 3.8 (s, 3 H), 3.92 (t, 1 H), 7.4 (q, 1 H), 7.7 (dd, 1 H), 8.6 (m, 2 H). Anal. ($C_{12}H_{16}N_2O_2S$) C, H, N, S.

trans-**Methyl *N*-Methyl-2-(3-pyridyl)tetrahydrothiopyran-2-carboximidothioate 1-Oxide (23).** To a solution of **8a** (1.34 g, 5 mmol) in dry THF (30 mL) and HMPA (2 mL) was added with stirring under argon at −30 °C a 1.6 M solution of *n*-BuLi in hexane (3.2 mL, 5 mmol) over 5 min followed by a solution of CH_3I (0.32 g, 5 mmol) in Et_2O (5 mL). The solution was allowed to warm to room temperature, stirred for 2 h, and then poured into glacial AcOH (1 mL) and EtOAc (100 mL). The solution was washed with water (3 × 25 mL), dried, and evaporated to give an oil which was purified by flash chromatography eluting with EtOAc/MeOH (9:1) to give **23**: yield 0.5 g (35%); mp 105–107 °C; NMR ($CDCl_3$) 1.4–2.0 (m, 3 H), 2.0 (s, 3 H), 2.05–2.5 (m, 3 H), 2.7–3.0 (m, 2 H), 3.42 (t, 1 H), 3.54 (s, 3 H), 7.36 (q, 1 H), 7.8 (d, 1 H), 8.6 (d, 1 H), 8.7 (s, 1 H). Anal. ($C_{13}H_{18}N_2OS_2$) C, H, N, S.

Methyl 2-(3-Pyridyl)tetrahydrothiopyran-2-carbodithioate (24). To a solution of sulfoxide **7** (R = 3-pyridyl, 32.6 g, 114 mmol) in CH_2Cl_2 (200 mL) was added over 1 h at room temperature P_2S_5 (12.7 g, 56 mmol) and the mixture stirred for 3 h. After this time the mixture was filtered, washed with water, dried, and subjected to flash chromatography using CH_2Cl_2 then EtOAc/cyclohexane (4:1) as eluent to give **24**: yield 12.6 g (41%); mp 89 °C; NMR ($CDCl_3$) 1.6–2.0 (m, 4 H), 2.55 (s, 3 H), 2.6 (m, 2 H), 2.91 (m, 1 H), 3.36 (m, 1 H), 7.25 (dd, 1 H), 7.95 (ddd, 1 H), 8.5 (dd, 1 H), 8.9 (d, 1 H).

cis-**Methyl 2-(3-Pyridyl)tetrahydrothiopyran-2-carbodithioate 1-Oxide (25).** A solution of 82.5% MCPBA (41.6 g, 200 mmol) in CH_2Cl_2 (500 mL) was added dropwise to a solution of **24** (54 g, 200 mmol) in CH_2Cl_2 (500 mL) at 20 °C and the solution stirred overnight. The mixture was filtered and evaporated to give a residue, which was subjected to flash chromatography eluting with CH_2Cl_2 and then with EtOAc followed by EtOAc/MeOH (80:20) to give firstly the *cis*-sulfoxide **25**: yield 9 g (16%); mp 123 °C; NMR ($CDCl_3$) 1.6–2.37 (m, 4 H), 2.53 (td, 1 H), 2.64 (s, 3 H), 2.98–3.25 (m, 3 H), 7.45 (dd, 1 H), 8.02 (ddd, 1 H), 8.63 (dd, 1 H), 8.87 (d, 1 H), and then the more polar *trans*-sulfoxide **7** (R = 3-pyridyl): yield 33.3 g (58%).

cis-*N*-**Methyl 2-(3-Pyridyl)tetrahydrothiopyran-2-carbothioamide 1-Oxide (26).** The reaction was conducted as in method E using the *cis*-sulfoxide **25** (5.7 g, 20 mmol) and methylamine. After flash chromatography using CH_2Cl_2/MeOH (95:5) as eluent and recrystallization from water there was obtained the cis-compound **26**: yield 3.0 g (56%); mp 154 °C; NMR ($CDCl_3$) 1.7–2.2 (m, 5 H), 3.2–3.4 (m, 3 H), 3.35 (d, 3 H), 7.4 (dd, 1 H), 7.9 (vbd, 1 H), 8.6 (bd, 1 H), 8.9 (bd, 1 H), 10.9 (bs, 1 H). Anal. ($C_{12}H_{16}N_2OS_2$) C, H, N, S.

