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Synthesis of 2-Aryl-2,3-dihydro-3-piperazinylmethyl-1,5-benzothiazepin-4(5*H*)-ones and Related Compounds[1)]

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A series of *trans*- (**12**) and *cis*-2-aryl-2,3-dihydro-3-piperazinylmethyl-1,5-benzothiazepin-4(5*H*)-ones (**13**) and related compounds were synthesized. Diethyl arylmethylenemalonates (**3**) were heated with 2-aminobenzenethiol (**4**) in the presence of triethylamine hydrochloride to afford *trans*-2-aryl-3-ethoxycarbonyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones (**7**) together with 2-arylbenzothiazoles (**6**). Heating of the adducts of **3** and **4** also gave **6** and **7**. Reduction of **7** yielded the 3-hydroxymethyl compounds (**8**), which were converted to the 3-chloromethyl (**9**), 3-methanesulfonyloxymethyl (**10**), and 3-(4-toluenesulfonyloxymethyl) compounds (**11**). Heating of **9**—**11** with piperazines gave **12** and **13**. Optical resolution of the 2-phenyl-3-piperazinylmethyl (**13a**) and 2-phenyl-3-(4-methylpiperazinylmethyl) compounds (**13b**) afforded (−)-**13a**, an active metabolite of (−)-**13b**, and (−)-**13b** (hydrochloride: BTM-1086), a potent anti-ulcer agent with gastric antisecretory and gastric mucosal blood flow-increasing activities, respectively.

Keywords——2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one; benzothiazole; configuration; optical resolution; anti-ulcer agent; BTM-1086

Thiazesim (**1**)[2)] and diltiazem (**2**)[3)] are well known as biologically active compounds having the 1,5-benzothiazepine skeleton. Thiazesim possesses antidepressant activity. Diltiazem hydrochloride is a coronary vasodilator and is widely used for the treatment of angina pectoris.

Peptic ulcer is generally thought to result from an imbalance between aggressive and defensive factors.[4)] It is considered that gastric acid and gastric mucosal blood flow are important components of the aggressive and defensive factors, respectively. A drug that acts effectively on both factors might be useful in the treatment of peptic ulcer.

We synthesized (−)-*cis*-2,3-dihydro-3-(4-methylpiperazinylmethyl)-2-phenyl-1,5-benzothiazepin-4(5*H*)-one [(−)-**13b**, hydrochloride: BTM-1086],[1a)] which has been proved to exhibit potent anti-ulcer activities in acute and chronic ulcer models.[5)] Furthermore, (−)-**13b** markedly inhibited basal and stimulated gastric secretion,[5,6)] and remarkably increased

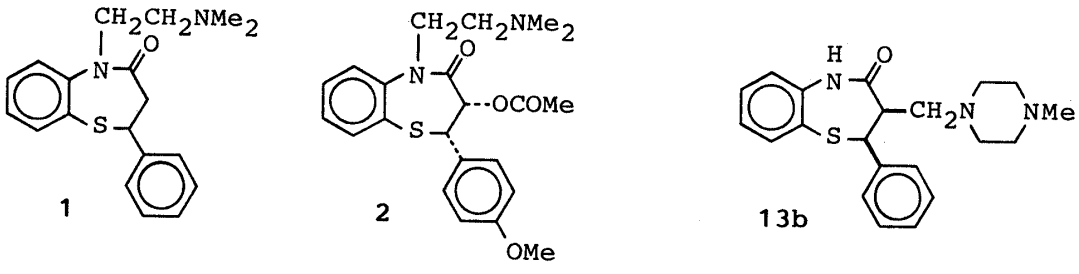


Fig. 1

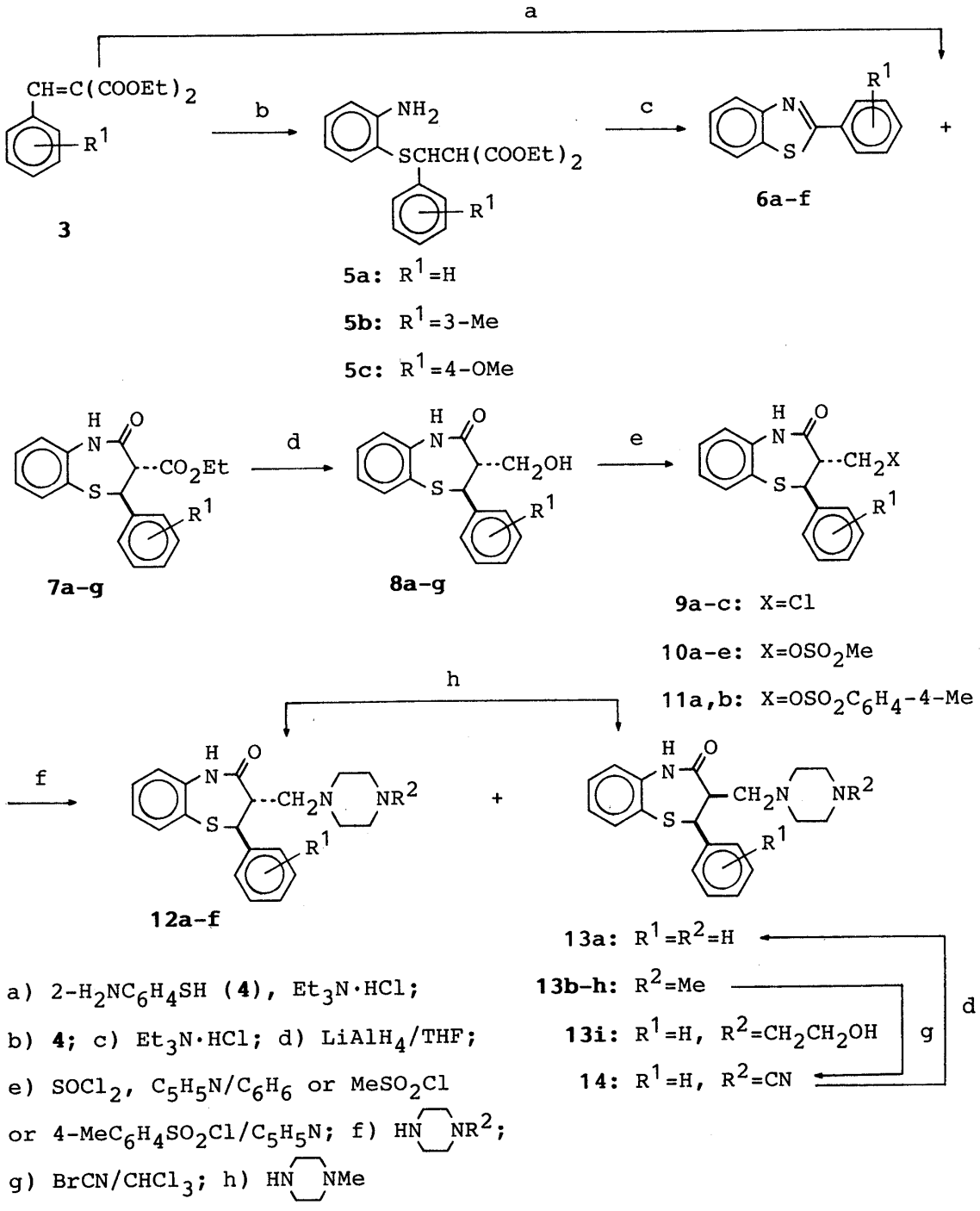


Chart 1

gastric mucosal blood flow.[5a] In this paper we describe the synthesis of (−)-**13b** and related compounds.

