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1,5-Benzoxathiepin Derivatives. II.¹⁾ Synthesis and Serotonin S₂-Receptor-Blocking Activity of Aminoalkyl-Substituted 3,4-Dihydro-2H-1,5-benzoxathiepin-3-ols and Related Compounds

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Novel 1,5-benzoxathiepin derivatives, 3,4-dihydro-2H-1,5-benzoxathiepin-3-ols with an aminoalkyl group at the 2-, 3- or 4-position, were synthesized and evaluated for serotonin S₂-receptor-blocking activity and adrenergic α_1 -receptor-blocking activity. Methyl 4-aminoalkyl-3-hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates showed significant S₂-receptor-blocking activities. Structure-activity relationships (including the results of a conformational study and skeletal modifications) were examined. In the series of 1,5-benzoxathiepin, 1-benzoxepin and 1-benzothiepin derivatives, methyl *cis*-3-hydroxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate hydrochloride (CV-5197) showed the most potent and the most selective S₂-receptor-blocking activity in the binding profile, and was chosen as a candidate for further pharmacological evaluation.

Keywords—seven-membered heterocycle; 1,5-benzoxathiepin derivative; aminoalkyl-substituted 3,4-dihydro-2H-1,5-benzoxathiepin-3-ol; serotonin S₂-receptor antagonist; structure-activity relationship; 1,5-benzoxathiepin derivative conformation; CV-5197

Serotonin (5-hydroxytryptamine, 5-HT) is known to act as a chemical mediator in a wide variety of physiological actions. Peroutka and Snyder demonstrated the existence of distinct populations of serotonin receptors, S₁ or 5-HT₁ and S₂ or 5-HT₂ receptors, based on the binding characteristics of radio-labeled serotonin and spiperone in rat brain homogenate, respectively.²⁾ Peripheral vascular serotonergic receptors have the pharmacological characteristics of receptors such as S₂-receptors in the central nervous systems.³⁾ Ketanserin, which is a potent and selective S₂-receptor antagonist, is a member of a new class of drugs possessing effective antihypertensive activity.⁴⁾ However, recent studies suggest that the antihypertensive effect of ketanserin in animal models is more related to its postsynaptic adrenergic α_1 -receptor-blocking activity than to its antagonism of vascular S₂-receptors, and the apparent role of serotonin in hypertension is still uncertain.⁵⁾ Nevertheless, platelet aggregation due to serotonin is mediated through S₂-receptors.⁶⁾ Furthermore, serotonin has an amplifying effect on vascular and platelet actions, which is also mediated through S₂-receptors.^{4,6,7)} Thus, the selective antagonism of S₂-receptors might be important in preventing peripheral circulatory disorders in which vasoconstriction and platelet aggregation are suggested to be involved. In a study of the structure-activity relationships of S₂-receptor antagonists, no distinct structural relationships among serotonin and antagonists were found except for the essential amino function in the molecules.⁸⁾ Diltiazem, classified as a Ca antagonist having a structure with the seven-membered 1,5-benzothiazepine skeleton, caused reduction of the serotonin-induced contraction in isolated rabbit basilar artery, whereas such a reduction was diminished in the aorta.⁹⁾

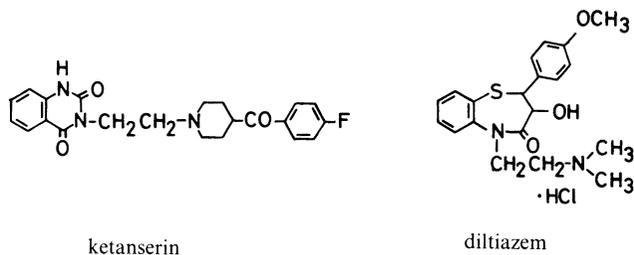
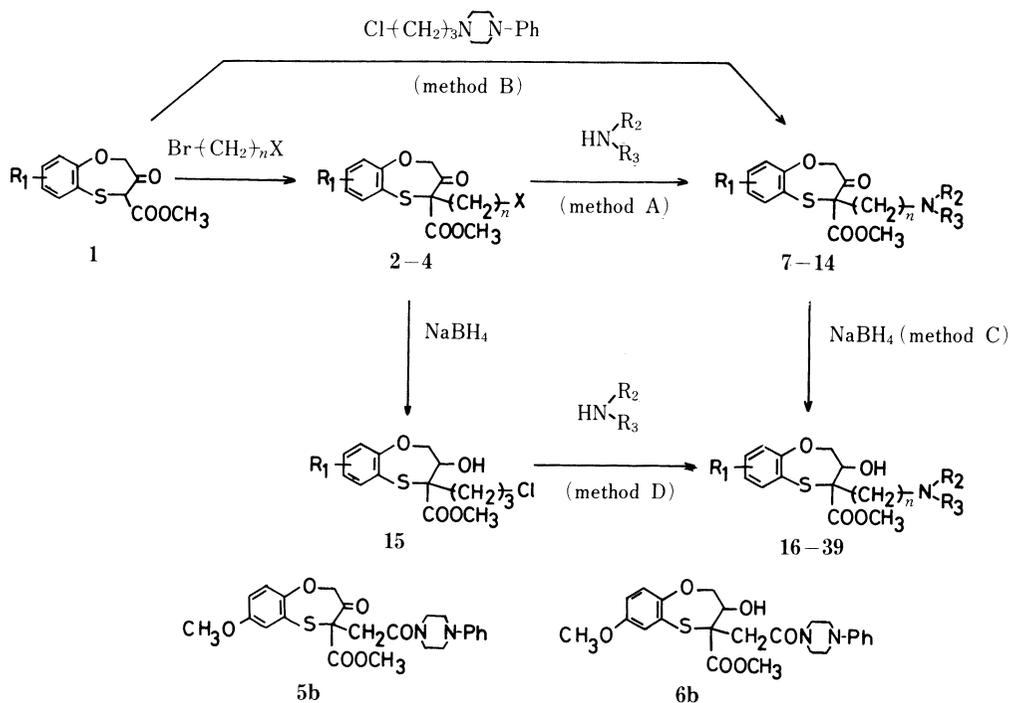


Chart 1

With the aim of finding a novel S_2 -receptor blocker, we synthesized 1,5-benzoxathiepin derivatives having structures analogous to 1,5-benzothiazepines and found that the 3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ols with an aminoalkyl group at the 4-position showed significant S_2 -receptor-blocking activities. In this paper, we report the syntheses of the 1,5-benzoxathiepins with an aminoalkyl group at the 2-, 3-, or 4-position and related compounds, and the structure-activity relationships of S_2 -receptor-blocking activity.

Synthesis of Aminoalkyl-Substituted 1,5-Benzoxathiepin Derivatives and Related Compounds

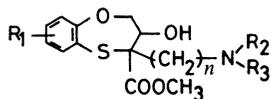
In the previous paper, we reported a novel synthetic route to the 1,5-benzoxathiepin skeleton and some modifications at its 2-, 3-, and 4-positions.¹⁾ We first examined the introduction of an aminoalkyl group into the 4-position of methyl 3-oxo-3,4-dihydro-2*H*-1,5-



a series: $\text{R}_1 = \text{H}$, b series: $\text{R}_1 = 7\text{-OCH}_3$,
 c series: $\text{R}_1 = 8\text{-OCH}_3$, d series: $\text{R}_1 = 7\text{-Cl}$,
 e series: $\text{R}_1 = 7\text{-CH}_3$, f series: $\text{R}_1 = 7\text{-OCH}_2\text{Ph}$,
 g series: $\text{R}_1 = 7\text{-OH}$

Chart 2

TABLE I. Physicochemical Properties of Methyl 4-Aminoalkyl-Substituted 3-Hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (16—39)



