[Chem. Pharm. Bull. 35(7)2825—2839(1987)]

Synthesis of 2-Phenylthiazolidine Derivatives as Cardiotonic Agents. IV.[1] Modification of the Phenylpiperazino Moiety of 2-(Phenylpiperazinoalkoxyphenyl)thiazolidine-3-carbothioamides and the Corresponding Carboxamides

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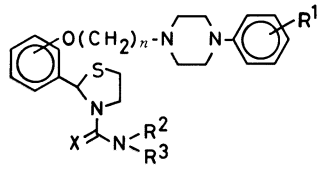
(Received November 28, 1986)

Examination of the structure–activity relationships of 2-(phenylpiperazinoalkoxyphenyl)-thiazolidine-3-carbothioamides and the corresponding carboxamides (**1**) as new cardiotonic agents was extended by the chemical modification of the phenylpiperazino moiety. The 4-phenylpiperidine (**13**), 4-phenyltetrahydropyridines (**17**), and related derivatives were prepared from the chlorides (**10**) through several intermediates (**12**, **14**, and **16**) and tested for cardiotonic activity. Generally, both the 4-phenylpiperidine (**13**) and 4-phenyltetrahydropyridine (**17**) derivatives exhibited potent positive inotropic activity comparable to that of **1**. The *N*-phenylpiperidines (**9**) and amide derivatives (**22**, **25**, and **28**) exhibited no significant positive inotropy. This is also the case for the phenylpropylamines (**29**) and the ethylenediamines (**30**), which are pseudo-ring analogues of **1** with respect to the piperazine moiety. The activity of the homopiperazine derivative (**23**) was approximately one-thirtieth of that of the corresponding piperazine derivative (**1**). Thus, the presence of the six-membered, basic azacycloalkane ring (piperidine or piperazine) with a 4-phenyl group at the end of the alkoxy side chain appears to be essential for the appearance of potent positive inotropic activity in this series of compounds.

Keywords——2-(phenylpiperidinoalkoxyphenyl)thiazolidine-3-carbothioamide; 2-(phenylpiperidinoalkoxyphenyl)thiazolidine-3-carboxamide; 2-(tetrahydropyridylalkoxyphenyl)thiazolidine-3-carbothioamide; 2-(tetrahydropyridylalkoxyphenyl)thiazolidine-3-carboxamide; 2-(phenylhomopiperazinoalkoxyphenyl)thiazolidine-3-carboxamide; 2-phenylthiazolidine; structure–activity relationship; positive inotropic activity; cardiotonic agent

The synthesis and cardiotonic activity of novel 2-phenylthiazolidine-3-carboxamides or carbothioamides (**1**) were described in our previous papers.[1-3] Many of these derivatives exhibited potent and long-lasting positive inotropic activity without producing significant effects on heart rate or blood pressure in anesthetized dogs. In those studies, the structure–activity relationships (SAR) of **1** were examined by varying the structural parameters such as substituents (R^1—R^3, X), length of the alkyl chain (*n*), position of the alkoxyl group, and the chirality at C_2 in the thiazolidine ring. Our continued interest in the SAR of **1** as a new type of cardiotonic agent led to further examination of the effects of modifying the phenylpiperazino moiety. This paper describes the synthesis and cardiotonic activity of the *N*-phenylpiperidine (**9**) and 4-phenylpiperidine (**13** and **17**) congeners, in which one of the two nitrogen atoms of the piperazine was replaced by carbon. Several amide derivatives (**22**, **25**, and **28**), pseudo-ring analogues (**29** and **30**), and the homopiperazine derivative (**23**) were also synthesized and



I

Chart 1

tested for cardiotonic activity.

Chemistry

The *N*-phenylpiperidine congeners (**9**) were synthesized through the sequence of reactions outlined in Chart 2. Wittig reaction of 1-phenyl-4-piperidone (**2**)[4] with methoxymethylenetriphenylphosphorane[5] followed by acidic hydrolysis gave the aldehyde (**3**) in 47% yield. The same procedure effected the homologation of **3** to **4** in 54% yield. Sodium borohydride ($NaBH_4$) reduction of **4** readily gave the alcohol (**5a**). Wittig reaction of **3** with formylmethylenetriphenylphosphorane[6] gave the α,β-unsaturated aldehyde (**6**) in 50% yield. Catalytic hydrogenation and subsequent $NaBH_4$ reduction of **6** gave the alcohol (**5b**) in 60% yield. Tosylation of **5a, b** followed by condensation with salicylaldehyde gave the substituted benzaldehydes (**8a, b**). Reaction of **8a, b** with cysteamine and then with methyl isothiocyanate (MeNCS) readily gave the thiazolidine-3-carbothioamides (**9a, b**).

The 4-phenylpiperidine derivatives (**13**), other carba analogues of phenylpiperazine, were synthesized by the two routes shown in Chart 3. Since this type of compounds exhibited potent cardiotonic activity (see below), a number of derivatives having various substituents were synthesized. Condensation of the chlorides (**10**)[2] with various 4-phenylpiperidines (**11**)[7] followed by acidic hydrolysis gave the substituted benzaldehydes (**12**) listed in Table I. Treatment of **12** with cysteamine and then with methyl isocyanate (MeNCO) or MeNCS gave the thiazolidine-3-carboxamides or 3-carbothioamides (**13**) (method A). Alternatively, condensation of the thiazolidines (**14**)[2] with **11** also afforded **13** (method B). The physical properties of **13** are summarized in Table II. The 4-phenyltetrahydropyridine derivatives (**17**) were also

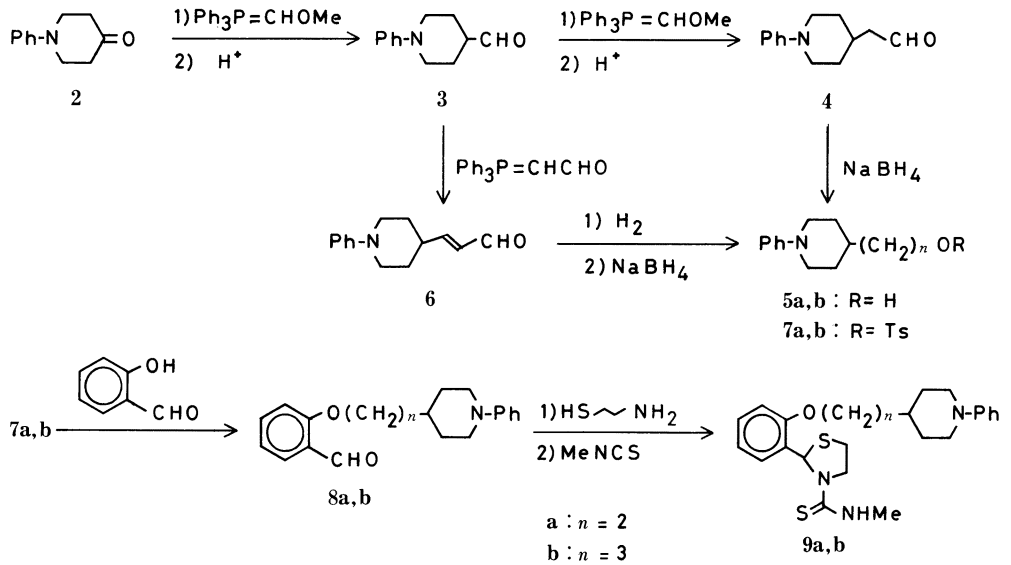
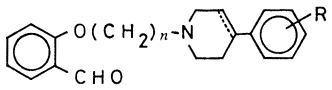


Chart 2

TABLE I. 2-Piperidinoalkoxybenzaldehydes (**12** and **16**)