Diethyl arylmethylenemalonates (**3**)[7] were heated with 2-aminobenzenethiol (**4**) in the presence of triethylamine hydrochloride to afford *trans*-2-aryl-3-ethoxycarbonyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones (**7a—g**) together with 2-arylbenzothiazoles (**6a—f**)[8] as by-products. Heating of ethyl 3-(2-aminophenylthio)-3-aryl-2-ethoxycarbonylpropionates (**5a—c**), the adducts of **3** and **4**, also gave **7a**, **7b**, and **7f** together with **6a**, **6b**, and **6f**, respectively. In the synthesis of **7a—g** from **3** and **4** or from **5**, the formation of diethyl malonate was confirmed. The reaction mechanism for the formation of **6** is considered to be as shown in

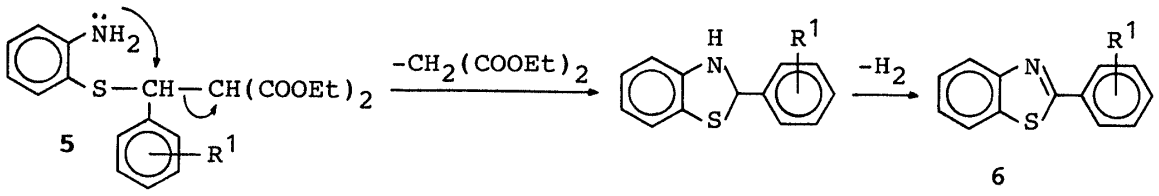


Chart 2

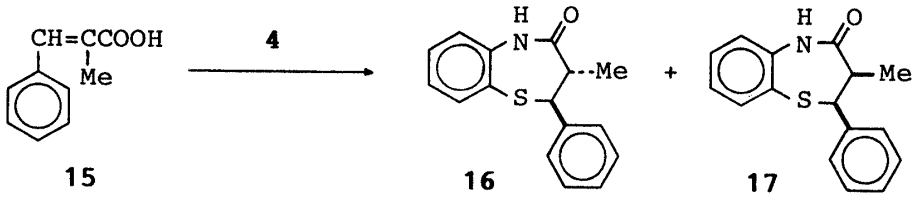


Chart 3

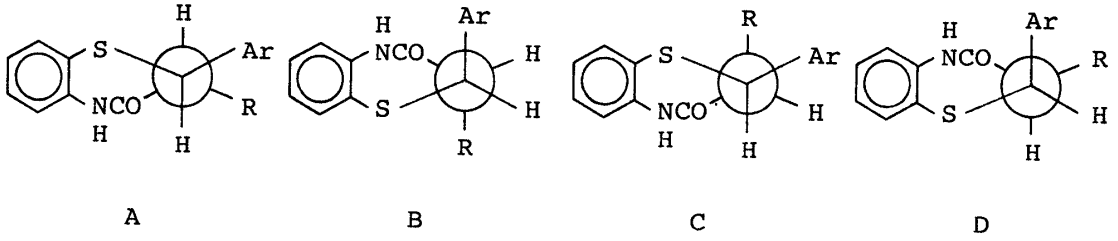


Fig. 2

Chart 2. Nucleophilic attack by the amino group upon the carbon atom at the benzyl position in **5** causes the formation of diethyl malonate and 2-arylbenzothiazolines, which change to **6** by autoxidation. It is well known that 2-substituted benzothiazolines are easily oxidized by air to give benzothiazoles.[9]

Reduction of **7a—g** with lithium aluminum hydride in tetrahydrofuran (THF) gave compounds **8a—g**, which were treated with thionyl chloride, methanesulfonyl chloride, and 4-toluenesulfonyl chloride to afford 3-chloromethyl- (**9a—c**), 3-methanesulfonyloxymethyl- (**10a—e**), and 3-(4-toluenesulfonyloxymethyl)-2-aryl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones (**11a, b**), respectively. Heating of **9—11** with piperazines gave *trans*- (**12a—f**)[10] and *cis*-2-aryl-2,3-dihydro-3-piperazinylmethyl-1,5-benzothiazepin-4(5*H*)-ones (**13a—i**). The data for **7—13** are summarized in Tables I and II. Compound **13b** was treated with bromine cyanide to give **14**. Reduction of **14** with lithium aluminum hydride also yielded **13a**.

In the proton nuclear magnetic resonance (^{1}H-NMR) spectra of compounds **7—12** and **13**, the coupling constants between the protons at the 2- and 3-positions were 11.0—12.5 and 6.3—6.8 Hz, respectively. The coupling constants of *trans*- (**16**)[2a,11] and *cis*-2,3-dihydro-3-methyl-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**17**), prepared by heating of 2-methyl-3-phenylpropenic acid (**15**) with **4**, were 11.7 and 6.5 Hz, respectively.

The ^{1}H-NMR spectral data for 3-substituted 2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-ones are presented in Table III. There are possible conformers A and B for the *trans* compounds and likewise C and D for the *cis* isomers, as presented in Fig. 2. The appearance of the larger coupling constant is possible only with the conformer A. We considered that the configurations are *trans* for **7—12** and *cis* for **13**.[12]

The structures of **12** and **13** were further confirmed by the following reactions. Heating of **12b** or **13b** in *N*-methylpiperazine gave a mixture of **12b** and **13b**. Desulfurization of **12b** and **13b** with W-4 Raney nickel in ethanol afforded 2-benzyl-3-(4-methylpiperazinyl)propion-

TABLE I. 2-Aryl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones (**7**—**11**)

Compd. No.	R^1	Yield (%)	mp (°C)	Appearance Recryst. solvent[b]	Formula	Analysis (%) Calcd (Found) C	H	N
7a	H	35 44[a]	198—200	Needles C–G	$C_{18}H_{17}NO_3S$	66.03 (66.05	5.24 5.18	4.28 4.19)
7b	3-Me	31 32[a]	177—179	Scales D–A	$C_{19}H_{19}NO_3S$	66.84 (66.49	5.61 5.54	4.10 3.79)
7c	3-Cl	35	195—197	Prisms C–G	$C_{18}H_{16}ClNO_3S$	59.75 (59.63	4.46 4.31	3.87 3.93)
7d	4-Me	37	183—185	Needles D–A	$C_{19}H_{19}NO_3S$	66.84 (67.08	5.61 5.81	4.10 4.31)
7e	4-Cl	49	204—206	Prisms D	$C_{18}H_{16}ClNO_3S$	59.75 (59.67	4.46 4.36	3.87 3.88)
7f	4-OMe	28 36[a]	190—192	Needles C–G	$C_{19}H_{19}NO_4S$	63.85 (63.69	5.36 5.42	3.92 3.86)
7g	3,4-$(OMe)_2$	30	193—196	Scales D–A	$C_{20}H_{21}NO_5S$	62.00 (62.06	5.46 5.48	3.62 3.25)
8a	H	92	246—248	Needles F–K	$C_{16}H_{15}NO_2S$	67.34 (67.30	5.30 5.24	4.91 4.82)
8a-d_2	H	86	230—233	Needles D–G	$C_{16}H_{13}D_2NO_2S$	66.87 (66.90	5.26 5.19	4.87 4.96)
8b	3-Me	91	213—216	Scales C–G	$C_{17}H_{17}NO_2S$	68.20 (67.92	5.72 5.73	4.68 4.65)
8c	3-Cl	79	233—236[c]	Needles C–G	$C_{16}H_{14}ClNO_2S \cdot 1/3\,H_2O$	58.98 (58.78	4.54 4.38	4.30 4.27)
8d	4-Me	73	227—229	Needles C–G	$C_{17}H_{17}NO_2S$	68.20 (68.12	5.72 5.78	4.68 4.53)
8e	4-Cl	66	237—239	Prisms F–K	$C_{16}H_{14}ClNO_2S$	60.09 (60.16	4.41 4.37	4.38 4.45)
8f	4-OMe	62	215—217	Needles J	$C_{17}H_{17}NO_3S$	64.74 (64.58	5.43 5.33	4.44 4.19)
8g	3,4-$(OMe)_2$	92	252—254	Needles F–I	$C_{18}H_{19}NO_4S$	62.59 (62.68	5.54 5.59	4.06 4.12)
9a	H	84	230—233	Needles B	$C_{16}H_{14}ClNOS$	63.26 (63.06	4.64 4.56	4.61 4.55)
9b	4-Cl	72	238—241[c]	Prisms C–H	$C_{16}H_{13}Cl_2NOS$	56.81 (56.93	3.87 3.81	4.14 4.12)
9c	4-OMe	81	231—235[c]	Needles C–H	$C_{17}H_{16}ClNO_2S$	61.16 (60.95	4.83 4.81	4.20 3.97)
10a	H	93	214—217	Needles D–H	$C_{17}H_{17}NO_4S_2$	56.18 (56.05	4.72 4.78	3.85 3.82)
10a-d_2	H	93	213—215	Scales D–G	$C_{17}H_{15}D_2NO_4S_2$	55.87 (55.87	4.69 4.70	3.83 3.90)
10b	3-Me	84	213—214	Needles C–G	$C_{18}H_{19}NO_4S_2$	57.27 (56.91	5.07 5.03	3.71 3.68)
10c	4-Me	87	205—207	Needles C–G	$C_{18}H_{19}NO_4S_2$	57.27 (57.51	5.07 5.16	3.71 3.75)
10d	4-Cl	92	228—230	Needles C–G	$C_{17}H_{16}ClNO_4S_2$	51.32 (51.28	4.05 3.96	3.52 3.49)
10e	3,4-$(OMe)_2$	91	214—219[c]	Needles D	$C_{19}H_{21}NO_6S_2$	53.89 (53.70	5.00 4.96	3.31 3.19)
11a	H	92	209—211	Prisms D–H	$C_{23}H_{21}NO_4S_2$	62.85 (62.74	4.82 4.78	3.19 3.10)
11b	3-Cl	80	192—195	Needles C–G	$C_{23}H_{20}ClNO_4S_2$	58.28 (58.31	4.25 4.22	2.96 2.94)