Compd. No.	R ₁	N<R ₂ R ₃	n	Meth- od ^{a)}	Yield (%)	mp (°C)	Formula	Analysis (%)		
								Calcd (Found)		
								C	H	N
<i>cis</i> -16b	7-OCH ₃	N<N-Ph	2	F	42	213—216	C ₂₄ H ₃₀ N ₂ O ₅ S· 2HCl	54.24 (54.14)	6.07 (6.08)	5.27 (5.29)
<i>cis</i> -17a	H	N<N-Ph	3	C	52	196—198	C ₂₄ H ₃₀ N ₂ O ₄ S· 2HCl	55.92 (55.73)	6.26 (6.15)	5.45 (5.51)
<i>trans</i> -17a	H	N<N-Ph	3	C	38	165—170	C ₂₄ H ₃₀ N ₂ O ₄ S· 2HCl·1/4 H ₂ O	55.43 (55.47)	6.30 (6.19)	5.39 (5.40)
<i>cis</i> -17b	7-OCH ₃	N<N-Ph	3	C D	47 56	154—155	C ₂₅ H ₃₂ N ₂ O ₅ S· HCl·2H ₂ O	55.09 (55.46)	6.84 (6.77)	5.14 (5.09)
<i>trans</i> -17b	7-OCH ₃	N<N-Ph	3	C	31	140—145	C ₂₅ H ₃₂ N ₂ O ₅ S· HCl·H ₂ O	56.97 (56.67)	6.69 (6.70)	5.31 (5.35)
<i>cis</i> -17c	8-OCH ₃	N<N-Ph	3	C	46	195—198	C ₂₅ H ₃₂ N ₂ O ₅ S· HCl·1/4 H ₂ O	58.47 (58.43)	6.57 (6.44)	5.46 (5.62)
<i>trans</i> -17c	8-OCH ₃	N<N-Ph	3	C	30	170—175	C ₂₅ H ₃₂ N ₂ O ₅ S· 2HCl·1/2 H ₂ O	54.12 (54.08)	6.36 (6.02)	5.05 (5.03)
<i>cis</i> -17d	7-Cl	N<N-Ph	3	C	42	205—207	C ₂₄ H ₂₉ ClN ₂ O ₄ S· 2HCl·1/2 H ₂ O	51.57 (51.77)	5.77 (5.79)	5.01 (4.97)
<i>trans</i> -17d	7-Cl	N<N-Ph	3	C	38	150—160	C ₂₄ H ₂₉ ClN ₂ O ₄ S· 2HCl	52.42 (52.24)	5.68 (5.76)	5.09 (4.97)
<i>cis</i> -17e	7-CH ₃	N<N-Ph	3	C	48	170—175	C ₂₅ H ₃₂ N ₂ O ₄ S· 2HCl	56.70 (56.73)	6.47 (6.54)	5.01 (5.04)
<i>trans</i> -17e	7-CH ₃	N<N-Ph	3	C	33	145—155	C ₂₅ H ₃₂ N ₂ O ₄ S· 2HCl·1/4 H ₂ O	56.23 (56.39)	6.51 (6.53)	5.25 (5.24)
<i>cis</i> -17f	7-OCH ₂ Ph	N<N-Ph	3	D	61	198—201	C ₃₁ H ₃₈ N ₂ O ₅ S· HCl	63.62 (63.32)	6.37 (6.41)	4.79 (4.52)
<i>cis</i> -17g	7-OH	N<N-Ph	3	E	64	207—209	C ₂₄ H ₃₀ N ₂ O ₅ S	62.86 (62.61)	6.59 (6.50)	6.11 (5.88)
<i>cis</i> -18b	7-OCH ₃	N<N-Ph	4	C	75	168—171	C ₂₆ H ₃₄ N ₂ O ₅ S· 2HCl	55.81 (55.92)	6.49 (6.54)	5.01 (5.04)
<i>trans</i> -18b	7-OCH ₃	N<N-Ph	4	C	11	128—130	C ₂₆ H ₃₄ N ₂ O ₅ S	64.17 (64.32)	7.04 (6.95)	5.76 (5.62)
<i>cis</i> -19b	7-OCH ₃	N<N-Ph	5	C	22	125—128	C ₂₇ H ₃₆ N ₂ O ₅ S· HCl·1 1/2 H ₂ O	57.48 (57.20)	7.14 (6.98)	4.97 (4.94)
<i>cis</i> -20b	7-OCH ₃	N<N-Ph Cl	3	C	55	145—150	C ₂₅ H ₃₁ ClN ₂ O ₅ S· 2HCl·1/2 H ₂ O	50.98 (50.67)	5.82 (6.12)	4.76 (4.61)
<i>trans</i> -20b	7-OCH ₃	N<N-Ph Cl	3	C	33	111—113	C ₂₅ H ₃₁ ClN ₂ O ₅ S·	59.22 (59.28)	6.16 (6.27)	5.52 (5.34)
<i>cis</i> -21b	7-OCH ₃	N<N-Ph OCH ₃	3	C	50	140—145	C ₂₆ H ₃₄ N ₂ O ₆ S· HCl·2H ₂ O	54.30 (54.57)	6.83 (6.64)	4.87 (4.70)
<i>trans</i> -21b	7-OCH ₃	N<N-Ph OCH ₃	3	C	20	170—175	C ₂₆ H ₃₄ N ₂ O ₆ S· 2HCl·H ₂ O	52.61 (52.99)	6.45 (6.24)	4.72 (4.72)
<i>cis</i> -22b	7-OCH ₃	N<N-Ph OCH ₃	3	C	55	185—193	C ₂₆ H ₃₄ N ₂ O ₆ S· 2HCl	54.26 (54.56)	6.30 (6.29)	4.87 (5.07)
<i>trans</i> -22b	7-OCH ₃	N<N-Ph OCH ₃	3	C	22	178—182	C ₂₆ H ₃₄ N ₂ O ₆ S· 2HCl	54.26 (54.05)	6.31 (6.36)	4.88 (4.66)
<i>cis</i> -23b	7-CH ₃	N<N-Ph Ph	3	C	65	133—135	C ₃₂ H ₃₈ N ₂ O ₅ S	68.30 (68.48)	6.81 (6.73)	4.98 (4.97)

TABLE I. (continued)

Compd. No.	R ₁	N< R ₂ R ₃	n	Meth- od ^{a)}	Yield (%)	mp (°C)	Formula	Analysis (%)		
								Calcd (Found)		
								C	H	N
<i>trans</i> - 23b	7-OCH ₃		3	C	33	173—176	C ₃₂ H ₃₈ N ₂ O ₅ S	68.30 (68.34)	6.81 (6.81)	4.98 (4.82)
<i>cis</i> - 24b	7-OCH ₃		3	C	63	173—176	C ₂₄ H ₃₁ N ₃ O ₅ S· 2HCl·1/2 H ₂ O	51.89 (51.96)	6.17 (6.40)	7.56 (7.32)
<i>trans</i> - 24b	7-OCH ₃		3	C	25	222—225	C ₂₄ H ₃₁ N ₃ O ₅ S· 2HCl	52.74 (52.31)	6.09 (6.02)	7.69 (7.65)
<i>cis</i> - 25b	7-OCH ₃		3	D	51	135—140	C ₂₆ H ₃₃ NO ₅ S· HCl·1/2 H ₂ O	60.39 (60.48)	6.82 (6.84)	2.71 (2.70)
<i>cis</i> - 26b	7-OCH ₃		3	D	36	140—150	C ₂₅ H ₃₁ FN ₂ O ₅ S· (2HCl·1/2 H ₂ O)	52.44 (52.71)	5.90 (5.82)	4.89 (4.79)
<i>cis</i> - 27b	7-OCH ₃		3	D	43	150—153	C ₂₇ H ₃₂ FN ₂ O ₆ S· HCl·H ₂ O	56.68 (56.71)	6.17 (6.08)	2.45 (2.46)
<i>cis</i> - 28b	7-OCH ₃		3	D	24	210—213	C ₂₃ H ₃₀ N ₄ O ₅ S· 2HCl·H ₂ O	48.85 (48.94)	6.06 (5.84)	9.91 (9.99)
<i>cis</i> - 29b	7-OCH ₃		3	D	35	142—145	C ₂₀ H ₃₀ N ₂ O ₅ S· 1/2 H ₂ O	57.29 (57.45)	7.45 (7.40)	6.68 (6.71)
<i>cis</i> - 30b	7-OCH ₃		3	D	47	205—210	C ₁₉ H ₂₉ NO ₆ S· HCl	52.59 (52.57)	6.50 (6.72)	3.23 (3.19)
<i>cis</i> - 31b	7-OCH ₃		3	D	34	185—188	C ₁₉ H ₂₉ NO ₅ S· HCl	54.34 (54.07)	7.20 (7.23)	3.34 (3.34)
<i>cis</i> - 32b	7-OCH ₃		3	D	41	— ^{b)}	C ₂₆ H ₃₅ N ₂ O ₇ S· HCl·1/2 H ₂ O	56.67 (56.68)	6.77 (6.97)	2.54 (2.51)
<i>cis</i> - 33b	7-OCH ₃		3	D	50	175—190	C ₂₅ H ₃₂ N ₂ O ₆ S· 2HCl·1/2 H ₂ O	52.63 (52.91)	6.18 (5.94)	4.91 (4.95)
<i>cis</i> - 34b	7-OCH ₃		3	D	65	175—180	C ₂₅ H ₃₂ N ₂ O ₆ S· 2HCl·H ₂ O	51.81 (52.00)	6.26 (6.02)	4.83 (4.72)
<i>cis</i> - 35b	7-OCH ₃		3	D	50	240—245	C ₂₅ H ₃₂ N ₂ O ₆ S· 2HCl	53.43 (53.20)	6.10 (5.97)	4.99 (5.21)
<i>cis</i> - 36f	7-OCH ₂ Ph		3	D	57	247—251	C ₃₁ H ₃₆ N ₂ O ₆ S· HCl	61.93 (61.91)	6.20 (6.01)	4.66 (4.65)
<i>cis</i> - 37f	7-OCH ₂ Ph		3	F	64	193—200	C ₂₅ H ₃₂ N ₂ O ₅ S· 2HCl·1/2 H ₂ O	54.15 (54.10)	6.36 (6.30)	5.05 (5.11)
<i>cis</i> - 38g	7-OH		3	E	72	226—229	C ₂₄ H ₃₀ N ₂ O ₆ S	60.74 (60.47)	6.37 (6.39)	5.90 (5.71)
<i>cis</i> - 39g	7-OH		3	E	90	233—240	C ₁₈ H ₂₆ N ₂ O ₅ S· 2HCl	47.47 (47.19)	6.20 (6.36)	6.15 (5.86)