Compd. No.	*n*	R	Yield (%)	mp (°C) (Recryst. solvent)[a]	^{1}H-NMR δ ($CDCl_3$, J=Hz)
12a	2	H	62.6	59—62 (A)	1.55—2.60 (7H, m), 2.89—3.35 (4H, m), 4.24 (2H, t, J=6), 6.85—7.95 (9H, m), 10.49 (1H, s)
12b	3	H	58.0	—[b]	1.53—2.69 (11H, m), 2.99—3.17 (2H, m), 4.16 (2H, t, J=6), 6.88—7.92 (9H, m), 10.53 (1H, s)
12c	2	3-F	65.9	—[b]	1.60—3.30 (11H, m), 4.27 (2H, t, J=6), 6.70—7.90 (8H, m), 10.56 (1H, s)
12d	3	3-F	63.3	—[b]	1.60—3.30 (13H, m), 4.17 (2H, t, J=6), 6.70—7.90 (8H, m), 10.45 (1H, s)
12e	2	3-Me	41.3	—[b]	1.50—2.70 (7H, m), 2.30 (3H, s), 2.70—3.30 (4H, m), 4.20 (2H, t, J=6), 6.70—7.90 (8H, m), 10.56 (1H, s)
12f	2	4-OMe	59.1	79—82[c] (B)	1.50—2.70 (7H, m), 2.70—3.30 (4H, m), 3.79 (3H, s), 4.28 (2H, t, J=6), 6.70—7.90 (8H, m), 10.56 (1H, s)
12g	3	4-OMe	71.9	52—56[d] (B)	1.50—2.80 (11H, m), 2.80—3.30 (2H, m), 3.76 (3H, s), 4.15 (2H, t, J=6), 6.70—8.00 (8H, m), 10.49 (1H, s)
16a	2	H	21.0	—[b]	2.45—3.10 (6H, m), 3.20—3.45 (2H, m), 4.20 (2H, t, J=6), 6.10 (1H, m), 6.70—7.90 (9H, m), 10.50 (1H, s)
16b	3	H	43.6	—[b]	1.77—2.31 (2H, m), 2.55—2.78 (6H, m), 3.13—3.18 (2H, m), 4.14 (2H, t, J=6), 6.10 (1H, m), 6.80—7.85 (9H, m), 10.46 (1H, s)
16c	2	3-F	61.4	—[b]	2.35—2.75 (2H, m), 2.80—3.10 (2H, m), 3.01 (2H, t, J=5.5), 3.25—3.50 (2H, m), 4.30 (2H, t, J=5.5), 6.12 (1H, m), 6.70—7.95 (8H, m), 10.51 (1H, s)
16d	3	3-F	63.7	—[b]	1.90—2.35 (2H, m), 2.40—3.00 (6H, m), 3.10—3.40 (2H, m), 4.18 (2H, t, J=6.5), 6.10 (1H, m), 6.70—7.90 (8H, m), 10.48 (1H, s)
16e	2	3-Me	40.5	—[b]	2.30—3.20 (6H, m), 2.38 (3H, s), 3.20—3.50 (2H, m), 4.30 (2H, t, J=6), 6.10 (1H, m), 6.70—7.90 (8H, m), 10.50 (1H, s)
16f	2	4-OMe	43.0	124—126[e] (B)	2.35—2.70 (2H, m), 2.70—3.20 (4H, m), 3.20—3.45 (2H, m), 3.79 (3H, s), 4.31 (2H, t, J=6), 5.97 (1H, m), 6.75—7.95 (8H, m), 10.50 (1H, s)
16g	3	4-OMe	39.1	90—93[f] (B)	1.80—2.30 (2H, m), 2.30—2.90 (6H, m), 3.00—3.30 (2H, m), 3.80 (3H, s), 4.20 (2H, t, J=6), 5.99 (1H, m), 6.70—7.90 (8H, m), 10.50 (1H, s)

a) A=Et_2O–hexane, B=AcOEt–hexane. *b*) Obtained as an oil. *c*) *Anal.* Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.15; H, 7.55; N, 4.03. *d*) *Anal.* Calcd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70; N, 3.96. Found: C, 74.59; H, 7.78; N, 3.91. *e*) *Anal.* Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.73; H, 6.81; N, 4.12. *f*) *Anal.* Calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 74.98; H, 7.28; N, 3.91.

synthesized in a similar manner *via* the aldehydes (**16**, Table I) or from **14**, and are listed in Table III.

The effect of conversion of the basic nitrogen in the piperazine moiety to an amido group was examined next. The amide derivatives (**22**, **25**, and **28**) were, therefore, synthesized by the usual method as outlined in Chart 4. Reaction of *N*-phenylethylenediamine (**18**) with benzyloxycarbonyl chloride (CbzCl) followed by treatment with bromoacetyl bromide and cyclization with potassium carbonate in dimethylformamide (DMF) gave the *N*-Cbz-piperazinone (**19**). Reductive removal of the Cbz group by the use of ammonium formate and palladium on carbon in methanol[8] gave the *N*-formyl derivative (**20**) and the desired