a) Yield from **5**. *b*) A, Et_2O; B, C_6H_6; C, $CHCl_3$; D, CH_2Cl_2; E, EtOH; F, DMF; G, petroleum ether; H, hexane; I, iso-PrOH; J, MeOH; K, H_2O. *c*) Decomposition.

TABLE II. 2-Aryl-2,3-dihydro-3-piperazinylmethyl-1,5-benzothiazepin-4(5*H*)-ones (**12**, **13**)

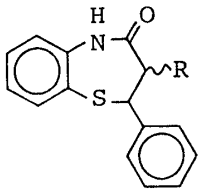
Compd. No.	R^1	R^2	Yield[a] (%)	mp (°C)	Appearance Recryst. solvent[b]	Formula	Analysis (%) Calcd (Found) C	H	N
12a	H	H	32	200—206[c]	Needles E	$C_{20}H_{23}N_3OS \cdot 1/5H_2O$	67.27 (67.41)	6.61 (6.64)	11.77 (11.84)
12b	H	Me	37 34,[d] 35[e]	257—260[c]	Needles D	$C_{21}H_{25}N_3OS$	68.63 (68.63)	6.86 (6.83)	11.43 (11.38)
12b-d_2	H	Me	30	237—240[c]	Needles D–A	$C_{21}H_{23}D_2N_3OS \cdot 1/2H_2O$	66.63 (66.82)	6.92 (6.87)	11.10 (10.93)
12c	3-Me	Me	30	207—210	Needles C–G	$C_{22}H_{27}N_3OS$	69.26 (69.01)	7.13 (7.05)	11.01 (10.90)
12d	3-Cl	Me	34[e]	219—222	Needles C–G	$C_{21}H_{24}ClN_3OS$	62.75 (62.68)	6.02 (5.98)	10.45 (10.40)
12e	4-Me	Me	32	237—238[c]	Needles D–A	$C_{22}H_{27}N_3OS \cdot 1/3H_2O$	68.18 (68.38)	7.20 (7.16)	10.84 (10.67)
12f	3,4-$(OMe)_2$	Me	38	210—212	Needles D–A	$C_{23}H_{29}N_3O_3S$	64.61 (64.72)	6.84 (6.79)	9.83 (9.84)
13a	H	H	19	185—188	Prisms I	$C_{20}H_{23}N_3OS$	67.96 (67.56)	6.56 (6.55)	11.89 (11.63)
13b	H	Me	30 18,[d] 25[e]	203—205	Prisms B–A	$C_{21}H_{25}N_3OS$	68.63 (68.64)	6.86 (6.85)	11.43 (11.40)
13b-d_2	H	Me	21	200—202	Prisms D–A	$C_{21}H_{23}D_2N_3OS$	68.26 (68.20)	6.82 (7.01)	11.37 (11.25)
13c	3-Me	Me	13	114—117	Prisms I–A	$C_{22}H_{27}N_3OS$	69.26 (69.16)	7.13 (7.48)	11.01 (10.74)
13d	3-Cl	Me	17[e]	197—200	Prisms C–E	$C_{21}H_{24}ClN_3OS$	62.75 (62.74)	6.02 (6.02)	10.45 (10.41)
13e	4-Me	Me	15	194—196	Prisms B–A	$C_{22}H_{27}N_3OS$	69.26 (69.45)	7.13 (7.18)	11.01 (10.88)
13f	4-Cl	Me	13 38[d]	245—248[c]	Prisms D–A	$C_{21}H_{24}ClN_3OS$	62.75 (62.92)	6.02 (5.92)	10.45 (10.43)
13g	4-OMe	Me	9[d]	191—193	Prisms B–A	$C_{22}H_{27}N_3O_2S$	66.47 (66.41)	6.85 (6.83)	10.57 (10.62)
13h	3,4-$(OMe)_2$	Me	12	165—167	Prisms D–A	$C_{23}H_{29}N_3O_3S \cdot 1/2H_2O$	63.28 (63.47)	6.93 (7.07)	9.63 (9.70)
13i	H	CH_2CH_2OH	10[d]	104—106	Prisms B–A	$C_{22}H_{27}N_3O_2S$	66.47 (66.59)	6.85 (6.90)	10.57 (10.57)

a) Yield from **10**. *b*) See footnote *b* in Table I. *c*) Decomposition. *d*) Yield from **9**. *e*) Yield from **11**.

anilide (**18**). Treatment of **12b** with W-4 Raney nickel in acetone gave **16** and 2-benzylpropionanilide (**19**)[14] in 20 and 31% yields, respectively. Under the same conditions, **13b** was recovered unchanged. Desulfurization of **16** with W-4 Raney nickel in ethanol or acetone gave **19**. Compounds **12b** and **13b** were treated with sulfuryl chloride in chloroform to afford 3-(4-methylpiperazinylmethyl)-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**25a**). Oxidation of **12b** and **13b** with 3-chloroperbenzoic acid gave 2,3-dihydro-3-methylene-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**20**). The formation of **20** might be explained by a mechanism involving oxidation of the nitrogen atom at the 1-position of the piperazinyl group of **12b** or **13b** and Cope degradation of the resulting *N*-oxide. The results are consistent with the proposed structures of **12** and **13**.

In the reaction of **9a** and **10a** with *N*-methylpiperazine, *trans*-3-[2-[(*E*)-2-phenylmethylene-3-(4-methylpiperazinyl)propionylamino]phenylthiomethyl]-2,3-dihydro-2-phenyl-

TABLE III. ^{1}H-NMR Data for 3-Substituted 2,3-Dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-ones in $CDCl_3$[a]