^{a)} Method E, catalytic reduction of the corresponding *O*-benzyl ether. Method F, see experimental section. ^{b)} Amorphous powder.

benzoxathiepin-4-carboxylates (**1a—f**) by alkylation of the reactive methine carbon (Chart 2). The ketoesters (**1a—f**) were alkylated with ω -halogenoalkyl bromides having a side chain of various lengths ($n=3—5$) in refluxing acetonitrile by using potassium carbonate and a catalytic amount of potassium iodide to yield a mixture of the desired *C*-alkylated compounds (30—40%) and *O*-alkylated enole ethers (10—20%) as a by-product. Chromatographic separation of the reaction mixture gave methyl 4-(ω -halogenoalkyl)-3-oxo-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (**2—4**). The 4-[2-oxo-2-(4-phenyl-1-piperazinyl)ethyl] derivative (**5b**) was prepared by alkylation of **1b** with 1-chloroacetyl-4-phenylpiperazine in 69% yield. Conversion of the halogeno moiety of **2—4** into the amino group by sub-

stitution with some amines was carried out by heating in *N,N*-dimethylformamide (DMF) at 70 °C in the presence of potassium carbonate and potassium iodide to give methyl 4-aminoalkyl-substituted 3-oxo-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (**7**–**14**) in fairly good yields (58–76%) (method A). Direct introduction of an *N*-phenylpiperazinylpropyl moiety into the 4-position of **1** by alkylation using 4-phenyl-1-piperazinylpropyl chloride gave *N*-phenylpiperazinylpropyl derivatives (**7a**–**e**) in 18–31% yields (method B). Reduction of **7**–**14** with sodium borohydride (NaBH₄) in an ice-cooled solution of methanol and tetrahydrofuran (THF), and subsequent separation of the resulting stereoisomeric products by column chromatography on silica gel gave methyl *cis*- and *trans*-4-aminoalkyl-3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (**17**–**24**) (method C) (Table I). The configurational nomenclature in this paper refers to the relative configuration between the 3-hydroxy group and the 2- or 4-substituent with higher priority. In each case, NaBH₄ reduction produced predominantly *cis*-alcohols over *trans*-isomers in the range of 1:1–2:1 ratios. Similar NaBH₄ reduction of **2b** and **2f** afforded *cis*-4-chloropropyl-3-ols (*cis*-**15b**, 63% and *cis*-**15f**, 50%) and *trans*-alcohols (*trans*-**15b**, 25% and *trans*-**15f**, 30%), respectively. Substitution of *cis*-**15b** and *cis*-**15f** with various kinds of amines gave *cis*-alcohols with a modified amino group (*cis*-**25**–*cis*-**36**) (method D). The *N*-phenylpiperazinylethyl derivative (*cis*-**16b**) was synthesized by NaBH₄ reduction of **5b**, followed by selective reduction of the amide moiety with sodium monoacetoxyborohydride¹⁰ in boiling THF. 7-Hydroxy derivatives (*cis*-**17g**, *cis*-**36g**, and *cis*-**39g**) were obtained by catalytic reduction of the corresponding 7-benzyloxy derivatives (*cis*-**17f**, *cis*-**36f**, and *cis*-**37f**) using palladium black as a catalyst in ethanol containing hydrochloric acid (method E). The stereochemistries of the compounds bearing substituents at the 3- and 4-positions were determined on the basis of various data including X-ray crystallographic analysis, proton nuclear magnetic resonance (¹H-NMR) spectral data and *R_f* values of each stereoisomer. The physicochemical properties of methyl *cis*- and *trans*-4-aminoalkyl-3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates (**16**–**39**) thus obtained are summarized in Table I.

The *N*-phenylpiperazinylpropyl group was introduced into the 2-position by converting the ester group of methyl 3-(3-oxo-3,4-dihydro-2*H*-1,5-benzoxathiepin-2-yl)propionates (**40b** and **40c**)¹ in three steps (Chart 3). Reduction of **40b** with NaBH₄ and subsequent chromatographic separation gave *cis*-**41b** (47%) and *trans*-**41b** (36%). On the other hand, similar reduction of **40c** gave *cis*-**41c** (86%) and a minor product (7%) which could not be

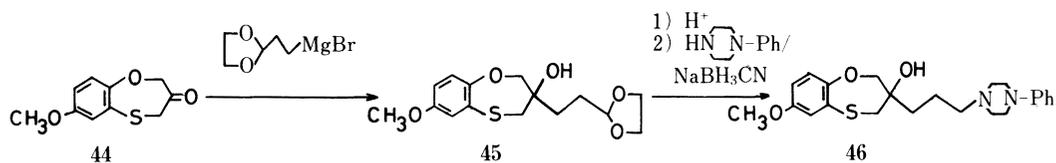
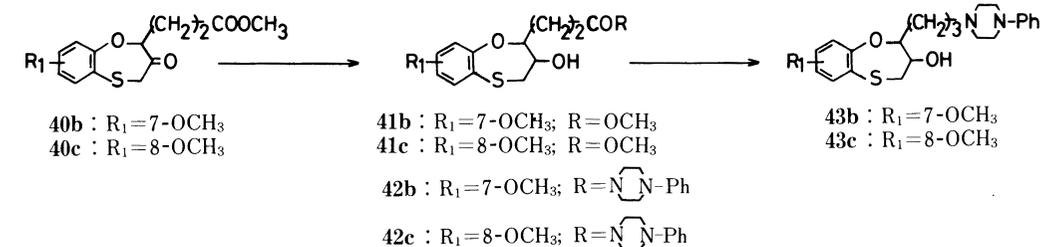


Chart 3

identified as *trans*-**41c**. Heating a mixture of the ester (*cis*-**41b**) and *N*-phenylpiperazine at 90 °C for 5 h afforded the amide (*cis*-**42b**), which was reduced with lithium aluminum hydride (LiAlH₄) in THF to yield *cis*-7-methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (*cis*-**43b**). Similarly, *trans*-**43b** and *cis*-**43c** were prepared via the amides (*trans*-**42b** and *cis*-**42c**).

Grignard reaction of 7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-one (**44**)¹¹ with 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide¹¹ in THF gave 3-(1,3-dioxolan-2-yl)ethyl-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (**45**) in 82% yield. Next, deprotection of the acetal group to aldehyde by treatment with dilute hydrochloric acid and subsequent reductive amination with *N*-phenylpiperazine using sodium cyanoborohydride afforded 7-methoxy-3-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-ol (**46**) in 57% yield (Chart 3).