N-**Methyl 2-(3-Pyridyl)tetrahydrothiopyran-2-carbothioamide 1,1-Dioxide (27).** To a solution of the sulfide **3** (R = 3-pyridyl, 19 g, 88 mmol) in CH_2Cl_2 (260 mL) was added dropwise at room temperature a solution of 83.5% MCPBA (37.7 g, 180 mmol) in CH_2Cl_2 (370 mL) at 20 °C and then it was stirred overnight. After neutralization with an aqueous $NaHCO_3$ solution, the aqueous phase was extracted with CH_2Cl_2 (200 mL). The combined organic extracts were washed with water (200 mL), dried, and concentrated. The residue was subjected to flash chromatography eluting with CH_2Cl_2 to give **4-chlorobutyl 3-pyridylmethyl sulfone**: Recrystallization from *i*-Pr_2O/EtOAc (3:1) yielded 11.2 g (51%) mp 84 °C. A solution of the above chloro sulfone (78 g, 0.31 mol) in dry THF (260 mL) was added dropwise over 2 h at 0 °C under N_2 to a solution of KO*t*-Bu (70 g, 0.62 mol) in dry THF (380 mL), and the mixture was stirred overnight. The solution was acidified with glacial AcOH, filtered, and concentrated to give a residue which was subjected to flash chromatography eluting with EtOAc/MeOH (8:2) to give **2-(3-pyridyl)tetrahydrothiopyran 1,1-dioxide**: yield 23 g (35%); mp 165 °C. A solution of the thiopyran dioxide (12.1 g, 57 mmol) in dry THF (110 mL) was added dropwise over 1 h at 20 °C under N_2 to a solution of KO*t*-Bu (14.3 g, 127 mmol) in dry THF (330 mL). After stirring at this temperature for 1 h, the solution was cooled to 0 °C and successive solutions of CS_2 (11 g, 144 mmol) in THF (33 mL) and MeI (21 g, 148 mmol) in dry THF (30 mL) were added, and the mixture was stirred for 1 h. The mixture was filtered and concentrated, and the residue was subjected to flash chromatography using EtOAc as eluent to give **methyl 2-(3-pyridyl)tetrahydrothiopyran-2-carbodithioate 1,1-dioxide**: yield 13 g (76%); mp 138 °C. A 33% w/v solution of $MeNH_2$ in EtOH (140 mL, 1.5 mol) was added dropwise at 20 °C to a solution of the dithioester (19.3 g, 64 mmol) in EtOH (370 mL). The mixture was stirred overnight at this temperature and the precipitated crystals **27** were collected. The mother liquors were concentrated, and the residue was subjected to flash chromatography using EtOAc as eluent. The chromatographically homogeneous fraction was combined with the precipitate and recrystallized from EtOAc to give **27**: yield 6.6 g (36%); mp 206 °C; NMR ($CDCl_3$) 1.9–2.3 (m, 4 H), 2.9 (ddd, 1 H), 3.2 (ddd, 1 H), 3.3 (ddd, 1 H), 3.4 (d, 3 H), 3.55 (bddd, 1 H), 7.4 (dd, 1 H), 7.9 (bddd, 1 H), 8.65 (bdd, 1 H), 8.8 (bd, 1 H), 10.15 (bs, 1 H). Anal. ($C_{12}H_{16}N_2O_2S_2$) C, H, N, S.

2-(3-Pyridyl)tetrahydrothiopyran-2-carboxylic acid (19). A solution of nitrile **10** (204 g, 1 mol) in concentrated HCl (2 L) was stirred overnight at reflux and then concentrated to half bulk. A solution of NH_4OH (d = 0.88) was added dropwise up to pH 4, and the precipitate was filtered, washed with water, and dried. Recrystallization from EtOH gave **19**: yield 173 g (78%); mp 200 °C; NMR (DMSO-d_6) 1.5–1.8 (m, 4 H), 2.5 (m, 3 H), 2.75 (ddd, 1 H), 7.4 (dd, 1 H), 7.95 (ddd, 1 H), 8.5 (dd, 1 H), 8.73 (bd, 1 H).