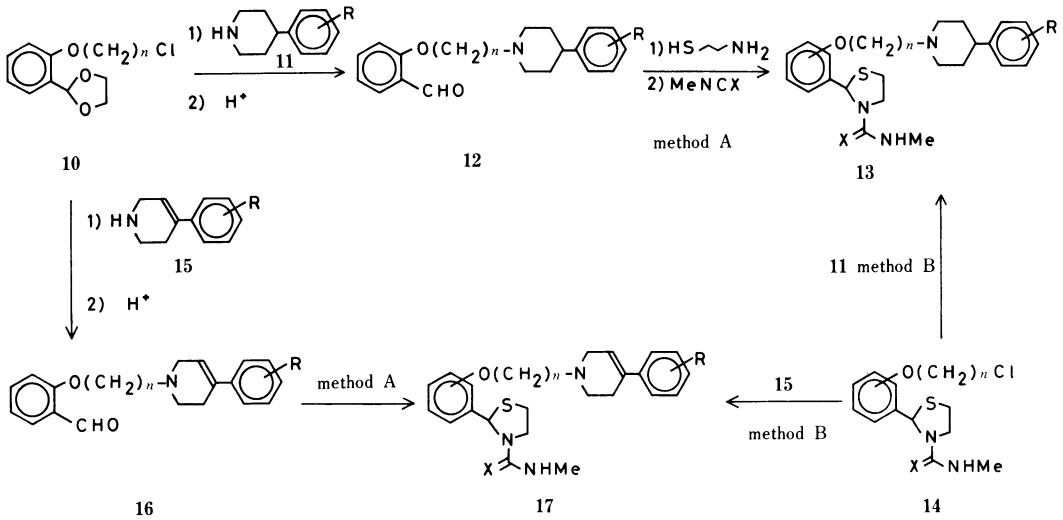


Chart 3

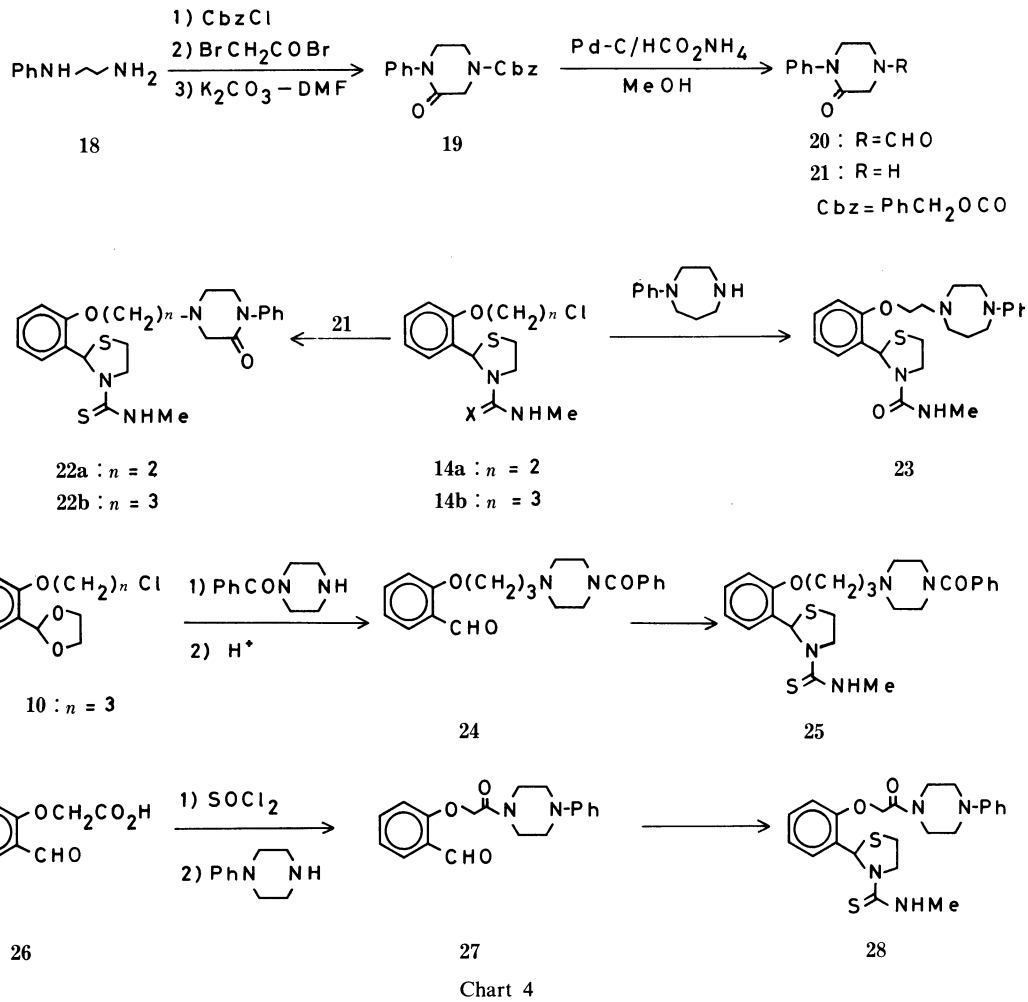


Chart 4

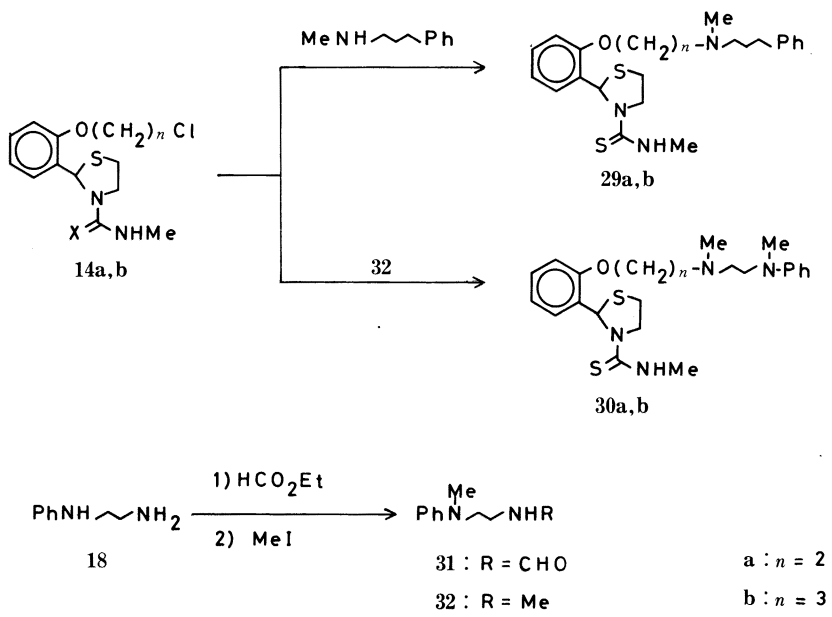


Chart 5

piperazinone (**21**) in 75.4 and 22.9% yields, respectively. Acidic hydrolysis of **20** readily gave **21**. Condensation of the thiazolidines (**14a, b**, X=S) with **21** gave the piperazinone derivatives (**22a, b**). Reaction of **10** ($n=3$)[2] with *N*-benzoylpiperazine[9] followed by acidic hydrolysis gave the aldehyde (**24**). The phenoxyacetic acid derivative (**26**)[3] was condensed with phenylpiperazine *via* the acid chloride to give the aldehyde (**27**). The benzaldehydes (**24** and **27**) were converted to the thiazolidine-3-carbothioamides (**25** and **28**), respectively. The homopiperazine derivative (**23**) was prepared by the reaction of **14a** (X=O) with *N*-phenylhomopiperazine.[10]

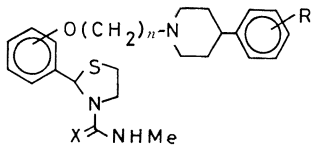
Finally, the straight chain derivatives (**29** and **30**), which may be looked upon as the pseudo-ring analogues of **13** and **1** with respect to the piperidine and piperazine moieties, were synthesized (Chart 5). Formylation of *N*-phenylethylenediamine (**18**) with ethyl formate followed by methylation with methyl iodide gave the formyl derivative (**31**) in 34% yield. Lithium aluminum hydride reduction of **31** readily gave the diamine (**32**). Condensation of **14a, b** (X=S) with *N*-methyl-3-phenylpropylamine[11] and **32** gave the thiazolidines (**29a, b** and **30a, b**), respectively.

Pharmacology and Structure–Activity Relationships

The positive inotropic activity of the piperidines (**13**), 4-phenyltetrahydropyridines (**17**), and related derivatives prepared in this study was determined by measuring the increase in the maximum derivative of left ventricular pressure ($LVdP/dt_{max}$) after i.v. administration to anesthetized dogs by the method reported previously.[12] The results for **13** and **17** are included in Tables II and III together with comparative data for amrinone.

Generally, both the 4-phenylpiperidine (**13**) and 4-phenyltetrahydropyridine (**17**) derivatives exhibited positive inotropic activity comparable to that of the 4-phenylpiperazine derivatives (**1**).[2] As for the positional isomers with respect to the piperidinoalkoxy group, *ortho* isomers were invariably more potent than the corresponding *para* isomers in both the 4-phenylpiperidine (**13**) and 4-phenyltetrahydropyridine (**17**) series. The piperidinoethoxy derivatives ($n=2$) always exhibited more pronounced activity than the corresponding propoxy derivatives ($n=3$) in both series. These SAR are in good accordance with the

TABLE II. 2-(Piperidinoalkoxyphenyl)thiazolidines (**13**)

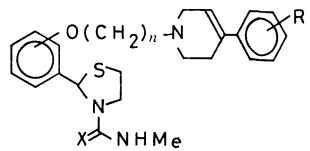


Compd. No.	Position[a]	*n*	R	X	Yield (%)	Method[b]	Salt[c]	mp (dec.) (°C) (Recryst. solvent)[d]	Formula and Analysis (%) Calcd (Found)			Myocardial contractility Anesthetized dog[e]		
										C	H	N	Dose mg/kg i.v.	LV$dP/dt_{max}$ Δ %	Duration min
13a	2	2	H	S	89.3	A	Ox	178—180 (A)	$C_{26}H_{33}N_3O_5S_2$	58.73 (58.56)	6.26 (6.49)	7.90 (7.94)	0.1	30	43
13b	2	3	H	S	51.0	A	HCl	109—129 (B)	$C_{25}H_{34}ClN_3OS_2 \cdot H_2O$	58.86 (58.82)	7.11 (7.04)	8.24 (8.08)	0.3	20	24
13c	2	2	H	O	84.0	B	Ox	168—169 (C)	$C_{26}H_{33}N_3O_6S$	60.56 (60.51)	6.45 (6.43)	8.15 (8.09)	0.1	45	23
13d	2	3	H	O	67.2	B	Ox	113—117 (D)	$C_{27}H_{35}N_3O_6S \cdot 1/2\,H_2O$	60.20 (60.56)	6.74 (6.61)	7.80 (7.94)	1	33	17
13e	2	2	3-F	S	71.9	A	Fum	138—139 (A)	$C_{28}H_{34}FN_3O_5S_2$	58.42 (58.51)	5.95 (6.02)	7.30 (7.18)	0.03	22	25
13f	2	3	3-F	S	90.0	A	Ox	189—191 (C)	$C_{27}H_{34}FN_3O_5S_2$	57.53 (57.49)	6.08 (6.07)	7.45 (7.46)	1	−11	—
13g	2	2	3-F	O	78.0	B	Ox	168—170 (C)	$C_{26}H_{32}FN_3O_6S$	58.52 (58.37)	6.04 (5.98)	7.87 (7.75)	0.01	28	5