The compound (**50b**) lacking the 4-methoxycarbonyl group in *cis*-**17b**, which showed the most potent antagonistic activity against S₂-receptors, was prepared in several steps from **2b** as illustrated in Chart 4. Heating **2b** in DMF at 100 °C for 6 h in the presence of aqueous lithium chloride afforded 4-(3-chloropropyl)-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-3-one (**47b**) in 48% yield. Either NaBH₄ reduction of **47b** and subsequent replacement of the chloro group by *N*-phenylpiperazine or initial amination of **47b** and subsequent NaBH₄ reduction gave the same single product, the structure of which was confirmed as the *cis*-isomer (*cis*-**50b**) by X-ray crystallographic analysis. In order to prepare the *trans*-isomer, we examined another synthetic route and found that decarboxylation of *cis*-4-(3-chloropropyl)-3-hydroxy-7-methoxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylic acid (*cis*-**51b**) obtained by alkaline hydrolysis of *cis*-**15b** with heating at 180 °C for 30 min gave *trans*-**48b** with stereochemical retention of the 3-hydroxy and 4-(3-chloropropyl) groups in 16% yield. Subsequent substitution reaction of *trans*-**48b** with *N*-phenylpiperazine gave *trans*-**50b**.

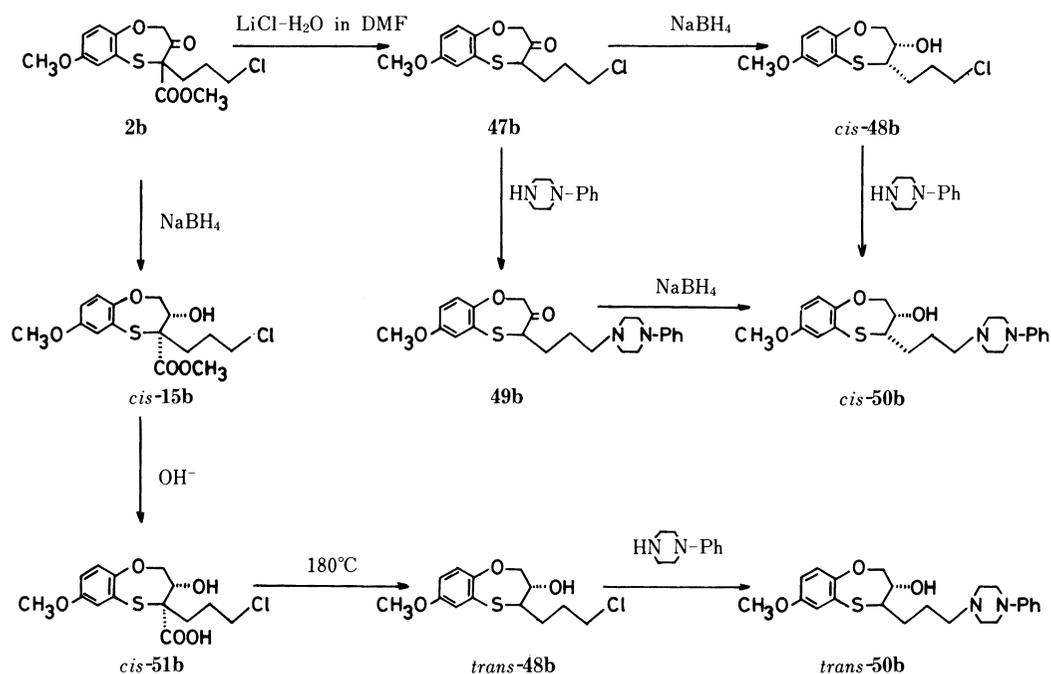


Chart 4

Removal of the 3-hydroxy group from *cis*-**17b** was unsuccessful. Tosylation of *cis*-**17b** with tosyl chloride in pyridine and subsequent catalytic reduction of the crude product using 10% palladium charcoal in ethyl acetate yielded two isomeric products (**52** and **53**) which were also obtained by reduction of *cis*-**15b** with red phosphorus and hydriodic acid in aqueous acetic acid, followed by treatment with *N*-phenylpiperazine. The infrared (IR) spectra of **52** and **53** showed similar absorptions to each other. The 400 MHz NMR spectrum of **52** exhibited two double doublets at δ 4.115 ($J=12.0, 5.4$ Hz) and 4.263 ($J=12.0, 2.1$ Hz) due to methylenic protons adjacent to the oxygen atom and a sextet (ddd) at δ 3.612 ($J=2.1, 5.4, 9.5$ Hz) assignable to the methine proton attached to the carbon bearing the sulfur atom. On irradiation at δ 3.612, the two double doublets were transformed into two doublets with geminal coupling ($J=12.0$ Hz). The $^1\text{H-NMR}$ spectrum of **53** showed similar signals with ABX coupling at δ 4.184 (1H, dd, $J=12.2, 2.0$ Hz), 4.439 (1H, dd, $J=12.2, 4.2$ Hz), and 3.599 (1H, ddd, $J=2.1, 4.2, 9.8$ Hz). These results indicate the presence of the OCH_2CHS group and the absence of the OCH_2CH_2 group as partial structures of **52** and **53**. Thus, the structures of **52** and **53** were assigned as isomeric methyl 5-(4-phenyl-1-piperazinyl)-2-(6-methoxy-1,4-benzoxathian-3-yl)pentanoates, which might be produced by rearrangement involving the episulfonium ion intermediates¹²⁾ generated by elimination of the hydroxy group at the 3-position. Compound **58**, which lacks the 3-hydroxy group in addition to the 4-ester of *cis*-**17b**, was synthesized as illustrated in Chart 5. Grignard reaction of 3-chloropropanal with 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide in THF gave 1-chloro-5-(1,3-dioxolan-2-yl)pentan-3-ol (**54**) in 73% yield. Then **54** was converted into 5-(1,3-dioxolan-2-yl)-3-mesyloxy-pentyl benzoate (**55**) by the reaction of **54** with sodium benzoate in DMF, followed by mesylation.

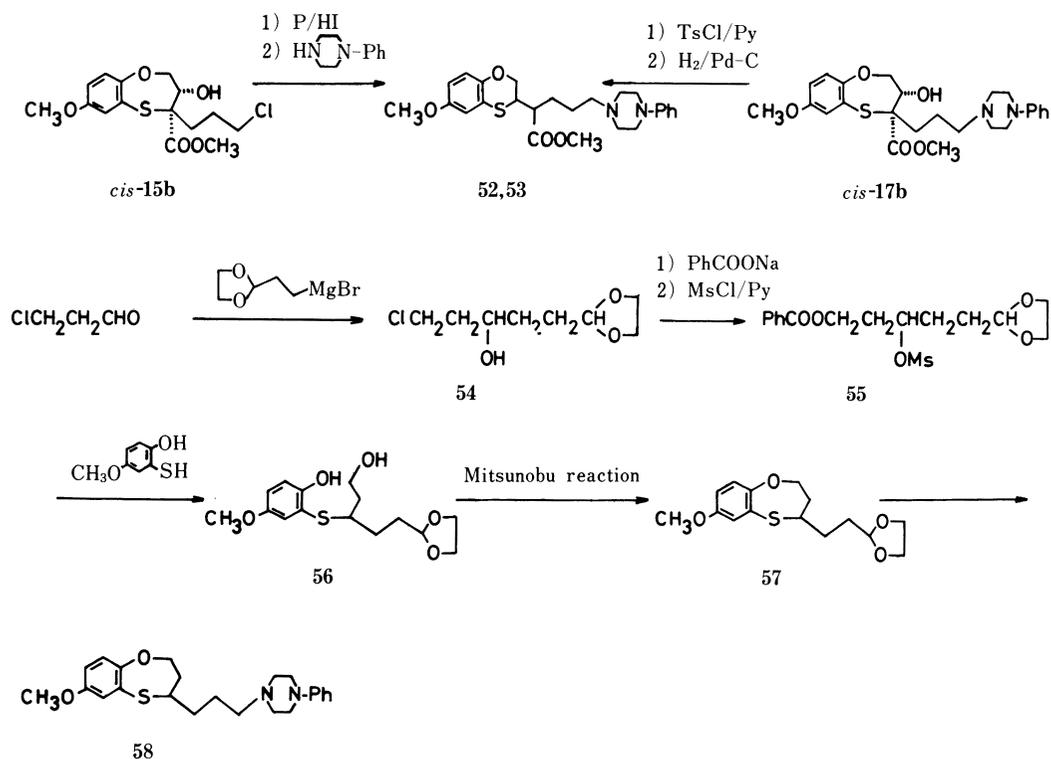


Chart 5

Treatment of **55** with 4-methoxy-2-mercaptophenol and subsequent alkaline hydrolysis gave the precursor (**56**) in 43% yield from **55**. Ring closure of **56** was conducted by means of the Mitsunobu reaction¹³⁾ using triphenylphosphine and ethyl azodicarbonate in toluene to afford 7-methoxy-4-[2-(1,3-dioxolan-2-yl)ethyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin (**57**, 71%), which was converted into the desired 7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin (**58**, 51%) by reductive amination after deprotection of the acetal group of **57**.