N-**Methyl 2-(3-Pyridyl)tetrahydrothiopyran-2-carboxamide (20).** The acid **19** (172 g, 0.77 mol) was added portionwise to $SOCl_2$ (700 mL) containing DMF (0.2 mL) and the mixture heated at reflux for 1.5 h, cooled, and concentrated. The residue was dissolved in CH_2Cl_2 (1.1 L), saturated with gaseous $MeNH_2$, and diluted with water (500 mL), and the organic layer was collected. The aqueous layer was extracted with CH_2Cl_2 (2 × 300 mL), and the combined organic extracts were dried and concentrated. The residue was crystallized from MeCN to give **20**: yield 127 g (70%); mp 112 °C; NMR ($CDCl_3$) 1.6–2.1 (m, 5 H), 2.65 (ddd, 1 H), 2.85 (ddd, 1 H), 3.0 (m, 4 H), 7.25 (dd, 1 H), 7.72 (bs, 1 H), 7.8 (bddd, 1 H), 8.5 (bdd, 1 H), 8.8 (bd, 1 H). Anal. ($C_{12}H_{16}N_2OS$) C, H, N, S.

N-**Methyl-2-(3-pyridyl)tetrahydrothiopyran-2-carbothioamide (28).** A mixture of Lawesson's reagent (128 g, 0.3 mol) and **20** (94.5 g, 0.4 mol) in toluene (1.3 L) were heated at reflux for 1.5 h. After cooling, water (1.4 L) and NH_4OH (1.4 L, d = 0.88) were added, and the mixture was extracted with EtOAc (2 × 300 mL). The combined extracts were washed with water (2 × 200 mL), dried, and concentrated. The residue was dissolved in 0.1 N HCl (600 mL) and the aqueous solution extracted with toluene (200 mL), treated with charcoal, and then neutralized with NaOH. The precipitate was filtered, dried, and recrystallized from EtOH to give **28**: yield 68.5 g (68%); mp 122 °C. Anal. ($C_{12}H_{16}N_2S_2$) C, H, N, S.

2-(3-Pyridyl)-1,3-dithiane (29). A solution of 3-pyridinecarboxaldehyde (45.5 g, 0.425 mol), 1,3-propanedithiol (97 g, 0.9 mol), and TsOH (6.6 g, 35 mmol) in 1,2-dichloroethane (4.2 L) was heated at reflux with a Dean-Stark apparatus. After cooling, the solution was washed with 2 N NaOH (1 L), and H_2O (1 L), dried, and concentrated to give an oil. The residue was purified by flash chromatography (eluent CH_2Cl_2) to give **29**: yield 18.6 g (22%); mp 63–65 °C.

2-(3-Pyridyl)-1,3-oxathiane (30) was similarly prepared from 3-pyridinecarboxaldehyde (16 g, 0.15 mol), 3-mercaptopropanol (48 g, 0.52 mol), and TsOH (2.25 g, 12 mmol) after chromatography (cyclohexane/EtOAc 7:3) as a yellow oil: 8.6 g (32%); NMR ($CDCl_3$) 2.15 (m, 2 H), 3.0 (m, 4 H), 7.3 (dd, 1 H), 7.8 (dd, 1 H), 8.55 (dd, 1 H), 8.7 (d, 1 H).

N-**Methyl-2-(3-pyridyl)-1,3-dithiane-2-carbothioamide (31).** To a 1.6 M soln of *n*-BuLi in hexane (89 mL, 0.14 mol) and a 50:50 mixture of THF/HMPA (55 mL) at −60 °C was added successively a solution of **29** (18.6 g, 95 mmol) in 1:1 THF/HMPA (55 mL) and then MeNCS (10.4 g, 0.14 mol) in 30 mL of the same mixture. When the addition was complete, the solution was allowed to warm to room temp over 1 h, H_2O (100 mL) added, and the

solution extracted with EtOAc (2 × 100 mL). The organic extracts were combined, dried, and concentrated to give an oil. The residue was subjected to flash chromatography using CH_2Cl_2 as eluent and the homogeneous fractions were recrystallized from MeCN to give **31**: yield 8.7 g (34%); mp 158 °C; NMR ($CDCl_3$) 2.1 (m, 2 H), 2.85–3.05 (m, 2 H), 3.3 (d, 3 H), 7.3 (dd, 1 H), 8.1 (ddd, 1 H), 8.58 (bdd, 1 H), 9.0 (bd, 1 H), 9.25 (bs, 1 H). Anal. ($C_{11}H_{14}N_2S_3$) C, H, N, S.