13h	2	3	3-F	O	42.2	B	Fum	145—146 (C)	$C_{29}H_{36}FN_3O_6S$ 60.72 6.32 7.32 (60.95 6.20 7.08)	0.1	36	19
13i	2	2	3-Me	S	79.3	A	Ox	152—153 (C)	$C_{27}H_{35}N_3O_5S_2 \cdot H_2O$ 57.53 6.61 7.45 (57.76 6.31 7.42)	0.3	26	18
13j	2	2	3-Me	O	72.0	B	Ox	163—164 (C)	$C_{27}H_{35}N_3O_6S$ 61.23 6.66 7.93 (61.47 6.78 8.07)	0.01	32	5
13k	2	2	3-OMe	S	63.5	B	Ox	154—156 (C)	$C_{27}H_{35}N_3O_6S_2$ 57.73 6.28 7.48 (57.53 6.38 7.60)	0.01	43	10
13l	2	2	3-OMe	O	85.2	B	Ox	142—145 (C)	$C_{27}H_{35}N_3O_7S$ 59.43 6.47 7.70 (59.53 6.48 7.86)	0.01	42	5
13m	2	2	4-OMe	S	76.7	A	Ox	185—187 (A)	$C_{27}H_{35}N_3O_6S_2$ 57.73 6.28 7.48 (57.63 6.24 7.49)	1	38	30
13n	2	3	4-OMe	S	85.0	A	Ox	188—189 (A)	$C_{28}H_{37}N_3O_6S_2$ 58.41 6.48 7.30 (58.44 6.46 7.31)	1	7	15
13o	4	2	H	S	55.4	B	Ox	104—105 (C)	$C_{26}H_{33}N_3O_5S_2$ 58.73 6.26 7.90 (58.58 6.31 7.95)	1	18	27
13p	4	3	H	S	59.8	B	Fum	176—177 (A)	$C_{29}H_{37}N_3O_5S_2$ 60.92 6.52 7.35 (60.69 6.56 7.38)	0.3	18	5
13q	4	2	H	O	98.0	B	Ox	*f*)	$C_{26}H_{33}N_3O_6S$ 60.56 6.45 8.15 (60.36 6.42 8.18)	0.3	27	23
13r	4	3	H	O	70.6	B	Ox	78—80 (E)	$C_{27}H_{35}N_3O_6S$ 61.23 6.66 7.93 (61.03 6.65 7.90)	1	8	20
Amrinone										0.3	25	25

a) The position of the alkoxyl group. *b*) See Experimental. *c*) Ox = oxalate, Fum = fumarate. *d*) A = MeOH–Et_2O, B = iso-PrOH–iso-Pr_2O, C = Me_2CO, D = Me_2CO–EtOH–Et_2O, E = Me_2CO–MeOH–hexane. *e*) For methodology, see reference 12. *f*) Amorphous powder. The spectral data of the free base (oil) were similar to those of **13a** and compatible with the assigned structure.

TABLE III. 2-(Tetrahydropyridylalkoxyphenyl)thiazolidines (**17**)

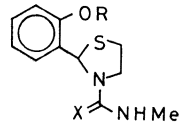


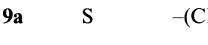
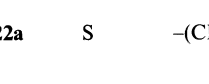
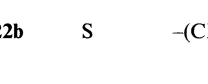
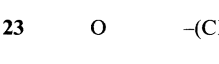
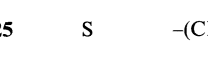
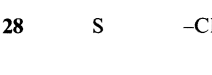
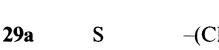
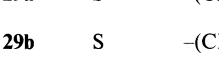
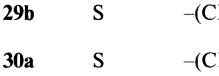
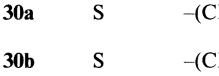
Compd. No.	Position[a]	n	R	X	Yield (%)	Method[b]	Salt[c]	mp (dec.) (°C) (Recryst. solvent)[d]	Formula and Analysis (%) Calcd (Found)			Myocardial contractility Anesthetized dog[e]		
									C	H	N	Dose mg/kg i.v.	LV$dP/dt_{max}$ Δ %	Duration min
17a	2	2	H	S	21.0	A	HCl	210—212 (A)	$C_{24}H_{30}ClN_3OS_2$			0.03	19	58
									60.54 (60.29)	6.35 (6.45)	8.83 (8.74)			
17b	2	3	H	S	20.3	A	HCl	207—210 (A)	$C_{25}H_{32}ClN_3OS_2 \cdot 1/2\,H_2O$			0.03	34	30
									60.16 (60.44)	6.66 (6.76)	8.42 (8.18)			
17c	2	2	H	O	61.0	B	Ox	183—184 (D)	$C_{26}H_{31}N_3O_6S$			0.03	31	32
									60.80 (60.96)	6.08 (5.92)	8.18 (8.06)			
17d	2	3	H	O	64.0	B	Ox	112—115 (E)	$C_{27}H_{33}N_3O_6S$			0.1	30	57
									61.46 (61.25)	6.30 (6.33)	7.96 (7.76)			
17e	2	2	3-F	S	59.5	A	Ox	158—159 (B)	$C_{26}H_{30}FN_3O_5S_2$			0.03	21	20
									57.02 (57.16)	5.52 (5.67)	7.67 (7.75)			
17f	2	3	3-F	S	54.8	A	Ox	201—202 (D)	$C_{27}H_{32}FN_3O_5S_2$			0.3	35	24
									57.74 (57.63)	5.74 (5.72)	7.48 (7.46)			
17g	2	2	3-F	O	58.0	B	Ox	179—181 (D)	$C_{26}H_{30}FN_3O_6S$			0.03	24	22
									58.74 (58.78)	5.69 (5.67)	7.90 (7.75)			

17h	2	3	3-F	O	34.8	B	Ox	139—142 (D)	$C_{27}H_{32}FN_3O_6S \cdot 1/2\,H_2O$ 58.47 6.00 7.58 (58.60 5.76 7.74)	1	−16	—
17i	2	2	3-Me	S	78.8	A	Ox	156—158 (D)	$C_{27}H_{33}N_3O_5S_2 \cdot H_2O$ 57.73 6.28 7.48 (57.40 5.91 7.72)	0.3	39	32
17j	2	3	3-Me	S	49.1	B	Ox	162—165 (G)	$C_{28}H_{35}N_3O_5S_2$ 60.30 6.33 7.54 (60.44 6.33 7.62)	0.1	27	22
17k	2	2	3-Me	O	49.0	B	Ox	175—176 (D)	$C_{27}H_{33}N_3O_6S$ 61.46 6.30 7.96 (61.28 6.26 7.74)	0.3	47	25
17l	2	2	3-OMe	S	35.3	B	Ox	151—152 (F)	$C_{27}H_{33}N_3O_6S_2$ 57.94 5.94 7.51 (58.04 6.05 7.49)	0.03	30	35
17m	2	2	3-OMe	O	58.1	B	Ox	177—178 (E)	$C_{27}H_{33}N_3O_7S$ 59.65 6.12 7.73 (59.81 6.14 7.78)	0.1	29	22
17n	2	2	4-OMe	S	88.1	A	Ox	144—146 (B)	$C_{27}H_{33}N_3O_6S_2$ 57.94 5.94 7.51 (57.80 5.93 7.61)	0.3	27	20
17o	2	3	4-OMe	S	89.8	A	Ox	188—190 (C)	$C_{28}H_{35}N_3O_6S_2$ 58.62 6.15 7.32 (58.53 6.10 7.40)	1	12	25
17p	4	2	H	S	48.4	B	Ox	116—120 (D)	$C_{26}H_{31}N_3O_5S_2 \cdot 1/3\,H_2O$ 58.30 5.96 7.84 (58.29 5.93 7.75)	0.03	−4	—
17q	4	3	H	S	53.8	B	Fum	167—169 (H)	$C_{29}H_{35}N_3O_5S_2$ 61.14 6.19 7.38 (61.03 6.21 7.41)	0.3	19	12
17r	4	2	H	O	84.0	B	Ox	120—121 (F)	$C_{26}H_{31}N_3O_6S \cdot 1/2\,C_2H_5OH$ 60.43 6.39 7.83 (60.71 6.58 7.70)	1	22	15
17s	4	3	H	O	51.0	B	Ox	115—116 (F)	$C_{27}H_{33}N_3O_6S$ 61.46 6.30 7.96 (61.26 6.37 7.93)	0.1	−9	—

a—c) See footnotes *a—c* in Table II, respectively. *d*) A = MeOH–EtOH–Et_2O, B = MeOH–Et_2O, C = aq. MeOH, D = Me_2CO, E = EtOH–Et_2O, F = EtOH, G = Me_2CO–EtOH–Et_2O, and H = Me_2CO–MeOH–Et_2O. *e*) See footnote *e* in Table II.