Modifications of the 3-hydroxy and the 4-ester groups of *cis*-**17b** were done by *O*-acetylation, *O*-carbamoylation using methyl isocyanate, alkaline hydrolysis, esterification of the resulting 4-carboxylic acid with diethyl sulfate, and lithium aluminum hydride reduction, to give the *O*-acetate (*cis*-**59b**), the 3-*N*-methylcarbamoyloxy derivative (*cis*-**60b**), 4-carboxylic acid (*cis*-**61b**), the 4-ethyl ester (*cis*-**62b**) and the 4-methanol (*cis*-**63b**), respectively (Chart 6).

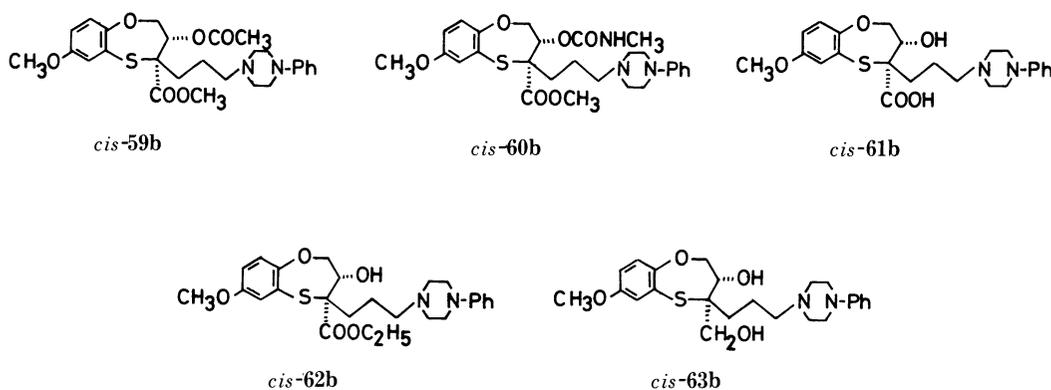


Chart 6

We also tried to prepare the 1-benzoxepin and 1-benzothiepin analogs of *cis*-**17b** in order to clarify the pharmacological significance of the hetero atoms in the 1,5-benzoxathiepin ring (Chart 7). Methyl 8-methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (**64**) was obtained by Dieckmann reaction of methyl 3-(4-methoxy-2-methoxycarbonylmethyl)oxy)phenylpropionate according to the method described by Huckle *et al.*¹⁴⁾ Methyl 3-oxo-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylates (**65** and **66**) were prepared by similar Dieckmann reaction according to the procedure of Huckle *et al.*¹⁴⁾ via the Newman's reaction¹⁵⁾ of methyl 2-hydroxyphenylpropionates. The syntheses of *N*-phenylpiperazinyl-propyl-substituted 1-benzoxepin and 1-benzothiepin derivatives (**73**, **74**, and **75**) from the ketoesters (**64**, **65**, and **66**) were done by methods similar to those described for 1,5-benzoxathiepin derivatives, involving alkylation with 3-bromo-1-chloropropane, subsequent NaBH_4 reduction and finally substitution with *N*-phenylpiperazine (Chart 7) (Table II).

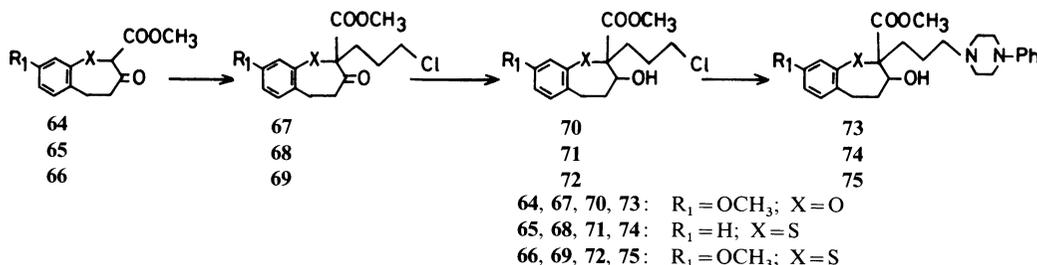
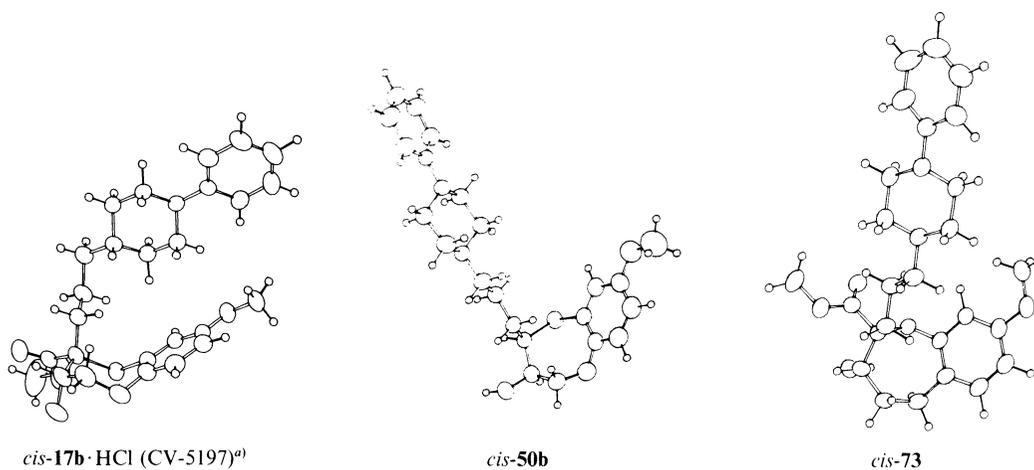


Chart 7

TABLE II. Physicochemical Properties of *N*-Phenylpiperazinylpropyl-Substituted 1-Benzoxepin and 1-Benzothiepin Derivatives (73–75)

Compd. No.	R ₁	X	Yield (%)	mp (°C)	Formula	Analysis (%)		
						Calcd (Found)		
						C	H	N
<i>cis</i> -73	OCH ₃	O	47	126–128	C ₂₆ H ₃₄ N ₂ O ₅	68.70 (68.42)	7.54 (7.62)	6.16 (6.02)
<i>trans</i> -73	OCH ₃	O	72	140–155	C ₂₆ H ₃₄ N ₂ O ₅ · 2HCl	59.20 (59.12)	6.88 (6.96)	5.31 (5.23)
<i>cis</i> -74	H	S	60	152–154	C ₂₅ H ₃₂ N ₂ O ₃ S	68.15 (68.40)	7.32 (7.34)	6.36 (6.36)
<i>cis</i> -75	OCH ₃	S	80	145–150	C ₂₆ H ₃₄ N ₂ O ₄ S · HCl · 1/2 H ₂ O	60.51 (60.39)	7.03 (7.36)	5.43 (5.49)

Fig. 1. X-Ray Structures of *cis*-17b · HCl, *cis*-50b, and *cis*-73
a) Shown without Cl⁻.

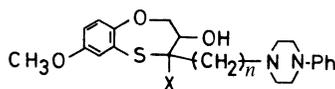
In the case of 1-benzothiepin derivatives, the hydride reduction of the 3-carbonyl moiety gave exclusively *cis*-alcohols (*cis*-71 and *cis*-72) without detectable stereoisomers on thin-layer chromatography (TLC). The configurations of these compounds were determined by X-ray crystallographic analysis of *cis*-71 and comparison of the 400 MHz NMR spectral data of the products (71 and 72).