Compd. No.	R	Configuration	C_2-H (*J*)	C_3-H (*J*)	Others
7a	CO_2Et	*trans*	5.13 (d) (11.2)	4.06 (d) (11.7)	1.07 (3H, t, *J*=7.0), 4.02 (2H, q, *J*=7.0), 7.03—7.72 (9H, m), 9.13 (1H, br s)
8a	CH_2OH	*trans*	4.76 (d) (11.7)	2.81—3.06 (m)	3.12—3.82 (3H, m), 6.90—7.70 (9H, m), 8.23 (1H, br s)
8a-d_2	CD_2OH	*trans*	4.81 (d) (12.0)	2.93 (d) (12.0)	3.53 (1H, br s), 7.07—7.74 (9H, m), 8.01 (1H, br s)
9a	CH_2Cl	*trans*	4.28 (d) (12.0)	3.33 (ddd) (12.0, 10.1, 2.7)	2.99 (1H, dd, *J*=10.1, 2.7), 3.97 (1H, t, *J*=10.1), 6.96—7.67 (9H, m), 8.06 (1H, br s)
10a	CH_2OMs	*trans*	4.30 (d) (12.3)	3.42 (ddd) (12.3, 9.5, 2.9)	2.93 (3H, s), 3.74 (1H, dd, *J*=9.5, 2.9), 4.59 (1H, t, *J*=9.5), 6.99—7.67 (9H, m), 8.18 (1H, br s)
10a-d_2	CD_2OMs	*trans*	4.30 (d) (12.3)	3.38 (d) (12.3)	2.93 (3H, s), 7.70—7.67 (9H, m), 7.89 (1H, br s)
12b	$CH_2N\langle\rangle NMe$	*trans*	4.23 (dt) (11.0, 5.0)	—[b]	1.80—2.45 [12H, m, 1.95 (1H, dt, *J*=11.0, 5.0), 2.17 (3H, s)], 3.00—3.42 (2H, m), 6.92—7.56 (9H, m), 8.17 (1H, br s)
12b-d_2	$CD_2N\langle\rangle NMe$	*trans*	4.23 (d) (11.8)	3.17 (d) (11.8)	1.96—2.39 [11H, m, 2.16 (3H, s)], 6.95—7.71 [10H, m, 7.65 (1H, br s)]
13b	$CH_2N\langle\rangle NMe$	*cis*	5.13 (d) (6.4)	2.97—3.30 (m)	1.92—2.55 [13H, m, 2.25 (3H, s)], 7.05—7.75 (9H, m), 8.50 (1H, br s)
13b-d_2	$CD_2N\langle\rangle NMe$	*cis*	5.11 (d) (6.4)	3.10 (d) (6.4)	1.95—2.55 [11H, m, 2.23 (3H, s)], 7.01—7.74 (9H, m), 8.71 (1H, br s)
16	Me	*trans*	4.24 (d) (11.7)	3.04 (dq) (11.7, 6.5)	0.97 (3H, d, *J*=6.5), 6.90—7.90 [10H, m, 7.77 (1H, br s)]
17	Me	*cis*	4.81 (d) (6.5)	3.06 (quint) (6.5)	0.85 (3H, d, *J*=6.5), 7.00—7.73 (9H, m), 7.86 (1H, br s)

a) Coupling constants (*J*) are given in Hz. *b*) Overlapped with the other signals.

1,5-benzothiazepin-4(5*H*)-one was isolated as an intermediate.[1b,c,15]

Some derivatives of **13b**, which possessed the most potent anti-ulcer activity, were synthesized. Compound **13a** was treated with benzyl chloride to give **21** and **13b** reacted with ethyl chloroformate to give **22**. Alkylation of **13b** and **13a** with alkyl halides yielded **23a—f** and **23g—i**, respectively. Treatment of **9a** with sulfuryl chloride gave **24**, which reacted with piperazines to afford 3-piperazinyl-2-phenyl-1,5-benzothiazepin-4(5*H*)-ones (**25a, b**).

In the screening test on water immersion stress-induced ulcers, the *cis* compounds **13a, b, e, 22**, and **23a** showed potent activity, and **13g** and **21** were moderately active. The *trans* isomers **12**, the desulfurized compound **18**, and the 2,3-dehydro compounds **25** exhibited no activity.

Compounds **13a** and **13b** were optically resolved with (+)- or (−)-tartaric acid in methanol. Compound (−)-**13a** was also prepared from (−)-**13b** *via* (−)-**14**. Compounds (+)-**13a** and (+)-**13b** exhibited weak anti-ulcer activity.

Compound (−)-**13b** (hydrochloride: BTM-1086) was confirmed to possess potent activities.[5,6] For example, (−)-**13b** exhibited potent anti-ulcer activities in acute and chronic

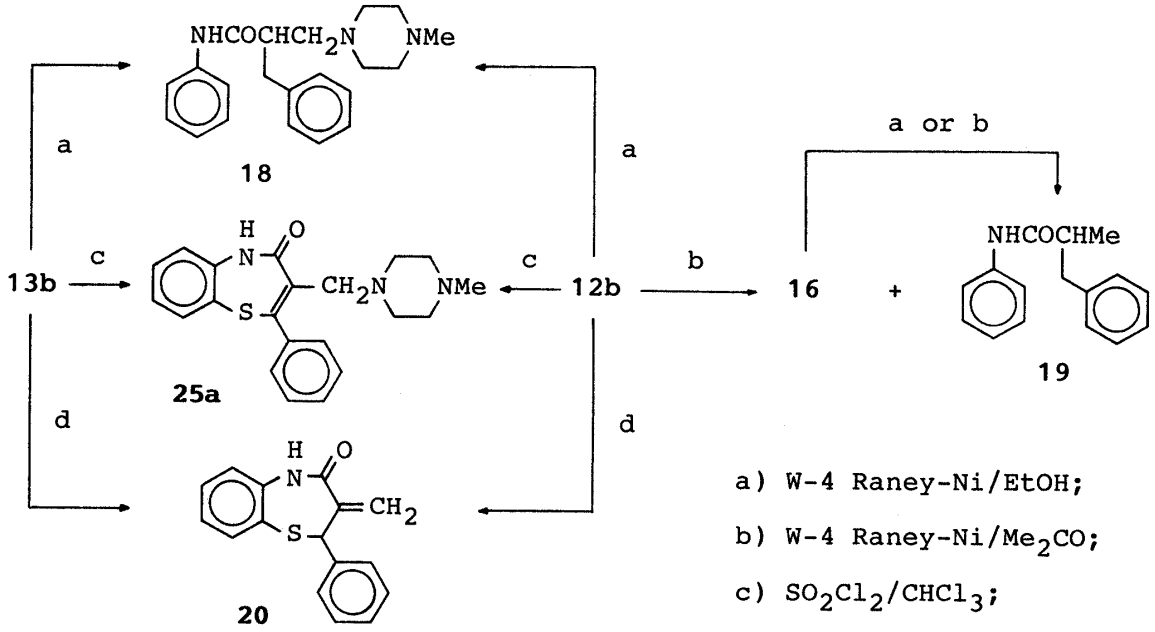


Chart 4

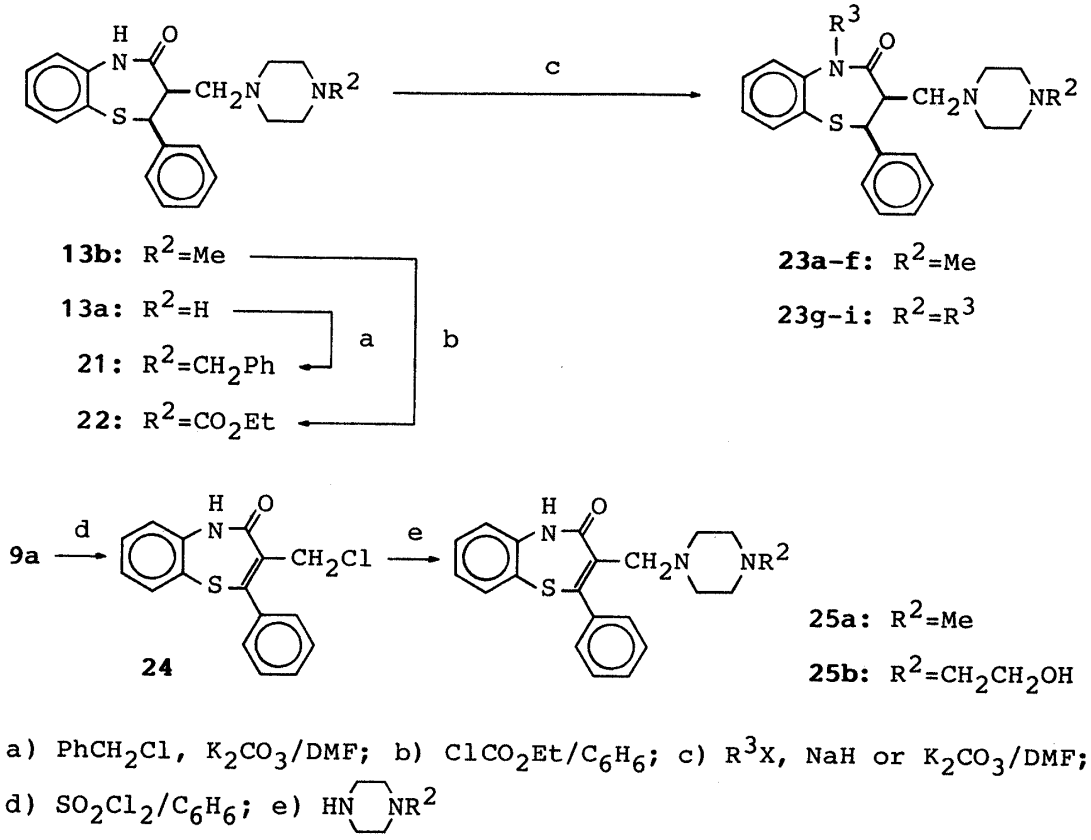


Chart 5

ulcer models,[5] and markedly inhibited basal gastric secretion and secretagogue-induced hypersecretion in rats and dogs.[5,6] Furthermore, (−)-**13b** increased gastric mucosal blood flow in normal rats, and gastric mucosal ischemia induced by indomethacin in rats was remarkably improved by (−)-**13b**.[5a] In addition, (−)-**13b** possesses potent and selective