TABLE IV. 2-(Aminoalkoxyphenyl)thiazolidines



Compd.	X	R	Dose mg/kg i.v.	Myocardial contractility Anesthetized dog[a] LVdP/dt_{max} Δ%	Duration min
9a	S		1	0	0
9b	S		1	0	0
22a	S		1	9	20
22b	S		1	25	7
23	O		0.1	28	21
25	S		1	−5	—
28	S		1	−4	—
29a	S		1	−8	—
29b	S		1	−21	—
30a	S		1	27	24
30b	S		1	14	25

a) See footnote *e* in Table II.

previous observation in the phenylpiperazine series (**1**).[2] Decrease in activity, previously seen with the phenylpiperazine series on converting the carboxamido group to the carbothioamido group, was not apparent in this series of compounds. Thus, no significant change in activity was noted between the carbothioamides (**13a** and **17a**) and the corresponding carboxamides (**13c** and **17c**). There is little uniformity in the effect of the substituents (R) on the benzene ring of **13** and **17**. In the piperidine series (**13**), a marked enhancement of activity was observed on fluoro substitution (**13a** *vs.* **13e** and **13c** *vs.* **13g**) in accordance with the previous experience in the piperazine series.[2] This favorable effect, however, was not apparent in the 4-phenyltetrahydropyridine series (**17**). Generally, 4-phenyltetrahydropyridine derivatives exhibited more potent positive inotropy than the corresponding piperidine derivatives. Compounds **17a—d** were thus from three to ten times more potent than **13a—d**.

None of the *N*-phenylpiperidines (**9**), amide derivatives (**22**, **25**, and **28**), and pseudo-ring derivatives (**29** and **30**) exhibited significant positive inotropy even at 1 mg/kg. The homopipe-

razine derivative (**23**) produced a 28% increase in $LVdP/dt_{max}$ at 0.1 mg/kg (Table IV). Thus, the activity of **23** is approximately one-thirtieth of that of the corresponding piperazine derivative (**1**, $R^1=R^2=H$, $R^3=Me$, X=O, *ortho* isomer), which exhibited a 30% increase in $LVdP/dt_{max}$ at 0.003 mg/kg.[2)]

In summary, the presence of the six-membered, basic azacycloalkane ring (piperidine or piperazine) with a 4-phenyl group as an amino function at the end of the alkoxy side chain appears to be essential for the appearance of potent positive inotropic activity in this series of compounds.

Further studies on the synthesis and SAR of 2-phenylthiazolidine-3-carbothioamides and the corresponding carboxamides as new cardiotonic agents are being continued.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi IR-215 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz on a JEOL PMX-60 spectrometer with tetramethylsilane (TMS) as an internal reference. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. Mass spectra (MS) were measured with a Hitachi RMU-6M instrument.

1-Phenyl-4-piperidinecarbaldehyde (3)——A solution of lithium diisopropylamide [prepared from diisopropylamine (6.92 g), BuLi (43.8 ml of 15% hexane solution), and tetrahydrofuran (THF) (50 ml)] was added to a stirred suspension of methoxymethyltriphenylphosphonium chloride[5)] (23.5 g, 0.064 mol) in THF (150 ml) at −20 °C. The mixture was stirred at −20 °C for 30 min, then a solution of **2**[4)] (9.35 g, 0.0534 mol) was added to the mixture at −40 °C, and the whole was stirred at room temperature overnight. The mixture was diluted with H_2O and extracted with AcOEt. The organic layer was dried and evaporated. The residue was purified by SiO_2 chromatography (C_6H_6) to give 6 g of an oil. A mixture of this oil, 10% HCl (20 ml), and THF (40 ml) was stirred at room temperature overnight, made basic with K_2CO_3, and extracted with AcOEt. The extracts were washed with H_2O, dried, and evaporated. The residue was purified by column chromatography (SiO_2, AcOEt–hexane (1:4)) to give 4.7 g (46.7% from **2**) of **3** as an oil. IR ν_{max}^{liquid} cm^{-1}: 1720, 1600, 1500. MS *m/z*: 189 (M^+), 161, 160, 132. ^{1}H-NMR ($CDCl_3$) δ: 1.70—2.10 (4H, m), 2.10—2.55 (1H, m), 2.55—3.15 (2H, m), 3.52 (1H, t, J=4 Hz), 3.74 (1H, t, J=4 Hz), 6.85—7.40 (5H, m), 9.70 (1H, s).

1-Phenyl-4-piperidineacetaldehyde (4)——This compound was obtained from **3** by the same procedure as described above in 54.3% yield as an oil. IR ν_{max}^{liquid} cm^{-1}: 1720. MS *m/z*: 203 (M^+), 175, 174. ^{1}H-NMR ($CDCl_3$) δ: 1.05—2.10 (5H, m), 2.30—3.10 (4H, m), 3.70 (2H, br d, J=12 Hz), 6.65—7.10 (5H, m), 9.80 (1H, t, J=2 Hz).

1-Phenyl-4-piperidineethanol (5a)——A mixture of **4** (2.9 g, 0.0143 mol), $NaBH_4$ (2.2 g, 0.0582 mol), and EtOH (30 ml) was stirred at room temperature for 1 h. The usual work-up and purification by SiO_2 chromatography (C_6H_6–AcOEt (4:1)) gave **5a** (2.6 g, 88.7%) as an oil. IR ν_{max}^{liquid} cm^{-1}: 3300, 1590. MS *m/z*: 205 (M^+), 204, 174. ^{1}H-NMR ($CDCl_3$) δ: 1.00—2.10 (8H, m), 2.70 (2H, br t, J=11 Hz), 3.50—4.00 (4H, m), 6.75—7.45 (5H, m).

3-(1-Phenyl-4-piperidyl)-2-propenal (6)——A solution of **3** (3 g, 0.0159 mol) and formylmethylenetriphenylphosphorane[6)] (4.83 g, 0.0159 mol) in benzene (40 ml) was refluxed overnight. Evaporation of the mixture and purification of the residue by SiO_2 chromatography (C_6H_6–AcOEt (9:1)) gave 1.7 g (50%) of **6** as an oil. IR ν_{max}^{liquid} cm^{-1}: 1680. MS *m/z*: 215 (M^+), 158. ^{1}H-NMR ($CDCl_3$) δ: 1.40—2.10 (4H, m), 2.55—3.10 (3H, m), 3.40—4.00 (2H, m), 6.12 (1H, dd, J=7 Hz and 2 Hz), 6.60—7.60 (6H, m).

1-Phenyl-4-piperidinepropanol (5b)——A mixture of **6** (1.7 g, 0.0079 mol), 10% Pd–C (0.5 g), and EtOH (30 ml) was hydrogenated at room temperature and ordinary pressure. The catalyst was filtered off, and $NaBH_4$ (1.2 g, 0.0317 mol) was added to the filtrate. After being stirred at room temperature for 1 h, the mixture was concentrated, diluted with H_2O, and extracted with AcOEt. The extracts were washed with H_2O, dried, and evaporated. Chromatographic purification of the residue (SiO_2, C_6H_6–AcOEt (4:1)) gave 1.04 g (60%) of **5b** as a wax. IR ν_{max}^{Nujol} cm^{-1}: 3280, 1590. MS *m/z*: 220, 219 (M^+), 218, 174, 132. ^{1}H-NMR ($CDCl_3$) δ: 1.05—2.10 (10H, m), 2.70 (2H, br t, J=12 Hz), 3.45—3.90 (4H, m), 6.60—7.40 (5H, m).

1-Phenyl-4-piperidineethanol *O*-Tosylate (7a)——A mixture of **5a** (2.6 g, 0.0127 mol), *p*-toluenesulfonyl chloride (2.9 g, 0.0152 mol), pyridine (4 ml), and CH_2Cl_2 (40 ml) was stirred at room temperature overnight. The mixture was worked up in the usual manner and purified by chromatography (SiO_2, C_6H_6–AcOEt (9:1)) to give 2.3 g (50%) of **7a** as an oil. IR ν_{max}^{liquid} cm^{-1}: 1600, 1360. MS *m/z*: 359 (M^+), 204, 188. ^{1}H-NMR ($CDCl_3$) δ: 1.00—1.95 (7H, m), 2.00—3.00 (5H, m), 3.65 (2H, br d, J=11 Hz), 4.10 (2H, t, J=6 Hz), 7.80 (2H, d, J=8 Hz).

1-Phenyl-4-piperidinepropanol *O*-Tosylate (7b)——The carbinol (**5b**) was tosylated in the same manner as described above to give 61.5% yield of **7b**, mp 78—80 °C (from AcOEt–hexane). *Anal.* Calcd for $C_{21}H_{27}NO_3S$: C, 67.53; H, 7.29; N, 3.75; S, 8.58. Found: C, 67.59; H, 7.24; N, 3.60; S, 8.38. IR ν_{max}^{Nujol} cm^{-1}: 1590, 1380. MS *m/z*: 373

(M^+), 202. ^{1}H-NMR ($CDCl_3$) δ: 1.00—2.20 (9H, m), 2.20—3.15 (5H, m), 3.70 (2H, br d, J=11 Hz), 4.06 (2H, t, J=6 Hz), 6.60—7.50 (7H, m), 7.80 (2H, d, J=8 Hz).