Configurations and Conformations of 1,5-Benzoxathiepin Derivatives and Related Compounds

The conformations of seven-membered compounds have been investigated theoretically and experimentally from the viewpoint of interconversion and pseudorotation.^{16,17)}

We first determined the configurations of *cis*-17b, *cis*-50b, *cis*-58b, *cis*-71, and *cis*-73 by X-ray crystallographic analysis and then examined the conformations in solution based on 400 MHz NMR spectra data. The X-ray results have shown that the chair form of the seven-membered ring is the common conformation for 1,5-benzoxathiepin (*cis*-17b, *cis*-50b, and *cis*-58b), 1-benzoxepin (*cis*-73), and 1-benzothiepin (*cis*-71) derivatives (Fig. 1). The most striking

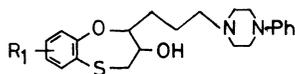
TABLE III. Selected 400 MHz NMR Spectral Data for 4-(4-Phenyl-1-piperazinyl)alkyl-3,4-dihydro-2H-1,5-benzoxathiepin-3-ols



Compd. No.	X	n	Salt	NMR (DMSO- <i>d</i> ₆) ^{a)}					
				Chemical shift δ (ppm)			Coupling constant (Hz)		
				C ₂ -H _a	C ₂ -H _b	C ₃ -H	<i>J</i> _{2a,3}	<i>J</i> _{2b,3}	<i>J</i> _{3,4}
<i>cis</i> -16b	COOCH ₃	2	2HCl	4.022	4.168	4.080	2.7	6.1	—
<i>cis</i> -17b	COOCH ₃	3	HCl	3.873	4.155	3.999	0—1.0	4.6	—
<i>cis</i> -17b	COOCH ₃	3	Free base	3.843	4.249	4.078	0—1.0	3.4	—
<i>trans</i> -17b	COOCH ₃	3	HCl	3.794	4.107	4.383	8.4	3.8	—
<i>cis</i> -18b	COOCH ₃	4	2HCl	3.920	4.151	4.017	2.3	5.6	—
<i>trans</i> -18b	COOCH ₃	4	2HCl	3.783	4.063	4.314	7.8	3.7	—
<i>cis</i> -19b	COOCH ₃	5	HCl	3.913	4.149	4.011	2.3	5.5	—
<i>cis</i> -50b	H	3	2HCl	3.776	4.017	4.152	8.5	3.8	3.8 ^{b)}
<i>trans</i> -50b	H	3	2HCl	3.855	4.329	3.785	4.9	2.8	7.7 ^{c)}

a) *cis*-17b (free base) was determined in CDCl₃ solution. b) δ 3.206 ppm (C₄-H). c) δ 3.031 ppm (C₄-H).

TABLE IV. Selected 400 MHz NMR Spectral Data for 2-[3-(4-Phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ols

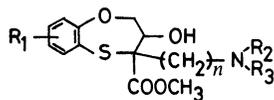


Compd. No.	R ₁	NMR (CDCl ₃)						
		Chemical shift δ (ppm)				Coupling constant (Hz)		
		C ₂ -H	C ₃ -H	C ₄ -H _a	C ₄ -H _b	<i>J</i> _{2,3}	<i>J</i> _{3,4a}	<i>J</i> _{3,4b}
<i>cis</i> -43b	7-OCH ₃	3.609	3.975	2.953	3.039	0—1.0	2.1	5.4
<i>trans</i> -43b	7-OCH ₃	3.96	3.96	2.735	3.534	— ^{a)}	4.8	2.3
<i>cis</i> -43c	8-OCH ₃	3.668	3.970	2.886	2.966	0—1.0	2.1	5.4

a) Not determined.

characteristic of *cis*-17b is the folded conformation of the whole molecule and the quasi-axial orientation of the sterically bulky *N*-phenylpiperazinylpropyl substituent. The 400 MHz NMR spectral data of the 4-[3-(4-phenyl-1-piperazinyl)propyl]-3-hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin derivatives also support the occurrence of solution conformations that are similar to the solid state conformations, except in the case of *trans*-50b (Table III). The rather large coupling constant in *trans*-17b (*J*_{2a,3} = 8.4 Hz) suggests the presence of a quasi-equatorial 3-hydroxy group in *trans*-17b, while the small values in *cis*-17b (*J*_{2a,3} = 0—1.0 Hz and *J*_{2b,3} = 4.6 Hz) indicate a major contribution of a conformation similar to the X-ray conformation in solution. The excellent agreement of the correlative *J* values of *cis*-50b and *trans*-17b indicates that these compounds possess similar conformations except for the structural difference of the absence or presence of the 4-ester moiety. However, the discrepancy between the *J* values in the NMR spectral data of *trans*-50b and *cis*-17b suggests that the major conformer of *trans*-50b differs from the X-ray conformer of *cis*-17b. The *J*_{3,4}

TABLE V. Biological Activities of Methyl 4-Aminoalkyl-3-hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates



Compd. No.	R ₁	N < $\begin{matrix} R_2 \\ R_3 \end{matrix}$	n	Serotonin S ₂ -blocking activity ^{a)}			Adrenaline α ₁ -blocking activity ^{b)}	
				10 ⁻⁵	10 ⁻⁶	10 ⁻⁷ M	10 ⁻⁵	10 ⁻⁶ M
<i>cis</i> -16b	7-OCH ₃		2	68			80	
<i>cis</i> -17a	H		3	100	77	3	100	30
<i>trans</i> -17a	H		3	100	18		100	75
<i>cis</i> -17b	7-OCH ₃		3		100	77	5	
<i>trans</i> -17b	7-OCH ₃		3	100	89	15	66	
<i>cis</i> -17c	8-OCH ₃		3	92	71	3	31	
<i>trans</i> -17c	8-OCH ₃		3	96	28		53	
<i>cis</i> -17d	7-Cl		3	100	85	31	45	
<i>trans</i> -17d	7-Cl		3	100	67	12	70	
<i>cis</i> -17e	7-CH ₃		3	100	77	40	35	
<i>trans</i> -17e	7-CH ₃		3	100	27	0	58	
<i>cis</i> -17g	7-OH		3	79	16		0	
<i>cis</i> -18b	7-OCH ₃		4	66			95	
<i>trans</i> -18b	7-OCH ₃		4	66	35		90	
<i>cis</i> -19b	7-OCH ₃		5	56			90	
<i>cis</i> -20b	7-OCH ₃		3	94	35		47	
<i>cis</i> -21b	7-OCH ₃		3	88	12		100	28
<i>cis</i> -24b	7-OCH ₃		3	100	77	55	100	18
<i>cis</i> -25b	7-OCH ₃		3	100	88	25	40	
<i>cis</i> -26b	7-OCH ₃		3	100	99	12	30	
<i>cis</i> -27b	7-OCH ₃		3	100	88	50	100	
<i>cis</i> -28b	7-OCH ₃		3	68			0	
<i>cis</i> -32b	7-OCH ₃		3	83	27		15	
<i>cis</i> -33b	7-OCH ₃		3	100	12		55	
<i>cis</i> -34b	7-OCH ₃		3	100	36	16	10	

TABLE V. (continued)

Compd. No.	R ₁	N $\begin{matrix} R_2 \\ R_3 \end{matrix}$	n	Serotonin S ₂ -blocking activity ^{a)}			Adrenaline α_1 -blocking activity ^{b)}	
				10 ⁻⁵	10 ⁻⁶	10 ⁻⁷ M	10 ⁻⁵	10 ⁻⁶ M
<i>cis</i> - 35b	7-OCH ₃		3	100	100	79	56	
<i>cis</i> - 38g	7-OH		3	100	0		8	

a) % inhibition of 5-HT-induced contraction in pig coronary artery. b) % inhibition of norepinephrine-induced contraction in rabbit aorta.