TABLE IV. 5-Alkyl-3-(4-alkylpiperazinylmethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-ones (**23**)

Compd. No.	R^2	R^3	Yield (%)	mp (°C) Recryst. solvent[a]	Formula	Analysis (%) Calcd (Found) C	H	N
23a	Me	Me	63	157—160 B–G	$C_{22}H_{27}N_3OS$	69.29 (69.19	7.13 7.14	11.01 10.90)
23b	Me	Et	45	173—176[b] E–A	$C_{23}H_{29}N_3OS \cdot 2HCl \cdot H_2O$	56.78 (56.50	6.01 5.93	8.64 8.60)
23c	Me	Pr	77	99—102 H	$C_{24}H_{31}N_3OS$	70.38 (70.30	7.63 7.71	10.26 10.25)
23d	Me	$CH_2CH=CH_2$	71	128—130 D–H	$C_{24}H_{29}N_3OS$	70.73 (70.72	7.17 7.00	10.31 10.07)
23e	Me	CH_2Ph	64	155—157 D–H	$C_{28}H_{31}N_3OS$	73.49 (73.26	6.83 6.77	9.18 8.91)
23f	Me	$CH_2C_6H_4$-4-Cl	43	150—153 D–H	$C_{28}H_{30}ClN_3OS$	67.11 (67.09	6.24 6.01	8.39 8.20)
23g	Et	Et	50	Oil	$C_{24}H_{31}N_3OS$			
23h	Pr	Pr	58	104—105 D–H	$C_{26}H_{35}N_3OS$	71.36 (71.25	8.06 8.00	9.60 9.71)
23i	Bu	Bu	63	150—153[b] E–A	$C_{28}H_{39}N_3OS \cdot 2HCl \cdot H_2O$	60.42 (60.23	7.06 6.98	7.55 7.72)

a) See footnote *b* in Table I. *b*) Dihydrochloride. Decomposition.

muscarine M_1-receptor antagonistic activity.[16]

Compound (−)-**13a** was a main metabolite of (−)-**13b** in plasma[17] and its anti-ulcer and antisecretory activities were nearly equal to those of (−)-**13b**.[17a]

Further investigation is in progress.

Experimental

All melting points were determined on a Yanagimoto MP-S3 apparatus and are uncorrected. ^{1}H-NMR spectra were recorded with a Hitachi R-90H or a JEOL PMX-60 spectrometer with tetramethylsilane as an internal standard. Infrared (IR) spectra were measured with a Hitachi 260-10 spectrometer. Mass spectra (MS) were taken on a JEOL JMS D-300 spectrometer and optical rotations were measured with a JASCO DIP-140 digital polarimeter. Column chromatography was carried out on Wakogel C-200 or activated alumina (about 300 mesh, Wako Pure Chemical Industries, Ltd.).

Ethyl 3-(2-Aminophenylthio)-3-aryl-2-ethoxycarbonylpropionates (5)——Ethyl 3-(2-aminophenylthio)-2-ethoxycarbonyl-3-phenylpropionate (**5a**): 2-Aminobenzenethiol (**4**, 32 g, 0.26 mol) was added dropwise to a solution of diethyl phenylmethylenemalonate (**3a**,[7c] 62 g, 0.25 mol) in iso-PrOH (100 ml) with stirring. After being stirred for 2 h, the whole was cooled in an ice bath. The resulting crystals were collected and recrystallized from iso-PrOH to afford colorless prisms (87 g, 94%), mp 70—71 °C. IR (KBr): 3440 and 3350 (NH_2), 1730 (COO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.93 (3H, t, J=7.2 Hz), 1.36 (3H, t, J=7.2 Hz), 3.88 (2H, q, J=7.2 Hz), 4.02 (1H, d, J=11.8 Hz), 4.15 (2H, br s), 4.28 (2H, q, J=7.2 Hz), 4.60 (1H, d, J=11.8 Hz), 6.36—6.66 (2H, m), 6.84—7.26 (7H, m). *Anal.* Calcd for $C_{20}H_{23}NO_4S$: C, 64.32; H, 6.21; N, 3.75. Found: C, 64.25; H, 6.26; N, 3.72.

The esters **5b** and **5c** were prepared in the same manner as described above.

5b: 95% yield, pale yellow oil. IR (neat): 3460 and 3360 (NH_2), 1750 and 1733 (COO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, t, J=6.9 Hz), 1.30 (3H, t, J=6.9 Hz), 2.22 (3H, s), 3.76—4.80 [8H, m, 3.94 (2H, q, J=6.9 Hz), 4.10 (1H, d, J=10.9 Hz), 4.31 (2H, q, J=6.9 Hz), 4.63 (1H, d, J=10.9 Hz)], 6.37—7.47 (8H, m).

5c: 86% yield, colorless needles (CH_2Cl_2–hexane), mp 68—70 °C. IR (KBr): 3480 and 3435 (NH_2), 1747 and 1717 (COO) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.94 (3H, t, J=7.2 Hz), 1.32 (3H, t, J=7.2 Hz), 3.73 (3H, s), 3.89 (2H, q, J=7.2 Hz), 3.96 (1H, d, J=11.4 Hz), 4.09—4.43 [4H, m, 4.26 (2H, q, J=7.2 Hz)], 4.58 (1H, d, J=11.4 Hz), 6.34—6.77 (4H, m), 6.81—7.15 (4H, m).

***trans*-2-Aryl-3-ethoxycarbonyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones (7)**——a) *trans*-3-Ethoxycarbonyl-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**7a**): A mixture of **3a** (248 g, 1.0 mol), **4** (126 g, 1.0 mol), and

$Et_3N \cdot HCl$ (4.0 g, 29 mmol) was heated at about 180 °C for 3.5 h. After being cooled, the reaction mixture was crystallized with Et_2O and petroleum ether. The resulting crystals were collected, washed with iso-PrOH, and dried to give **7a** (114 g, 35%). IR (KBr): 3160 (NH), 1753 (COO), 1674 (CON) cm^{-1}. The filtrate was concentrated *in vacuo* to give an oil. A part of the oil was chromatographed on an alumina column with CH_2Cl_2 to give the product, which was recrystallized from hexane, yielding 2-phenylbenzothiazole (**6a**, 30%) as colorless needles, mp 114—115 °C (lit.[8e] 114 °C).

b) *trans*-3-Ethoxycarbonyl-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (**7f**): A mixture of **5c** (4.8 g, 12 mmol) and $Et_3N \cdot HCl$ (1.0 g, 7.3 mmol) was heated at 180 °C for 3 h. The reaction mixture was chromatographed on an alumina column with CH_2Cl_2 and then Me_2CO. The first fraction gave 2-(4-methoxyphenyl)benzothiazole (**6f**), which was recrystallized from AcOEt–hexane to give colorless needles (1.1 g, 38%), mp 123—125 °C (lit.[8d] 121—122 °C). The second fraction gave **7f**, which was recrystallized from $CHCl_3$–petroleum ether to give colorless needles (1.6 g, 36%), mp 190—192 °C. IR (KBr): 3480 (NH), 1742 (COO), 1687 (CON) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.09 (3H, t, J=7.2 Hz), 3.76 (3H, s), 3.94 (1H, d, J=11.2 Hz), 4.01 (2H, q, J=7.2 Hz), 5.08 (1H, d, J=11.2 Hz), 6.80 (2H, A_2B_2 type d, J=9.6 Hz), 7.04—7.68 (6H, m), 8.18 (1H, br s).