2-(2-(1-Phenyl-4-piperidyl)ethoxy)benzaldehyde (8a)——A mixture of **7a** (2.3 g, 0.0064 mol), salicylaldehyde (0.78 g, 0.0064 mol), K_2CO_3 (0.81 g, 0.0064 mol), and DMF (40 ml) was heated at 50 °C overnight. The mixture was concentrated, diluted with H_2O, and extracted with AcOEt. The extracts were washed with H_2O, dried, and evaporated. The residue was purified by chromatography (SiO_2, hexane–AcOEt (4:1)) to give 1.41 g (71.2%) of **8a**, mp 46—49 °C (from AcOEt–hexane). *Anal.* Calcd for $C_{20}H_{23}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.51; H, 7.38; N, 4.49. IR ν_{max}^{Nujol} cm^{-1}: 1680. MS *m/z*: 309 (M^+), 188, 158. ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.30 (7H, m), 2.30—3.10 (2H, m), 3.50—3.90 (2H, m), 4.16 (2H, t, J=6 Hz), 6.60—8.00 (9H, m), 10.50 (1H, s).

2-(3-(1-Phenyl-4-piperidyl)propoxy)benzaldehyde (8b)——Condensation of **7b** with salicylaldehyde in the same manner as described for **7a** gave 93.8% yield of **8b**, mp 65—67 °C (from AcOEt–hexane). *Anal.* Calcd for $C_{21}H_{25}NO_2$: C, 77.99; H, 7.79; N, 4.33. Found: C, 78.05; H, 7.75; N, 4.27. IR ν_{max}^{Nujol} cm^{-1}: 1680. MS *m/z*: 323 (M^+), 203, 158. ^{1}H-NMR ($CDCl_3$) δ: 1.00—2.30 (9H, m), 2.45—3.10 (2H, m), 3.70 (2H, br d, J=12 Hz), 4.10 (2H, t, J=6 Hz), 6.65—7.95 (9H, m), 10.48 (1H, s).

***N*-Methyl-2-(2-(2-(1-phenyl-4-piperidyl)ethoxy)phenyl)thiazolidine-3-carbothioamide (9a)**——A mixture of **8a** (1.4 g, 0.00453 mol), cysteamine hydrochloride (0.57 g, 0.00498 mol), NaOH (0.21 g, 0.0052 mol), and EtOH (40 ml) was stirred at room temperature for 2 h. MeNCS (0.46 g, 0.00634 mol) was added, and the whole was stirred at room temperature overnight and then refluxed for 1 h. The reaction mixture was concentrated, diluted with H_2O, and extracted with AcOEt. Evaporation of the dried extracts gave, after recrystallization from AcOEt–hexane, 1.55 g (77.6%) of **9a**, mp 151—152 °C. IR ν_{max}^{Nujol} cm^{-1}: 3420, 1590. MS *m/z*: 441 (M^+), 367, 335, 290, 188, 185. ^{1}H-NMR ($CDCl_3$) δ: 1.10—2.30 (7H, m), 2.40—3.30 (7H, m), 3.70 (2H, br d, J=12 Hz), 4.00—4.80 (4H, m), 5.40 (1H, br s), 6.34 (1H, s), 6.60—7.60 (9H, m). The fumarate was recrystallized from Me_2CO–hexane and had mp 152—153 °C. *Anal.* Calcd for $C_{28}H_{35}N_3O_5S_2$: C, 60.30; H, 6.33; N, 7.53; S, 11.50. Found: C, 60.47; H, 6.32; N, 7.77; S, 11.45.

***N*-Methyl-2-(2-(3-(1-phenyl-4-piperidyl)propoxy)phenyl)thiazolidine-3-carbothioamide (9b)**——Treatment of **8b** with cysteamine and then with MeNCS in the same manner as described above gave 50.6% yield of **9b**, mp 126—130 °C (from AcOEt–hexane). The fumarate was recrystallized from Me_2CO–hexane and had mp 129—131 °C (dec.). *Anal.* Calcd for $C_{29}H_{37}N_3O_5S_2$: C, 60.92; H, 6.52; N, 7.35; S, 11.22. Found: C, 60.81; H, 6.46; N, 7.38; S, 11.37.

2-(2-(4-Phenyl-1-piperidyl)ethoxy)benzaldehyde (12a)——A mixture of **10** (n=2)[2] (2.84 g, 0.0124 mol), 4-phenylpiperidine (**11**, R=H, 2 g, 0.0124 mol), K_2CO_3 (1.89 g, 0.0137 mol), and DMF (20 ml) was heated at 80 °C for 22 h. The mixture was diluted with H_2O and extracted with AcOEt. The extracts were washed with H_2O, dried, and evaporated. The residue was purified by chromatography (SiO_2, C_6H_6–AcOEt (3:2)) to give 2.74 g of an oil. A mixture of this oil, 10% HCl (20 ml), and MeOH (20 ml) was heated at 70 °C for 20 min. The mixture was diluted with H_2O, made basic with 10% aq. NaOH, and extracted with benzene. The extracts were washed with H_2O, dried, and evaporated. Recrystallization of the residue from Et_2O–hexane gave 1.54 g (62.6%) of **12a**, mp 59—62 °C. IR ν_{max}^{Nujol} cm^{-1}: 1680. MS *m/z*: 309 (M^+), 174. *Anal.* Calcd for $C_{20}H_{33}NO_2$: C, 77.64; H, 7.49; N, 4.53. Found: C, 77.52; H, 7.54; N, 4.41. The substituted benzaldehydes (**12b—g**) were prepared in a similar manner and their physical properties are summarized in Table I.

***N*-Methyl-2-(2-(2-(4-phenyl-1-piperidyl)ethoxy)phenyl)thiazolidine-3-carbothioamide (13a) (Method A)**——A mixture of **12a** (1.5 g, 0.00485 mol), cysteamine hydrochloride (0.61 g, 0.00534 mol), NaOH (0.22 g, 0.00558 mol), and EtOH (30 ml) was refluxed for 1 h. MeNCS (0.57 g, 0.00776 mol) was then added to the mixture, and the whole was refluxed for 1.5 h. The mixture was evaporated, diluted with H_2O, and extracted with AcOEt. The extracts were washed with H_2O, dried, and evaporated. Recrystallization of the residue from aq. EtOH gave 1.91 g (89.3%) of **13a**, mp 141—142 °C. IR ν_{max}^{Nujol} cm^{-1}: 3220, 1600. MS *m/z*: 441 (M^+), 368, 308. ^{1}H-NMR ($CDCl_3$) δ: 1.60—2.10 (4H, m), 2.10—2.60 (3H, m), 2.80—3.40 (10H, m), 4.10—4.80 (4H, m), 5.64 (1H, br), 6.35 (1H, s), 6.75—7.60 (9H, m). Analytical data are included in Table II. The thiazolidine-3-carbothioamides (**13**) prepared by method A are listed in Table II.

***N*-Methyl-2-(4-(3-(4-phenyl-1-piperidyl)propoxy)phenyl)thiazolidine-3-carboxamide (13r) (Method B)**——A mixture of 1.89 g (0.006 mol) of **14** (X=O, *para*-substituted, n=3),[2] NaI (0.9 g, 0.006 mol), K_2CO_3 (0.83 g, 0.006 mol), 4-phenylpiperidine (**11**, R=H, 0.97 g, 0.006 mol), and DMF (20 ml) was heated at 80 °C overnight. The usual work-up gave 1.86 g (70.6%) of **13r**, mp 129—131 °C (from AcOEt–Me_2CO–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3380, 1620. MS *m/z*: 439 (M^+), 382, 381, 322, 174. ^{1}H-NMR ($CDCl_3$) δ: 1.50—2.35 (9H, m), 2.35—2.90 (6H, m), 2.90—3.30 (4H, m), 3.60—4.50 (5H, m), 6.33 (1H, s), 6.90 (2H, d, J=9 Hz), 7.25 (5H, s), 7.23 (2H, d, J=9 Hz). *Anal.* Calcd for $C_{25}H_{33}N_3O_2S$: C, 68.30; H, 7.57; N, 9.56; S, 7.29. Found: C, 68.57; H, 7.62; N, 9.67; S, 7.13. Analytical data are included in Table II. Other 4-phenylpiperidine derivatives (**13**) prepared by method B are listed in Table II.