TABLE VI. Biological Activities of 3-(4-Phenyl-1-piperaziny)propyl-Substituted 3,4-Dihydro-2*H*-1,5-benzoxathiepin Derivatives and Related Analogs

Compd. No.	Serotonin S ₂ -blocking activity ^{a)}			Adrenaline α_1 -blocking activity ^{b)}
	10 ⁻⁵	10 ⁻⁶	10 ⁻⁷ M	10 ⁻⁵ M
7b	100	80	2	63
<i>cis</i> - 43b	56	13		50
<i>trans</i> - 43b	42	0		77
<i>cis</i> - 43c	100	63		53
46	25	0		99
<i>cis</i> - 50b	99	35		50
<i>trans</i> - 50b	72			55
58	58			60
<i>cis</i> - 59b	100	92	19	40
<i>cis</i> - 60b	100	47		72
<i>cis</i> - 62b	100	83	19	0
<i>cis</i> - 63b	90	17	0	50
<i>cis</i> - 73	100			44
<i>trans</i> - 73	100	24		62
<i>cis</i> - 74	96	60		36
<i>cis</i> - 75	100	69		31

a) % inhibition of 5-HT-induced contraction in pig coronary artery. b) % inhibition of norepinephrine-induced contraction in rabbit aorta.

value (7.7 Hz) of *trans*-**50b** suggests a substantial contribution of quasi-equatorial orientation of the *N*-phenylpiperazinypropyl group at the 4-position. In the case of the derivatives with a side chain of various lengths (**16**, **18** and **19**), it was deduced that the main conformation of each stereoisomer was similar to that found for the corresponding isomer of **17b** on the basis of the NMR spectral data, supposing the half-chair conformation for the seven-membered ring. On the other hand, the equatorial orientation of the *N*-phenylpiperazinypropyl moiety at the 2-position was estimated from the NMR spectral data of *cis*-**43b**, **c** and *trans*-**43b** (Table IV). X-ray crystallographic analyses and the NMR spectral data of 1-benzoxepin (**73**) and 1-benzothiepin (**74** and **75**) derivatives indicated that these compounds also had major conformers similar to those observed in **17b**. The main contribution of *trans*-1,2-diaxial orientation of the sterically bulky substituents for *cis*-**17b** in contrast with *trans*-**50b** is readily rationalizable in terms of the stabilizing effect associated with the favorable hydrogen bonding between the 3-hydroxy function and the 4-ester carbonyl in *cis*-**17b** compared with

trans-**50b**, lacking the ester group.

Biological Results and Discussion

The S₂-receptor-blocking activity and selectivity toward S₂-receptors over adrenergic α₁-receptors of the aminoalkyl-substituted 1,5-benzoxathiepin derivatives and related compounds synthesized in this paper were evaluated in terms of ability to antagonize serotonin-induced contraction in the isolated pig coronary artery and to block norepinephrine-induced contraction in the isolated rabbit aorta. The results of *in vitro* evaluation are shown in Tables V and VI.

Methyl 4-aminoalkyl-3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates showed significant S₂-receptor-blocking activities. The inhibitory potency for serotonin-induced contraction increased in the order of 3 > 2, 4 > 5 of side chain length (*n*). The substituents on the benzene ring of the 1,5-benzoxathiepin skeleton also influenced the biological activities. Introduction of the methoxy group into the 7-position (**17b**) resulted in marked enhancement of the activity, whereas shift of the methoxy group from the 7- to the 8-position diminished the effect. Substituents of the amino group in the side chain also caused changes (**17b**, **20b**—**35b**) in the structure-activity relationships. The nitrogen atom attached to the 4-propyl group might play an important role in the interaction with S₂-receptors since the 4-phenylpiperidyl derivative (*cis*-**25b**) showed activity comparable to that of the *N*-phenylpiperazinyl derivative (*cis*-**17b**). The presence of the aromatic ring within a distance of two or three methylenic chains from the nitrogen atom described above seemed to be preferable for S₂-receptor-blocking activity. Among the stereochemical isomers, the *cis*-isomers, rather than the *trans*-isomers, showed more potent and more selective antagonism toward S₂-receptors over adrenergic α₁-receptors. When the 3-(4-phenyl-1-piperazinyl)propyl moiety was introduced into the 2-position, the presence of the methoxy group at the 8-position (*cis*-**43c**) instead of the 7-position (**43b**) was critical for the manifestation of biological activities. On the other hand, substitution of the 3-(4-phenyl-1-piperazinyl)propyl group at the 3-position (**46**) resulted in a marked reduction of S₂-receptor-blocking activity and considerably increased inhibitory potency for adrenergic α₁-receptors. In the series of methyl aminoalkyl-substituted 3-hydroxy-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylates, methyl *cis*-3-hydroxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2*H*-1,5-benzoxathiepin-4-carboxylate hydrochloride (*cis*-**17b**, CV-5197) showed the most potent S₂-receptor-blocking activity and the highest selectivity over the adrenergic α₁-blocking activity. Some modifications of the 3-hydroxy and 4-ester groups of *cis*-**17b** gave the following results. The activities were unchanged upon modifications of the 3-hydroxy group, *e.g.*, *O*-acetate (*cis*-**59b**) and *N*-methylcarbamoyloxy (*cis*-**60b**) derivatives and the 3-carbonyl compound (**7b**). Removal of the 4-ester moiety gave quite different results in different stereochemical isomers. The *cis*-isomer (*cis*-**50b**) showed activities comparable to those of *trans*-**17b**. However, the S₂-receptor-blocking activity of *trans*-**50b** was 100 times less potent than that of *cis*-**17b** in spite of the configurational retention of the 3-hydroxy and 4-aminoalkyl moieties in both molecules. Removal of the 3-hydroxy and 4-ester groups (**58**) resulted in further reduction of the activity. Ring-contraction of 1,5-benzoxathiepin skeleton (**52** and **53**) resulted in loss of S₂-receptor antagonistic activity. In the series of skeletal modifications, methyl *cis*-3-hydroxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (*cis*-**74**) showed almost equipotent activity to the corresponding 1,5-benzoxathiepin derivative (*cis*-**17a**). However, introduction of the methoxy group (*cis*-**75**) did not produce the potentiation of the activity that was observed in the case of the 1,5-benzoxathiepins (**17a**→**17b**), and the inhibitory potency of the 1-benzoxepin derivative (*cis*-**73**) was 10 times less than that of *cis*-**17b** in spite of the conformational similarity between the two compounds (Fig. 1). These results suggest that the oxygen atom in the 1,5-benzoxathiepin ring of *cis*-**17b**

might also play a significant role in the interaction with S₂-receptors.

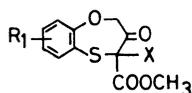
X-Ray crystallographic analyses of known S₂-receptor antagonists have shown that ketanserin,¹⁸⁾ metergoline,¹⁹⁾ piperperon,²⁰⁾ and haloperidol²¹⁾ have a common extended conformation, but spiperone, with the neuroleptics displaying dopamine-blocking activity and potent S₂-receptor-blocking activity as well, had the folded conformation.²²⁾ A recent investigation by Azibi *et al.* showed the conformational flexibility of spiperone and confirmed the existence of extended and folded conformers in two polymorphs of spiperone by X-ray analysis.²³⁾ The structure-activity relationships in our study indicate that the favorable structure interacting with S₂-receptors approximates the folded conformation proposed as the preferred form of spiperone.²⁴⁾ A consideration of the folded conformation shown by the X-ray analysis of *cis*-**17b** (CV-5197) suggests that two aromatic rings, a 7-methoxy group, a 3-quasi-axial hydroxy group along with the oxygen atom in the skeleton and the essential nitrogen atom attached to the 4-propyl side chain are significant for the biological activity.

Further evaluation of CV-5197 revealed higher selectivity for the S₂ binding sites than the S₁ ones in the radioligand binding assay in rat brain synaptosomes and practically no inhibitory action on any other agonist, including histamine and acetylcholine.²⁵⁾ The detailed pharmacological profiles of CV-5197 and its actions on circulatory disorders in experimental animal models will be described elsewhere.²⁶⁾

Experimental

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. IR spectra were obtained with Hitachi 215 and 260-10 spectrophotometers. ¹H-NMR spectra were measured with Varian T-60, EM-390, and JEOL JNM-GX400 NMR spectrometers and the 60 MHz spectral data are given, unless otherwise mentioned. Mass spectra (MS) were taken on JEOL JMS-01SC and Hitachi M-80A (high-resolution MS)

TABLE VII. Physicochemical Properties of Methyl 4-Substituted 3-Oxo-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (**2**—**5**)



Compd. No.	R ₁	X	Yield (%)	mp (C)	Formula	Analysis (%)		
						Calcd	Found	
						C	H	N
2b	7-OCH ₃	(CH ₂) ₃ Cl	44	64—65	C ₁₅ H ₁₇ ClO ₅ S	52.33 (52.25)	5.10 (4.97)	
2c	8-OCH ₃	(CH ₂) ₃ Cl	42	Oil	C ₁₅ H ₁₇ ClO ₅ S	52.33 (52.14)	5.10 (5.23)	
2d	7-Cl	(CH ₂) ₃ Cl	32	Oil	C ₁₄ H ₁₄ Cl ₂ O ₄ S	48.15 (48.36)	4.04 (4.27)	
2e	7-CH ₃	(CH ₂) ₃ Cl	37	Oil	C ₁₅ H ₁₇ ClO ₄ S	54.79 (54.52)	5.21 (5.48)	
2f	7-OCH ₂ Ph	(CH ₂) ₃ Cl	36	88—89	C ₂₁ H ₂₁ ClO ₅ S	59.93 (59.89)	5.03 (5.02)	
3b	7-OCH ₃	(CH ₂) ₂ Br	32	Oil	C ₁₆ H ₁₉ BrO ₅ S	47.65 (47.39)	4.75 (4.86)	
4b	7-OCH ₃	(CH ₂) ₃ Br	31	Oil	C ₁₇ H ₂₁ BrO ₅ S	48.92 (48.81)	5.07 (5.26)	
5b	7-OCH ₃	CH ₂ CON ₆ NPh	69	146—148	C ₂₄ H ₂₆ N ₂ O ₆ S	61.26 (61.40)	5.57 (5.60)	5.94 (5.90)

mass spectrometers. In the NMR spectra, chemical shifts are given in the δ (ppm) scale with tetramethylsilane as an internal standard.