The esters **7b**—**g** were prepared in the same manner as described for **7a**, and **7a** and **7b** were also prepared as described for **7f**. The data are presented in Table I. 2-(3-Methylphenyl)- [**6b**, mp 64—66 °C (lit.[8c] mp 63—64 °C)], 2-(3-chlorophenyl)- [**6c**, mp 96—97 °C (lit.[8e] mp 96 °C)], 2-(4-methylphenyl)- [**6d**, mp 86—88 °C (lit.[8d] mp 85—86 °C)], and 2-(4-chlorophenyl)benzothiazole [**6e**, mp 118—120 °C (lit.[8f] mp 116.5 °C)] were also isolated as by-products.

***trans*-2-Aryl-2,3-dihydro-3-hydroxymethyl-1,5-benzothiazepin-4(5*H*)-ones (8)**——*trans*-2,3-Dihydro-3-hydroxymethyl-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**8a**): The ester **7a** (450 g, 1.38 mol) was added in portions to a suspension of $LiAlH_4$ (50 g, 1.32 mol) in THF (2000 ml) below 30 °C with stirring in an ice bath. After being stirred for 2 h at room temperature, the reaction mixture was poured into a mixture of hydrochloric acid and ice-water and allowed to stand overnight. The crystals were collected, washed with H_2O and then iso-PrOH, and dried to give **8a** (360 g, 92%). An analytical sample was obtained as colorless needles by recrystallization from *N*,*N*-dimethylformamide (DMF)–H_2O. IR (KBr): 3480 (OH), 3180 (NH), 1675 (CON) cm^{-1}.

Compounds **8a**-d_2 and **8b**—**g** were prepared similarly. The data are presented in Table I.

***trans*-2-Aryl-3-chloromethyl-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-ones (9)**——*trans*-3-Chloromethyl-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**9a**): Thionyl chloride (3.6 g, 30 mmol) was added dropwise to a mixture of **8a** (5.7 g, 20 mmol) and pyridine (1.6 g, 20 mmol) in C_6H_6 (30 ml) with stirring and then the whole was refluxed for 1 h. The solvent was evaporated off *in vacuo* and H_2O was added to the residue. The crystals were collected, washed with MeOH, and recrystallized from C_6H_6 to give colorless needles (5.1 g, 84%), mp 230—233 °C. IR (KBr): 3160 (NH), 1690 (CON) cm^{-1}.

Compounds **9b** and **9c** were prepared similarly. The data are presented in Table I.

***trans*-2-Aryl-2,3-dihydro-3-sulfonyloxymethyl-1,5-benzothiazepin-4(5*H*)-ones (10, 11)**——*trans*-2,3-Dihydro-3-methanesulfonyloxymethyl-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**10c**): Methanesulfonyl chloride (1.3 g, 11 mmol) was added dropwise to a solution of **8d** (3.0 g, 10 mmol) in pyridine (15 ml) in an ice bath. After being stirred for 2 h at room temperature, the reaction mixture was diluted with H_2O. The resulting crystals were collected and washed with H_2O and then iso-PrOH. Recrystallization from $CHCl_3$–petroleum ether gave colorless needles (3.3 g, 87%), mp 205—207 °C. ^{1}H-NMR ($CDCl_3$) δ: 2.32 (3H, s), 2.93 (3H, s), 3.36 (1H, ddd, J=12.3, 9.6, 3.0 Hz), 3.74 (1H, dd, J=9.6, 3.0 Hz), 4.26 (1H, d, J=12.3 Hz), 4.58 (1H, t, J=9.6 Hz), 6.86—7.68 (8H, m), 8.13 (1H, br s).

Compounds **10a**, **10a**-d_2, **10b**, **d**, **e** and **11** were prepared in the same manner as described above. The data are presented in Table I.

***trans*- (12) and *cis*-2-Aryl-2,3-dihydro-3-piperazinylmethyl-1,5-benzothiazepin-4(5*H*)-ones (13)**——a) *trans*- (**12a**) and *cis*-2,3-Dihydro-2-phenyl-3-piperazinylmethyl-1,5-benzothiazepin-4(5*H*)-one (**13a**): 1) The mesylate **10a** (100 g, 0.275 mol) was added to a mixture of piperazine (200 g, 2.33 mol) and pyridine (100 ml) at 110 °C with stirring. Heating and stirring were continued for 3.5 h. The reaction mixture was poured into ice-water and the precipitate was collected and dissolved in CH_2Cl_2. The solution was washed with H_2O and dried over $MgSO_4$. The solvent was evaporated off and the residual oil was dissolved in EtOH. Maleic acid (77 g, 0.664 mol) was added to the solution to give the maleate of **13a**, which was recrystallized twice from EtOH. The free base obtained from the maleate was recrystallized from iso-PrOH to give colorless prisms (18.5 g, 19%), mp 185—188 °C. IR (Nujol): 1675 (CON) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.88—2.49 (6H, m), 2.62—2.85 (4H, m), 3.09 (1H, dt, J=6.6, 6.2 Hz), 5.06 (1H, d, J=6.6 Hz), 6.98—7.70 (10H, m). MS *m*/*z*: 353 (M^+, 23), 323 (36), 320 (13), 311 (60), 267 (12), 234 (13), 115 (15), 100 (18), 99 (100). The acidic filtrate was concentrated *in vacuo* and the residue was dissolved in H_2O. The solution was made alkaline with 10% NaOH, and extracted with CH_2Cl_2. The extract was washed with H_2O and dried over $MgSO_4$. After removal of the solvent, the residue was recrystallized from EtOH to give **12a** as colorless needles (31.4 g, 32%), mp 200—206 °C (dec.). ^{1}H-NMR ($CDCl_3$) δ: 1.78—2.34 (6H, m), 2.46—2.79 (4H, m), 3.01—3.37 (2H, m), 4.07—4.36 (1H, m), 6.92—7.63 (9H, m).

2) Compound **14** (9.6 g, 25 mmol) was added in portions to a suspension of $LiAlH_4$ (2.0 g, 53 mmol) and THF (200 ml) in an ice bath. After being stirred for 5 min, the reaction mixture was poured into ice-water and extracted with CH_2Cl_2. The organic layer was extracted with 10% HCl. The aqueous layer was made alkaline with 10% NaOH

and extracted with $CHCl_3$. The extract was washed with H_2O and dried over $MgSO_4$. The solvent was evaporated and the residual oil was crystallized with C_6H_6. Recrystallization from iso-PrOH gave **13a** as colorless prisms (4.6 g, 51%), mp 185—188 °C.

b) *trans*- (**12b**) and *cis*-2,3-Dihydro-3-(4-methylpiperazinylmethyl)-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**13b**): A mixture of **10a** (36.3 g, 0.10 mol) and *N*-methylpiperazine (100 ml) was refluxed for 3 h. After being cooled, the reaction mixture was poured into H_2O and extracted with CH_2Cl_2. The extract was washed with H_2O and dried over $MgSO_4$. The solvent was evaporated off *in vacuo* and the residue was crystallized with CH_2Cl_2 and Et_2O. The crystals were collected, washed with MeOH, and recrystallized from CH_2Cl_2 to afford **12b** as colorless needles (13.6 g, 37%), mp 257—260 °C (dec.). IR (KBr): 3150 (NH), 1692 (CON) cm^{-1}. MS *m/z*: 367 (M^+, 7.1), 114 (21), 113 (100). The filtrate was concentrated *in vacuo* and maleic acid (26 g, 0.224 mol) was added to a solution of the residual oil in EtOH. The crystals were collected, washed with hot EtOH, and dissolved in H_2O. The aqueous solution was made alkaline with 10% NaOH and extracted with CH_2Cl_2. The extract was concentrated to give the free base, which was recrystallized from C_6H_6–Et_2O to give **13b** as colorless prisms (11.0 g, 30%), mp 203—205 °C. IR (KBr): 3150 (NH), 1690 (CON) cm^{-1}. MS *m/z*: 367 (M^+, 2.4), 276 (12), 267 (8), 234 (8), 153 (13), 114 (18), 113 (100).