***N*-Methyl-2-(3-pyridyl)-1,3-oxathiane-2-carbothioamide (32)** was similarly prepared from **30** (8.7 g, 47 mmol): yield 2.9 g (24%); mp 194 °C; NMR ($CDCl_3$) 1.65 (m, 1 H), 2.05 (m, 1 H), 2.7 (ddd, 1 H), 2.9 (ddd, 1 H), 3.2 (d, 3 H), 3.8 (ddd, 1 H), 4.2 (bd, 1 H), 7.4 (dd, 1 H), 8.2 (bddd, 1 H), 8.6 (bdd, 1 H), 8.9 (bd, 1 H), 9.1 (bs, 1 H). Anal. ($C_{11}H_{14}N_2OS_2$) C, H, N, S.

2-(3-Pyridyl)tetrahydrothiophene-2-carbonitrile (33). A solution of 3-bromopropyl thiocyanate (282 g, 1.57 mol) in toluene (430 mL) was added dropwise over 20 min to a mixture of 3-pyridylacetonitrile (156 g, 1.32 mol), 50% aqueous NaOH (432 g, 5.4 mol), and benzyltriethylammonium chloride (6.5 g, 28 mmol). During the addition the mixture was allowed to warm to 50 °C and then stirred for 1 h at 67 °C, cooled, diluted with water, and extracted with EtOAc (2 × 250 mL). The combined organic layers were washed with H_2O (500 mL) and extracted with 5 N HCl (250 mL), and the acidic solution was washed with EtOAc, neutralized with NH_4OH (d = 0.88), and extracted with EtOAc (2 × 250 mL). The organic layer was washed with H_2O (100 mL), dried, and concentrated, and the residue was recrystallized from i-Pr_2O to give **33**: yield 145 g (58%); mp 45 °C; NMR ($CDCl_3$) 2.1–2.9 (m, 4 H), 3.3 (m, 2 H), 7.4 (dd, 1 H), 8.0 (dd, 1 H), 8.5 (dd, 1 H), 8.9 (d, 1 H).

2-(3-Pyridyl)tetrahydrofuran-2-carbonitrile (34). A solution of 1-bromo-3-(tetrahydro-2*H*-pyran-2-yloxy)propane (51.3 g, 0.23 mol) in toluene (30 mL), 3-pyridylacetonitrile (23.9 g, 0.2 mol), 50% aqueous NaOH (80 g, 1 mol), and benzyltriethylammonium chloride (2.3 g, 0.01 mol) were similarly reacted to give α-[3-(tetrahydro-2*H*-pyran-2-yloxy]propyl]-3-pyridineacetonitrile after flash chromatography (eluting with EtOAc/cyclohexane 7:3) as a yellow oil: yield 43 g (83%). The THP ether (43 g, 0.165 mol) was dissolved in 1 N HCl (800 mL, 0.8 mol) and the solution stored overnight at 20 °C, washed with EtOAc (100 mL), neutralized with 2 N NaOH, and extracted with EtOAc (2 × 200 mL). The organic extracts were combined, dried, and concentrated to give α-(3-hydroxypropyl)-3-pyridineacetonitrile as a yellow oil: 27.5 g (95%). A solution of the above nitrile (27.5 g, 0.156 mol) in toluene (30 mL) was added dropwise over 10 min to a stirred mixture of 50% aqueous NaOH (200 g, 2.5 mol), CCl_4 (120 mL), and benzyltriethylammonium chloride (2 g, 9 mmol). The mixture was allowed to warm to 40 °C during the addition and then stirred for a further 1 h at 20 °C, diluted with water (150 mL), and extracted with CH_2Cl_2 (2 × 250 mL). The organic layers were combined, dried, and concentrated to give an oil, which was purified by flash chromatography to afford **34** as a yellow oil: yield 10 g (37%).