2-(1,2,5,6-Tetrahydro-4-phenyl-1-pyridyl)alkoxybenzaldehydes (16)——These compounds were prepared by the condensation of **10** with **15**[13] in the same manner as described for the piperidine derivative (**12**) and are listed in Table I.

2-((1,2,5,6-Tetrahydro-4-phenyl-1-pyridyl)alkoxy)phenyl-*N*-methylthiazolidine-3-carboxamides or -carbothioamides (17)——These compounds were prepared from the aldehyde (**16**) by method A or from **14** by method B in the same manner as described for the piperidine derivative (**13**). Their physical properties are summarized in Table

III.

4-Benzyloxycarbonyl-1-phenyl-2-piperazinone (19)——*N*-Phenylethylenediamine (**18**) (8 g, 0.0587 mol) was allowed to react with CbzCl (10 g, 0.0587 mol) and NEt_3 (6.54 g, 0.0645 mol) in THF (150 ml) in the usual manner to give 15.8 g of the *N*-Cbz derivative. Schotten–Baumann reaction of this material with bromoacetyl bromide (12.2 g, 0.06 mol) and 10% aq. NaOH (30 ml) in AcOEt (150 ml) gave 22.4 g of the bromoacetyl derivative as an oil. A mixture of this oil, K_2CO_3 (25 g), and DMF (120 ml) was stirred at room temperature for 2 d. An insoluble material was filtered off, and the filtrate was evaporated, diluted with H_2O, and extracted with AcOEt. Evaporation of the extracts and purification of the residue by chromatography (SiO_2, C_6H_6–AcOEt (5 : 1)) gave 12.7 g (79.7% from **18**) of **19**, mp 87—88 °C (from Et_2O–hexane). IR ν_{max}^{Nujol} cm^{-1}: 1700, 1665, 1600, 1500. MS *m/z*: 310 (M^+), 219, 196, 191, 175, 91. ^{1}H-NMR ($CDCl_3$) δ: 3.60—4.00 (4H, m), 4.36 (2H, s), 5.21 (2H, s), 7.20—7.60 (10H, m). *Anal.* Calcd for $C_{18}H_{18}N_2O_3$: C, 69.66; H, 5.85; N, 9.03. Found: C, 69.87; H, 5.80; N, 8.89.

1-Phenyl-2-piperazinone (21)——A mixture of **19** (12.3 g, 0.0396 mol), HCO_2NH_4 (5 g, 0.0792 mol), 10% Pd–C (2.4 g), and MeOH (150 ml) was stirred at room temperature for 10 min and evaporated. The residue was chromatographed over SiO_2 and eluted with $CHCl_3$–EtOH (20 : 1). The first eluate gave 6.1 g (75.4%) of the *N*-formyl derivative (**20**), mp 97—99 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 1650, 1595, 1495, 750, 690. MS *m/z*: 204 (M^+), 160, 106, 77. ^{1}H-NMR ($CDCl_3$) δ: 3.60—4.00 (4H, m), 4.18 (1H, s), 4.16 (1H, s), 7.10—7.60 (5H, m), 8.11 (1H, s). *Anal.* Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.72; H, 5.88; N, 13.58. The second eluate gave, after recrystallization from Et_2O–hexane, 1.6 g (22.9%) of **21**, mp 93—94 °C. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1640, 1585, 1490, 760, 690. MS *m/z*: 176 (M^+), 148, 106, 77. ^{1}H-NMR ($CDCl_3$) δ: 1.88 (1H, s), 3.09—3.25 (2H, m), 3.65 (2H, s), 3.58—3.74 (2H, m), 7.16—7.52 (5H, m). *Anal.* Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.35; H, 6.80; N, 15.85. Refluxing of the *N*-formyl derivative (**20**) with conc. HCl in MeOH gave **21** in 92.8% yield.

***N*-Methyl-2-(2-(2-(3-oxo-4-phenylpiperazino)ethoxy)phenyl)thiazolidine-3-carbothioamide (22a)**——A mixture of **14a** (X=S)[2] (2.5 g, 0.00789 mol), **21**·HCl (1.75 g, 0.00789 mol), K_2CO_3 (2.18 g, 0.0158 mol), NaI (1.18 g, 0.00789 mol), and DMF (20 ml) was heated at 80 °C overnight. The mixture was worked up in the usual manner and purified by chromatography (SiO_2, $CHCl_3$–AcOEt–Me_2CO (5 : 4 : 1)). Recrystallization from $CHCl_3$–MeOH–hexane gave 0.82 g (22.8%) of **22a**, mp 207—209 °C. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1640. MS *m/z*: 456 (M^+), 383, 306, 203, 202, 200. ^{1}H-NMR ($CDCl_3$–DMSO-d_6) δ: 2.80—3.30 (9H, m), 3.40 (2H, s), 3.71 (2H, br t, J=7 Hz), 3.95—4.00 (5H, m), 6.80—7.50 (9H, m). *Anal.* Calcd for $C_{23}H_{28}N_4O_2S_2$: C, 60.50; H, 6.18; N, 12.27; S, 14.04. Found: C, 60.29; H, 6.09; N, 12.43; S, 14.28. The oxalate was recrystallized from $CHCl_3$–MeOH–hexane and had mp 125—127 °C (dec.). *Anal.* Calcd for $C_{25}H_{30}N_4O_6S_2$: C, 54.93; H, 5.53; N, 10.25; S, 11.73. Found: C, 54.93; H, 5.66; N, 10.35; S, 11.35. The propoxy analogue (**22b**) was similarly obtained by the condensation of **14b** (X=S) with **21** in 38.3% yield. mp 190—195 °C (from $CHCl_3$–AcOEt–hexane). The oxalate was recrystallized from MeOH and had mp 178—179.5 °C (dec.). *Anal.* Calcd for $C_{26}H_{32}N_4O_6S_2 \cdot 0.25\,H_2O$: C, 55.25; H, 5.80; N, 9.91; S, 11.34. Found: C, 55.28; H, 5.91; N, 9.90; S, 11.38.

2-(2-(2-(Hexahydro-4-phenyl-1,4-diazepin-1-yl)ethoxy)phenyl)-*N*-methylthiazolidine-3-carboxamide (23)——A mixture of **14** (X=O, n=2, 1.65 g, 0.0055 mol), hexahydro-4-phenyl-1,4-diazepine[10] (0.97 g, 0.0055 mol), K_2CO_3 (0.76 g, 0.0055 mol), NaI (0.82 g, 0.0055 mol), and DMF (20 ml) was allowed to react in the same manner as described above. Chromatographic purification (SiO_2, AcOEt–MeOH (30 : 1)) gave 1.84 g (76%) of **23**, mp 117—120 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3325, 1630, 1595, 760. MS *m/z*: 440 (M^+), 425, 382, 203, 189. ^{1}H-NMR ($CDCl_3$) δ: 1.80—2.20 (2H, m), 2.60—3.30 (11H, m), 3.40—3.80 (4H, m), 3.80—4.60 (5H, m), 6.20 (1H, s), 6.50—7.40 (9H, m). The oxalate was recrystallized from Me_2CO–Et_2O and had mp 168—170 °C (dec.). *Anal.* Calcd for $C_{26}H_{34}N_4O_6S$: C, 58.85; H, 6.46; N, 10.56; S, 6.04. Found: C, 59.12; H, 6.55; N, 10.64; S, 5.97.

2-(3-(4-Benzoylpiperazino)propoxy)benzaldehyde (24)——A mixture of *N*-benzoylpiperazine hydrochloride[9] (2.3 g, 0.01 mol), **10**[2] (n=3; 2.43 g, 0.01 mol), K_2CO_3 (4 g, 0.029 mol), and DMF (30 ml) was heated at 80—100 °C overnight. The usual work-up and chromatographic purification (SiO_2, $CHCl_3$–acetone (4 : 1)) gave 2.29 g (64.9%) of **24** as an oil. IR ν_{max}^{liquid} cm^{-1}: 1685, 1635, 1600. MS *m/z*: 352 (M^+), 218, 203, 148, 105. ^{1}H-NMR ($CDCl_3$) δ: 1.93—2.25 (2H, m), 2.40—2.93 (6H, m), 3.30—3.80 (4H, m), 4.10 (2H, t, J=6 Hz), 6.93—8.26 (4H, m), 7.40 (5H, s).