Compounds **12b**-d_2, **12c**—**f**, **13b**-d_2, and **13c**—**i** were also prepared in the same manner as described for **12b** and **13b**. The data are presented in Table II.

***cis*-3-(4-Cyanopiperazinylmethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (14)**——Compound **13b** (25 g, 68 mmol) was added to a solution of BrCN (11 g, 0.104 mol) in $CHCl_3$ (200 ml) with stirring, and the whole was refluxed for 2 h. The solvent was evaporated off *in vacuo* and the residue was chromatographed on a silica gel column with CH_2Cl_2 to give an oil (22.5 g, 88%). IR (KBr): 2240 (CN), 1680 (CON) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.95—2.57 (6H, m), 2.88—3.21 (5H, m), 4.98 (1H, d, J=6.6 Hz), 6.97—7.67 (9H, m), 8.43 (1H, br s). Maleate: Colorless needles (EtOH), mp 187—189 °C. *Anal.* Calcd for $C_{21}H_{22}N_4OS \cdot C_4H_4O_4$: C, 60.71; H, 5.30; N, 11.33. Found: C, 60.52; H, 5.32; N, 11.24.

***trans*- (16) and *cis*-2,3-Dihydro-3-methyl-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (17)**——A mixture of 2-methyl-3-phenylpropenic acid (**15**, 60 g, 0.37 mol) and **4** (46 g, 0.37 mol) was heated at 180 °C for 10 h. The reaction mixture was allowed to cool and the oily product was crystallized with isopropyl ether. Recrystallization from CH_2Cl_2–isopropyl ether gave **16** as colorless needles (26.3 g, 27%), mp 236—239 °C (lit.[2a] 236—238 °C). The filtrate was concentrated *in vacuo* and the residual oil was crystallized with isopropyl ether. Recrystallization from CH_2Cl_2–isopropyl ether gave **17** as colorless prisms (6.8 g, 6.9%), mp 178—180 °C. *Anal.* Calcd for $C_{16}H_{15}NOS$: C, 71.34; H, 5.61; N, 5.20. Found: C, 71.49; H, 5.56; N, 5.26.

Interconversion of 12b and 13b in *N*-Methylpiperazine——A mixture of **12b** (500 g, 1.36 mol) and *N*-methylpiperazine (1200 ml) was refluxed for 24 h with stirring, and then the reaction mixture was allowed to stand overnight. The crystals were collected, washed with MeOH, and dried to recover **12b** (370 g). The filtrate was concentrated *in vacuo* to give an oil, which was crystallized with MeOH. The crystals were collected, washed with MeOH, and dried to give crude **13b** (59 g, 12%), which contained about 10% of **12b**.

Refluxing of **13b** in *N*-methylpiperazine for 24 h gave **12b** and **13b** in 58% and 9% yields, respectively.

Desulfurization of 12b and 13b with Raney Nickel——a) **13b**: A mixture of **13b** (2.0 g, 5.4 mmol), W-4 Raney nickel prepared from nickel alloy (10 g), and EtOH (30 ml) was refluxed for 10 h with stirring. The catalyst was filtered off. The filtrate was concentrated *in vacuo* and the residue was chromatographed on an alumina column with CH_2Cl_2. The product was recrystallized from petroleum ether to give **18** as colorless needles (1.1 g, 60%), mp 99—101 °C. IR (KBr): 3270 (NH), 1660 (CON) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.18—2.90 [15H, m, 2.31 (3H, s)], 3.20—3.50 (1H, m), 6.95—7.63 (10H, m), 10.70 (1H, br s). MS *m/z*: 337 (M^+, 63), 281 (100), 246 (65), 153 (85), 115 (88). *Anal.* Calcd for $C_{21}H_{27}N_3O$: C, 74.74; H, 8.07; N, 12.45. Found: C, 74.88; H, 8.18; N, 12.63.

b) **12b**: A mixture of **12b** (2.0 g, 5.4 mmol), W-4 Raney nickel prepared from nickel alloy (10 g), and Me_2CO (30 ml) was refluxed for 4 h with stirring. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was chromatographed on a silica gel column with CH_2Cl_2. The first fraction afforded **19**, which was recrystallized from CH_2Cl_2 to give colorless needles (0.4 g, 31%), mp 109—110 °C (lit.[14] 127—128 °C). ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, d, J=6.5 Hz), 2.40—3.21 (3H, m), 6.79 (1H, br s), 6.93—7.50 (10H, m). MS *m/z*: 239 (M^+, 54), 119 (34), 93 (100), 91 (90). *Anal.* Calcd for $C_{16}H_{17}NO$: C, 80.33; H, 7.16; N, 5.86. Found: C, 80.03; H, 6.84; N, 6.09. The second fraction afforded **16**, which was recrystallized from CH_2Cl_2–hexane to give colorless needles (0.3 g, 20%), mp 236—239 °C.

Desulfurization of **12b** also afforded **18** in 56% yield in the same manner as described for **13b**. Treatment of **13b** in the same manner as described for **12b** resulted in recovery of the starting material.

Desulfurization of 16 with Raney Nickel——Treatment of **16** with W-4 Raney nickel in EtOH or Me_2CO gave **19** in 67% or 46% yield in the same manner as described for **13b** or **12b**. In desulfurization in Me_2CO, the starting material **16** was recovered in 27% yield.

Reaction of 12b and 13b with SO_2Cl_2——**12b**: Sulfuryl chloride (1.6 g, 12 mmol) was added dropwise to a solution of **12b** (3.7 g, 10 mmol) in $CHCl_3$ (100 ml) with stirring and the whole was warmed at about 60 °C for 1 h. The organic layer was washed with aqueous K_2CO_3 and dried over $MgSO_4$. The solvent was evaporated off and the residue was chromatographed on an alumina column with AcOEt to give **25a**. Recrystallization from EtOH gave

colorless needles (0.62 g, 17%), mp 219—221 °C. This product was identical with an authentic sample.

The similar reaction of **13b** with SO_2Cl_2 gave **25a** in 14% yield.

Reaction of 12b and 13b with 3-Chloroperbenzoic Acid——13b: 3-Chloroperbenzoic acid (4.5 g, 26 mmol) was added in portions to a solution of **13b** (2.0 g, 5.4 mmol) in $CHCl_3$ (50 ml) and the whole was stirred for 5 h. The reaction mixture was washed with aqueous Na_2CO_3 and dried over $MgSO_4$. After removal of the solvent, the oil was purified on a silica gel column with AcOEt and then AcOEt–MeOH (2 : 1). The product was recrystallized from CH_2Cl_2–Et_2O to give **20** as colorless prisms (0.5 g, 34%), mp 160—163 °C. IR (KBr): 3170 (NH), 1669 (CON) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.83 (1H, d, J=1.1 Hz), 5.37 (2H, m), 6.97—7.77 (9H, m), 9.13 (1H, br s). *Anal.* Calcd for $C_{16}H_{13}NOS$: C, 71.88; H, 4.90; N, 5.24. Found: C, 71.55; H, 4.79; N, 5.28.

The similar reaction of **12b** gave **20** in 19% yield.

***cis*-3-(4-Benzylpiperazinylmethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (21)**——A mixture of **13a** (5.0 g, 14 mmol), benzyl chloride (4.0 g, 32 mmol), K_2CO_3 (10 g, 72 mmol), and DMF (50 ml) was heated at 80—90 °C with stirring for 4 h. After being cooled, the reaction mixture was diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give an oil (4.8 g, 76%). ^{1}H-NMR ($CDCl_3$) δ: 1.90—2.53 (10H, m), 2.83—3.25 (1H, m), 3.45 (2H, s), 5.09 (1H, d, J=6.8 Hz), 6.90—7.70 (14H, m). Dihydrochloride: Colorless needles (H_2O–EtOH–AcOEt), mp 218—223 °C (dec.). *Anal.* Calcd for $C_{27}H_{29}N_3OS \cdot 2HCl \cdot 1/2H_2O$: C, 61.71; H, 6.14; N, 8.00. Found: C, 61.79; H, 6.06; N, 8.04.