1-(3-Pyridyl)cyclopentanecarbonitrile (38). This compound was prepared from 3-pyridylacetonitrile (40 g, 0.34 mol) and 1,4-dibromobutane (80.3 g, 0.37 mol) as described for **33** to give a red oil: yield 42 g (72%).

1-(3-Pyridyl)cyclohexanecarboxylic Acid Ethyl Ester (37). A mixture of ethyl 3-pyridylacetate (16.5 g, 0.1 mol) and KOt-Bu (24.7 g, 0.22 mol) were stirred in dry DMF (250 mL) for 0.5 h at room temperature under argon. 1,5-Dibromopentane (25 g, 0.1 mol) was then added dropwise and stirred for 4 h at room temperature and allowed to stand overnight. The solution was acidified with 10% aqueous HCl (100 mL) and washed with Et_2O (100 mL), and the aqueous phase was basified with $NaHCO_3$ solution. The aqueous solution was extracted with Et_2O (3 × 250 mL), and the ethereal extracts were combined, washed with saturated $NaHCO_3$ solution and brine (100 mL), dried, and concentrated to give **37**: yield 20.96 g (90%); NMR ($CDCl_3$) 1.2 (t, 3 H) 1.3 (m, 1 H), 1.5 (m, 1 H), 1.7 (m, 4 H), 2.0 (m, 3 H), 2.5 (d, 1 H), 4.15 (q, 2 H), 4.97 (t, 1 H), 7.24 (m, 1 H), 7.85 (dd, 1 H), 8.5 (dd, 1 H), 8.68 (s, 1 H).

2-(3-Pyridyl)tetrahydrothiophene-2-carboxylic Acid (41a). A solution of the nitrile **33** (34 g, 18 mmol) in concentrated HCl (400 mL) was stirred overnight at reflux and then concentrated to half bulk. A solution of NH_4OH (d = 0.88) was added dropwise up to pH 4, and the precipitate was filtered, washed with water, and dried. Recrystallization from EtOH gave **41a**: yield 11.5 g (30%); mp 184 °C; NMR (DMSO-d_6) 1.8–2.15 (m, 3 H), 2.8–3.1 (m, 3 H), 7.4 (dd, 1 H), 7.8 (dd, 1 H), 8.4 (dd, 1 H), 8.65 (d, 1 H), 12.7 (vbs, 1 H). Anal. ($C_{10}H_{11}NO_2S$) C, H, N, S.

2-(3-Pyridyl)tetrahydrofuran-2-carboxylic acid (41b) was prepared by the reaction of nitrile **34** (10 g, 57 mmol) with concentrated HCl (100 mL) at 70 °C for 3 h followed by concentration. The acid was used directly in the synthesis of carboxamide **42b**.

1-(3-Pyridyl)cyclopentanecarboxylic acid (41d) was prepared from nitrile **38** (42 g, 0.224 mol) and concentrated HCl (420 mL) as in **41a** but heating at 70 °C for 5 h: yield 32 g (69%); mp 148 °C.

1-(3-Pyridyl)cyclohexanecarboxylic Acid (41c). An ice-cold soln of NaOH (15.94 g, 0.4 mol) in water (250 mL) was added slowly with stirring to a solution of ester **37** (30.96 g, 0.13 mol) in MeOH (250 mL) at 0 °C. The reaction mixture was stirred for 2 h and then allowed to stand at room temperature for 48 h. The solvent was evaporated and the residue treated with EtOAc (50 mL). The aqueous solution was acidified to pH 5 with glacial AcOH and extracted into EtOAc (3 × 150 mL). The combined extracts were dried and concentrated to give a residue which was recrystallized from EtOAc to give **41c**: yield 7.35 g (36%); mp 167 °C; NMR ($CDCl_3$) 1.4–1.82 (m, 8 H), 2.4–2.6 (m, 1 H), 5.1 (b, 2 H), 7.25 (m, 1 H), 7.8 (dd, 1 H), 8.42 (dd, 1 H), 8.68 (s, 1 H). Anal. ($C_{12}H_{15}NO_2$) C: calcd 70.2; found 69.3; H, N.