2-(2-(3-(4-Benzoylpiperazino)propoxy)phenyl)-*N*-methylthiazolidine-3-carbothioamide (25)——The usual treatment of **24** with cysteamine and MeNCS gave **25** in 88.8% yield as an oil. IR ν_{max}^{Nujol} cm^{-1}: 3300, 1620. MS *m/z*: 484 (M^+), 411, 351, 229, 203, 201. ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.12 (2H, m), 2.99 (3H, d, J=4.6 Hz), 3.40—3.80 (4H, m), 5.44—5.52 (12H, m), 6.32 (1H, s), 6.82—7.18 (4H, m), 7.36 (5H, m). The hydrochloride was recrystallized from EtOH and had mp 206—208 °C (dec.). *Anal.* Calcd for $C_{25}H_{33}ClN_4O_2S_2$: C, 57.62; H, 6.38; Cl, 6.80; N, 10.75; S, 12.31. Found: C, 57.48; H, 6.41; Cl, 6.82; N, 10.66; S, 12.18.

2-(((4-Phenylpiperazino)carbonyl)methoxy)benzaldehyde (27)——A mixture of the carboxylic acid (**26**)[3] (2.8 g, 0.016 mol), $SOCl_2$ (3 ml), and benzene (20 ml) was refluxed for 2 h and evaporated. The residual acid chloride was allowed to react with phenylpiperazine (2.64 g, 0.0165 mol), 10% aq. NaOH (20 ml), and CH_2Cl_2 (40 ml) with vigorous stirring. The mixture was evaporated, and the residue was dissolved in 10% aq. HCl (10 ml) and MeOH (30 ml). The mixture was evaporated, diluted with H_2O, made basic with 10% aq. NaOH, and extracted with AcOEt. The extracts were washed with H_2O, dried, and evaporated. Chromatographic purification of the residue gave 2.9 g (59.7%) of **27**, mp 117—118 °C (from AcOEt–hexane). IR ν_{max}^{Nujol} cm^{-1}: 1670, 1655, 1590, 760. ^{1}H-NMR ($CDCl_3$) δ:

3.06—3.22 (4H, m), 3.68—3.84 (4H, m), 4.86 (2H, s), 6.75—7.92 (9H, m), 10.48 (1H, s). *Anal.* Calcd for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.21; N, 8.64. Found: C, 70.31; H, 6.19; N, 8.60.

***N*-Methyl-2-(2-(((4-phenylpiperazino)carbonyl)methoxy)phenyl)thiazolidine-3-carbothioamide (28)**——Reaction of **27** with cysteamine and MeNCS in the usual manner gave 92.1% yield of **28**, mp 188—189 °C (from $CHCl_3$–EtOH). IR ν_{max}^{Nujol} cm^{-1}: 3280, 1630, 1595, 750. MS *m/z*: 382, 220, 202, 160, 132 (M^+ was not seen). ^{1}H-NMR ($CDCl_3$) δ: 2.98 (3H, d, J=4.5 Hz), 4.89 and 5.04 (2H, ABq, J=15 Hz), 6.63 (1H, s), 6.74—7.40 (9H, m). *Anal.* Calcd for $C_{23}H_{28}N_4O_2S_2$: C, 60.50; H, 6.18; N, 12.27; S, 14.04. Found: C, 60.51; H, 6.15; N, 12.36; S, 13.76.

***N*-Methyl-2-(2-(2-(*N*-methyl-3-phenylpropylamino) ethoxy) phenyl) thiazolidine-3-carbothioamide (29a)**——Condensation of **14a** (X=S) with *N*-methyl-3-phenylpropylamine[11] by the usual method gave **29a** in 84% yield as an oil. IR ν_{max}^{liquid} cm^{-1}: 3400, 3300, 1590. MS *m/z*: 429 (M^+), 356, 295, 162, 160, 91, 71, 58. ^{1}H-NMR ($CDCl_3$) δ: 1.50—2.10 (2H, m), 2.20—3.20 (14H, m), 3.90—4.90 (4H, m), 5.40—5.80 (1H, m), 6.25 (1H, s), 6.70—7.50 (9H, m). The oxalate, mp 171—172 °C (dec.), was recrystallized from EtOH. *Anal.* Calcd for $C_{25}H_{33}N_3O_5S$: C, 57.78; H, 6.40; N, 8.09; S, 12.34. Found: C, 57.47; H, 6.35; N, 8.33; S, 12.30.

The propoxy analogue (**29b**) was similarly prepared from **14b** (X=S) in 82% yield. The oxalate, mp 152—153 °C (dec.), was recrystallized from EtOH. *Anal.* Calcd for $C_{26}H_{35}N_3O_5S$: C, 58.51; H, 6.61; N, 7.87; S, 12.01. Found: C, 58.57; H, 6.50; N, 8.07; S, 12.14.

***N*-(2-(Methylphenylamino)ethyl)formamide (31)**——A mixture of *N*-phenylethylenediamine (**18**) (4.09 g, 0.03 mol) and HCO_2Et (50 ml) was refluxed for 1.5 h and evaporated. Chromatography (SiO_2, $CHCl_3$–AcOEt (30 : 1)) of the residue gave 4.79 g of the *N*-formate as an oil. A mixture of this oil (3.8 g, 0.0231 mol), MeI (4.68 g, 0.033 mol), K_2CO_3 (3.83 g, 0.028 mol), and DMF (20 ml) was heated at 40—50 °C for 4 h. The mixture was diluted with AcOEt and washed with sat. NaCl. The organic layer was dried and evaporated. The residue was purified by chromatography (SiO_2, $CHCl_3$–AcOEt (10 : 1)) to give 1.83 g (34.2% from **18**) of **31** as an oil. IR ν_{max}^{liquid} cm^{-1}: 3350, 3270, 1660, 1590, 750, 690. MS *m/z*: 178 (M^+), 120. ^{1}H-NMR ($CDCl_3$) δ: 2.92 (3H, s), 3.30—3.80 (4H, m), 5.70—6.20 (1H, m), 6.60—7.00 (3H, m), 7.10—7.50 (2H, m), 8.13 (1H, br s).

***N*,*N'*-Dimethyl-*N*-phenylethylenediamine (32)**——A mixture of **31** (1.92 g, 0.0108 mol), lithium aluminum hydride (0.61 g, 0.0161 mol), and THF (40 ml) was refluxed for 4 h. The usual work-up and chromatographic purification (SiO_2, $CHCl_3$–MeOH (10 : 1)) gave 1.74 g (98%) of **32** as an oil. IR ν_{max}^{liquid} cm^{-1}: 3300, 1600, 750. MS *m/z*: 164 (M^+), 120. ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 2.79 (2H, t, J=6 Hz), 2.94 (3H, s), 3.45 (2H, t, J=6.4 Hz), 6.5—7.5 (5H, m).

***N*-Methyl-2-(2-(2-(methyl(2-(methylphenylamino)ethyl)amino)ethoxy)phenyl)thiazolidine-3-carbothioamide (30a)**——Condensation of **14a** (X=S) and **32** in the usual manner gave **30a** in 64% yield as an oil. IR ν_{max}^{liquid} cm^{-1}: 3400, 3300, 1590. MS *m/z*: 444 (M^+), 371, 324, 251, 133, 120, 73, 70. ^{1}H-NMR ($CDCl_3$) δ: 2.43 (3H, s), 2.95 (3H, s), 2.00—3.20 (9H, m), 3.30—3.70 (2H, m), 3.80—4.90 (4H, m), 5.40—5.70 (1H, m), 6.30 (1H, s), 6.50—7.50 (9H, m). The oxalate, mp 181—182 °C (dec.), was recrystallized from EtOH. *Anal.* Calcd for $C_{25}H_{34}N_4O_5S_2$: C, 56.16; H, 6.41; N, 10.48; S, 11.99. Found: C, 56.17; H, 6.34; N, 10.60; S, 11.75.

The propoxy analogue (**30b**) was similarly obtained by the condensation of **14b** (X=S) and **32** in 78% yield. The oxalate was recrystallized from EtOH and had mp 167—168 °C (dec.). *Anal.* Calcd for $C_{26}H_{36}N_4O_5S_2$: C, 56.91; H, 6.61; N, 10.21; S, 11.69. Found: C, 57.11; H, 6.60; N, 10.42; S, 11.97.

Acknowledgements The authors are grateful to Dr. S. Saito, Director of the Organic Chemistry Research Laboratory, Dr. H. Nakajima, Director of the Biological Research Laboratory, Dr. T. Yamazaki, Professor of Toyama Medical and Pharmaceutical University, and Dr. K. Masuda, Professor of the same university, for their interest and encouragement. Thanks are also due to the staff of the Analytical Division of this laboratory for measurement of spectra and elemental analyses.

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