***cis*-3-(4-Ethoxycarbonylpiperazinylmethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (22)**——Ethyl chloroformate (3.8 g, 35 mmol) was added dropwise to a mixture of **13b** (10 g, 27 mmol) and C_6H_6 (160 ml) with stirring, and the whole was refluxed for 0.5 h. The solvent was evaporated off *in vacuo* and the residue was chromatographed on an alumina column with CH_2Cl_2 to give **22**, which was recrystallized from CH_2Cl_2–Et_2O to give colorless needles (8.3 g, 72%), mp 160—162 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.23 (3H, t, J=7.1 Hz), 1.82—2.69 (6H, m), 2.95—3.62 (5H, m), 4.11 (2H, q, J=7.1 Hz), 5.14 (1H, d, J=6.6 Hz), 7.03—7.82 (9H, m), 8.81 (1H, br s). *Anal.* Calcd for $C_{23}H_{27}N_3O_3S$: C, 64.92; H, 6.40; N, 9.87. Found: C, 64.67; H, 6.27; N, 9.80.

5-Alkyl-3-(4-alkylpiperazinylmethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-ones (23)——a) 5-Allyl-2,3-dihydro-3-(4-methylpiperazinylmethyl)-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**23d**): Sodium hydride in oil (60%, 1.0 g, 25 mmol) was added in portions to a solution of **13b** (3.7 g, 10 mmol) in DMF (30 ml). After being stirred for 0.5 h, allyl bromide (1.3 g, 11 mmol) was added to the mixture, and stirring was continued for 2 h. The reaction mixture was poured into H_2O and extracted with AcOEt. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give an oil, which was chromatographed on a silica gel column with CH_2Cl_2. Recrystallization from CH_2Cl_2–hexane gave colorless prisms (2.9 g, 71%), mp 128—130 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.92—2.69 (13H, m), 2.82—3.32 (1H, m), 4.49—4.76 (2H, m), 4.82—5.44 [3H, m, 4.92 (1H, d, J=6.7 Hz)], 5.65—6.33 (1H, m), 7.00—7.79 (9H, m).

b) 5-Butyl-3-(4-butylpiperazinylmethyl)-2,3-dihydro-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**23i**): Sodium hydride in oil (60%, 1.0 g, 25 mmol) was added in portions to a solution of **13a** (1.0 g, 2.8 mmol) in DMF (10 ml). After being stirred for 0.5 h, butyl bromide (1.4 g, 10 mmol) was added to the mixture, and stirring was continued for 5 h. The reaction mixture was warmed at *ca.* 50 °C for 1 h, poured into H_2O, and extracted with Et_2O. The ether layer was extracted with 10% HCl, and the aqueous layer was washed with C_6H_6, made alkaline with 10% Na_2CO_3, and extracted with Et_2O. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give an oil (0.92 g, 71%).

Compounds **23a**—**c**, **23e**, and **23f** were prepared in the same manner as described for **23d**, and **23g** and **23h** were prepared as described for **23i**. The data are presented in Table IV.

3-Chloromethyl-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (24)——Sulfuryl chloride (3.2 g, 24 mmol) was added dropwise to a mixture of **9a** (6.0 g, 20 mmol) and C_6H_6 (60 ml) at 50 °C and then the whole was heated at 70 °C for 0.5 h. After removal of the solvent, the residue was recrystallized from CH_2Cl_2–hexane to afford colorless needles (5.7 g, 95%), mp 210—213 °C. IR (KBr): 3140 (NH), 1650 (CON) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 4.33 (2H, s), 6.95—7.60 (9H, m), 9.07 (1H, br s). *Anal.* Calcd for $C_{16}H_{12}ClNOS$: C, 63.68; H, 4.01; N, 4.64. Found: C, 63.61; H, 3.96; N, 4.75.

2-Phenyl-3-piperazinyl-1,5-benzothiazepin-4(5*H*)-ones (25)——3-(4-Methylpiperazinylmethyl)-2-phenyl-1,5-benzothiazepin-4(5*H*)-one (**25a**): A mixture of **24** (3.0 g, 10 mmol) and *N*-methylpiperazine (15 ml) was heated on a water bath for 2 h. The reaction mixture was poured into H_2O, made alkaline with Na_2CO_3, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was recrystallized from EtOH to afford colorless needles (3.3 g, 91%), mp 219—221 °C. IR (KBr): 3180 (NH), 1655 (CON) cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.07 (3H, s), 1.77—2.50 (8H, m), 3.24 (2H, s), 6.93—7.70 (9H, m), 9.46 (1H, br s). *Anal.* Calcd for $C_{21}H_{23}N_3OS$: C, 69.01; H, 6.34; N, 11.50. Found: C, 69.25; H, 6.50; N, 11.41.

Compound **25b** was obtained similarly.

25b: 90% yield, colorless prisms (EtOH), mp 227—231 °C. ^{1}H-NMR (DMSO-d_6) δ: 1.77—2.48 (10H, m), 3.18 (2H, s), 3.41 (2H, t, J=6.1 Hz), 6.98—7.82 (9H, m).

(+)- and (−)-*cis*-2,3-Dihydro-3-piperazinylmethyl-2-phenyl-1,5-benzothiazepin-4(5*H*)-ones [(+)- and (−)-13]——a) (−)-*cis*-2,3-Dihydro-3-(4-methylpiperazinylmethyl)-2-phenyl-1,5-benzothiazepin-4(5*H*)-one [(−)-**13b**]: (−)-

Tartaric acid (24.5 g, 0.16 mol) was added in portions to a hot solution of **13b** (50 g, 0.136 mol) in MeOH (200 ml). The solution was allowed to cool and the crystals were collected and washed with MeOH. The tartrate was recrystallized from MeOH to give colorless scales, mp 191—193 °C. The (−)-base, obtained from the tartrate, was recrystallized from CH_2Cl_2–petroleum ether to afford colorless prisms (14.5 g, 58%), mp 196—198 °C, $[\alpha]_D^{20}$ −46° (c=2.4, $CHCl_3$). Hydrochloride: Colorless prisms (MeOH–iso-PrOH), mp 256—260 °C (dec.), $[\alpha]_D^{20}$ −63° (c=2.0, H_2O). *Anal.* Calcd for $C_{21}H_{25}N_3OS \cdot HCl$: C, 62.44; H, 6.49; N, 10.40. Found: C, 62.35; H, 6.37; N, 10.48. Dihydrochloride: Colorless needles (H_2O–MeOH), mp 229—231 °C (dec.), $[\alpha]_D^{20}$ −56° (c=0.4, H_2O). *Anal.* Calcd for $C_{21}H_{25}N_3OS \cdot 2HCl$: C, 57.27; H, 6.18; N, 9.54. Found: C, 57.65; H, 6.42; N, 9.80.

b) (−)-*cis*-2,3-Dihydro-3-piperazinylmethyl-2-phenyl-1,5-benzothiazepin-4(5*H*)-one [(−)-**13a**]: This compound was prepared in 41% yield *via* (−)-**14** from (−)-**13b**, in the same manner as described for **13a** and **14**. Colorless prisms (iso-PrOH–C_6H_6), mp 175—179 °C, $[\alpha]_D^{20}$ −43.7° (c=1.0, $CHCl_3$). Dihydrochloride: Colorless needles (EtOH), mp 209—214 °C, $[\alpha]_D^{20}$ −69.5° (c=1.0, H_2O). *Anal.* Calcd for $C_{20}H_{23}N_3OS \cdot 2HCl$: C, 56.34; H, 5.91; N, 9.85. Found: C, 56.36; H, 5.92; N, 9.86.

Compound (−)-**13a** was also resolved in 60% yield in the same manner as described for (−)-**13b**. Compound (+)-**13b** was prepared using (+)-tartaric acid in the same manner as described for (−)-**13b**.

(+)-**13b**: 62% yield, colorless prisms (CH_2Cl_2), mp 196—198 °C, $[\alpha]_D^{20}$ +46° (c=2.4, $CHCl_3$). Dihydrochloride: Colorless needles (H_2O–MeOH), mp 229—231 °C (dec.), $[\alpha]_D^{20}$ +55° (c=0.4, H_2O). *Anal.* Calcd for $C_{21}H_{25}N_3OS \cdot 2HCl$: C, 57.27; H, 6.18; N, 9.54. Found: C, 57.60; H, 6.45; N, 9.77.

References and Notes

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