***N*-Methyl-2-(3-pyridyl)tetrahydrothiophene-2-carboxamide (42a).** The amide was prepared from acid **41a** (9.7 g, 46 mmol) by the method as described for **20**. The crude product was recrystallized from i-Pr_2O/CH_3CN (50:50) to give **42a**: yield 6.8 g (66%); mp 123 °C; NMR ($CDCl_3$) 1.85–2.4 (m, 3 H), 2.85 (d, 3 H), 3.0–3.3 (m, 3 H), 7.3 (dd, 1 H), 7.8 (dd, 1 H), 8.5 (dd, 1 H), 8.75 (d, 1 H).

***N*-Methyl-2-(3-pyridyl)tetrahydrofuran-2-carboxamide (42b).** The intermediate acid **41b** (prepared as above) was converted to **42b** by a similar method to that described for **20**. The crude product was purified by flash chromatography, eluting with cyclohexane/EtOAc (7:3), then neat EtOAc: yield 5.2 g (44%); mp 107 °C.

***N*-Methyl-1-(3-pyridyl)cyclopentanecarboxamide (42d).** The amide was similarly prepared from acid **41d** (21.8 g, 0.114 mol) as described for **20**. The crude product was purified by flash chromatography, eluting with cyclohexane/EtOAc (1:1) to give **42d**: yield 13.2 g (57%); mp 130 °C.

***N*-Methyl-1-(3-pyridyl)cyclohexanecarboxamide Hydrate (42c).** The amide was similarly prepared from acid **41c** as described for **20**. Recrystallization from cyclohexane gave **42c**: yield 3.6 g (52%); mp 107–109 °C; NMR ($CDCl_3$) 1.4 (m, 1 H), 1.6 (m, 4 H), 1.92 (bs, 1 H), 2.02 (m, 2 H), 2.3 (m, 2 H), 2.74 (s, 3 H), 5.44 (s, 1 H), 7.28 (m, 1 H), 7.73 (dd, 1 H), 8.52 (d, 1 H), 8.65 (s, 1 H). Anal. ($C_{13}H_{18}N_2O \cdot 0.15H_2O$) C, H, N.

***N*-Methyl-2-(3-pyridyl)tetrahydrothiophene-2-carbothioamide (35).** The amide **42a** (6.8 g, 31 mmol) was treated with 9.3 g (23 mmol) of Lawesson's reagent as described for **28**. The crude product was recrystallized from EtOH to give **35**: yield 4.9 g (66%); mp 133 °C; NMR ($CDCl_3$) 1.85 (m, 1 H), 2.1 (m, 1 H), 2.45 (ddd, 1 H), 3.1 (m, 2 H), 3.3 (d, 3 H), 3.65 (m, 1 H), 7.25 (dd, 1 H), 7.75 (ddd, 1 H), 8.5 (bdd, 1 H), 8.65 (bd, 1 H), 9.8 (bs, 1 H). Anal. ($C_{11}H_{14}N_2S_2$) C, H, N, S.

***N*-Methyl-2-(3-pyridyl)tetrahydrofuran-2-carbothioamide (36).** The amide **42b** (5 g, 24 mmol) was treated with Lawesson's reagent (7.7 g, 19 mmol) as described for **28**. The crude product was subjected to flash chromatography eluting with cyclohexane/EtOAc (6:4) and the concentrate recrystallized from i-Pr_2O/EtOH (8:2) to give **36**: yield 1.5 g (28%); mp 128 °C; NMR ($CDCl_3$) 1.95 (m, 2 H), 2.5 (m, 1 H), 3.2 (d, 3 H), 3.25 (m, 1 H), 4.1 (m, 2 H), 7.25 (dd, 1 H), 8.1 (ddd, 1 H), 8.5 (bdd, 1 H), 8.9 (bd, 1 H), 9.0 (bs, 1 H). Anal. ($C_{13}H_{18}N_2S$) C, H, N, S.

***N*-Methyl-1-(3-pyridyl)cyclohexanecarbothioamide (39).** P_2S_5 (6.12 g, 13.7 mmol) was added portionwise to a stirred solution of **42c** (2.5 g, 11.4 mmol) in pyridine (20 mL). The mixture was heated at 90 °C for 2 h, then poured into saturated $NaHCO_3$ solution (100 mL), extracted with EtOAc (3 × 100 mL), dried, and evaporated. The residue was recrystallized from EtOAc to give **39**: yield 1.73 g (65%); mp 163–166 °C; NMR

($CDCl_3$) 1.32–1.55 (m, 4 H), 1.64–1.72 (m, 2 H), 1.9 (s, 1 H), 2.26–2.34 (m, 2 H), 2.44–2.56 (m, 2 H), 3.1 (d, 3 H), 7.3 (m, 2 H), 7.8 (dd, 1 H), 8.54 (d, 1 H), 8.65 (s, 1 H). Anal. ($C_{13}H_{18}N_2S$) C, H, N, S.

***N*-Methyl-1-(3-pyridyl)cyclopentanecarbothioamide (40).** The amide **42d** (10 g, 49 mmol) was treated with Lawesson's reagent (14.9 g, 37 mmol) as described for **28**. The crude product was recrystallized from EtOH to give **40**: yield 7.7 g (71%); mp 169 °C; NMR ($CDCl_3$) 1.65–1.87 (m, 4 H), 2.2–2.7 (m, 4 H), 3.15 (d, 3 H), 7.3 (bs, 1 H), 7.35 (dd, 1 H), 7.8 (bd, 1 H), 8.5 (bd, 1 H), 8.65 (bd, 1 H). Anal. ($C_{12}H_{16}N_2S$) C, H, N, S.

In Vitro Potassium Channel Opening Activity. Male Sprague Dawley rats (200–300 g) were sacrificed and the thoracic aorta removed, cleaned of extraneous fat, and cut into four rings. Each ring was cut into transverse strips and gently rubbed to remove endothelium. The strips of tissue were placed in 20 mL water-jacketed organ baths containing Krebs bicarbonate buffer maintained at 37 °C and gassed with 95% O_2/5% CO_2. Tissues were attached to force-displacement transducers and isometric contractions recorded. Aortae were equilibrated for 90 min under a resting tension of 2 g. Tissues preparations were exposed to 20 mmol KCl. When the maximum mechanical effect had developed, the ability of test compounds to relax the tissues was examined using a cumulative dose–response protocol. As soon as the maximum inhibitory effect of a given concentration of compound had been produced, tissues were exposed to a further concentration of relaxant. To determine whether the relaxants identified were opening an ATP-sensitive K^+ channel the ability of 5 μM glibenclamide, a blocker of this channel, to reverse relaxation was assessed. Drug activity is expressed as IC_{90} values, that is the concentration of drug producing a 90% reduction in maximum contraction produced by 20 mmol KCl. Materials included the Krebs bicarbonate buffer solution which had the following composition (mmol): NaCl, 118; KCl, 4.7; $MgSO_4 \cdot 7H_2O$, 1.2; $CaCl_2$, 2.5; KH_2PO_4, 1.2; $NaHCO_3$, 1.2; glucose, 10.1. All drugs were dissolved in DMSO.

Intravenous Hypotensive Activity in Anaesthetized Rats. Hypotensive studies were conducted in male Sprague Dawley rats (280–350 g) anaesthetized with pentobarbitone sodium (60 mg/kg ip). Blood pressure was recorded from a cannulated carotid artery (PDCR 75 physiological pressure transducer, Lectromed chart recorder) and the blood pressure signal acquired and analyzed using a DEC MINC computer system to obtain measurements of systolic, diastolic, and mean blood pressure (MBP). The trachea was cannulated and artificial ventilation applied (66 breaths/min, 10 mL/kg stroke volume). Compounds were administered via a jugular vein as 15-min intrevenous infusions, each rat receiving only one infusion. Blood pressure monitoring continued for at least 30 min after administration of a compound, and the maximum change in MBP from the preinfusion control period was found. Typically, two or more dose levels of each compound were examined in three or four rats. An estimate of the dose level of a compound inducing a fall in MBP of 30 mm Hg (ED_{30mmHg}) was made using linear regression of change in MBP vs log dose. The compounds were dissolved in polyethylene glycol 200 containing 0.01 N HCl, the resulting solution being diluted 1 to 10 with saline (0.9%) for administration.

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Supplementary Material Available: Tables listing fractional coordinates, anisotropic thermal factors, bond lengths, valence angles, and torsional angles (6 pages). Ordering information is given on any current masthead page.