Reactions were run at room temperature unless otherwise noted, and followed by TLC on Merck F-254 silicagel plates. Standard work-up procedures were as follows. The reaction mixture was partitioned between the indicated solvent and water. The organic extract was washed with water (H_2O). The extract was dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. Chromatographic separation was done on Merck Silica gel 60 with the indicated eluant.

Methyl 4-(ω -Halogenoalkyl)-3-oxo-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (2–5, Table VII)—A typical example of the experimental procedure used to obtain 2–5 is as follows. A mixture of methyl 7-methoxy-3-oxo-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (**1b**) (2.0 g, 7 mmol), 1-bromo-3-chloropropane (2.3 g, 15 mmol), K_2CO_3 (1.5 g, 11 mmol), KI (1.2 g, 7 mmol) and CH_3CN (30 ml) was refluxed with stirring under an N_2 stream for 3 h. After filtration of the reaction mixture, the filtrate was concentrated *in vacuo*. The residue was diluted with H_2O and worked up (AcOEt; H_2O). The residue was subjected to column chromatography on silica gel (hexane: CH_2Cl_2 : AcOEt = 30:15:1). Compound **2b** (1.12 g, 44%) was obtained from the first fraction as colorless prisms (recrystallized from EtOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1760, 1725, 1600, 1485, 1260, 1240, 1210, 1175, 1040. $^1\text{H-NMR}$ (CDCl_3) δ : 1.8–2.2 (4H, m), 3.57 (2H, t, $J=6$ Hz, CH_2Cl), 3.73 (3H, s), 3.75 (3H, s), 4.47 (1H, d, $J=18$ Hz, $\text{C}_2\text{-H}$), 4.73 (1H, d, $J=18$ Hz, $\text{C}_2\text{-H}$), 6.55 (1H, dd, $J=8, 2$ Hz, $\text{C}_8\text{-H}$), 6.57 (1H, d, $J=2$ Hz, $\text{C}_6\text{-H}$), 6.88 (1H, d, $J=8$ Hz, $\text{C}_9\text{-H}$).

The second fraction yielded methyl 3-(3-chloropropoxy)-7-methoxy-2H-1,5-benzoxathiepin-4-carboxylate (0.38 g, 15%) as a colorless oil. MS m/z : 344, 346 (M^+). IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 1720 (ester). $^1\text{H-NMR}$ (CDCl_3) δ : 2.18 (2H, m), 3.70 (2H, t, $J=6$ Hz, CH_2Cl), 3.72 (3H, s), 3.80 (3H, s), 4.10 (2H, t, $J=6$ Hz, OCH_2CH_2), 5.10 (2H, s, $\text{C}_2\text{-H}$). Compounds 2–5 were prepared by similar alkylation of **1a–f** with the corresponding ω -halogenoalkylbromides, and their physical data are listed in Table VII.

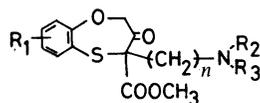
Methyl cis- and trans-3-Hydroxy-7-methoxy-4-[2-oxo-2-(4-phenyl-1-piperazinyl)ethyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (cis- and trans-6b)— NaBH_4 (0.38 g, 10 mmol) was added in small portions to a solution of **5b** (3.1 g, 6.7 mmol) in MeOH (50 ml). The mixture was stirred for 1 h and then poured into ice- H_2O . The resulting precipitates were collected by filtration and recrystallized from AcOEt to give *cis*-**6b** (1.8 g, 57%) as colorless prisms, mp 213–215 °C. *Anal.* Calcd for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_6\text{S}$: C, 61.00; H, 5.97; N, 5.93. Found: C, 60.87; H, 5.84; N, 5.86. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3500 (OH), 1740 (ester), 1650 (amide). $^1\text{H-NMR}$ (400 MHz) (CDCl_3) δ : 3.907 (1H, dd, $J=1.2, 13.2$ Hz, $\text{C}_2\text{-H}$), 4.128 (1H, dd, $J=1.2, 4.4$ Hz, $\text{C}_3\text{-H}$), 4.341 (1H, dd, $J=4.4, 13.2$ Hz, $\text{C}_2\text{-H}$). Chromatographic purification of the mother liquor gave *trans*-**6b** (0.4 g, 13%) as a colorless oil, which was converted into the hydrochloride, colorless crystals, mp 170–180 °C (dec.). *Anal.* Calcd for $\text{C}_{24}\text{H}_{28}\text{N}_2\text{O}_6\text{S} \cdot \text{HCl} \cdot 1/2\text{H}_2\text{O}$: C, 55.64; H, 5.83; N, 5.40. Found: C, 55.38; H, 5.73; N, 5.44. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3550, 1740, 1650. $^1\text{H-NMR}$ (400 MHz) ($\text{DMSO-}d_6$) δ : 4.082 (1H, dd, $J=5.7, 12.6$ Hz, $\text{C}_2\text{-H}$), 4.185 (1H, ddd, $J=2.2, 5.7, 7.3$ Hz, $\text{C}_3\text{-H}$), 4.300 (1H, dd, $J=2.2, 12.6$ Hz, $\text{C}_2\text{-H}$), 5.546 (1H, d, $J=7.3$ Hz, OH).

Methyl 4-Aminoalkyl-Substituted 3-Oxo-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (7–14, Table VIII)—A typical example of the experimental procedure used to obtain 7–14 is as follows. Method A) A mixture of **2b** (56 g, 0.16 mol), *N*-phenylpiperazine (40 g, 0.26 mol), K_2CO_3 (34 g, 0.25 mol), KI (5.5 g, 33 mmol) and DMF (250 ml) was stirred at 70 °C for 7 h. The reaction mixture was poured into ice- H_2O and extracted with AcOEt. The organic layer was worked up and the residue was recrystallized from MeOH to give **7b** (57 g, 75%) as colorless crystals. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 1755 (ester), 1720 (CO), 1600, 1485, 1265, 1240, 1225, 1205, 1045. $^1\text{H-NMR}$ (CDCl_3) δ : 1.2–3.3 (14H, m), 3.68 (3H, s), 3.72 (3H, s), 4.38 (1H, d, $J=18$ Hz, $\text{C}_2\text{-H}$), 4.72 (1H, d, $J=18$ Hz, $\text{C}_2\text{-H}$), 6.4–7.4 (8H, m). Method B) A mixture of **1b** (5 g, 19 mmol), 3-(4-phenyl-1-piperazinyl)propyl chloride (6.7 g, 28 mmol), K_2CO_3 (4.65 g, 34 mmol), KI (3 g, 18 mmol) and CH_3CN (150 ml) was refluxed with stirring for 4 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was diluted with H_2O and extracted with AcOEt. The organic layer was worked up and the residue was purified by column chromatography on silica gel (hexane: AcOEt = 2:1) to give **7b** (2.7 g, 31%) as colorless crystals. Compounds 7–14 were similarly prepared by the substitution of 2–4 with the corresponding amines (method A) or by the alkylation of **1** with 3-(4-phenyl-1-piperazinyl)propyl chloride (method B), and their physical data are listed in Table VIII.

Methyl cis- and trans-4-(3-Chloropropyl)-3-hydroxy-7-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (cis- and trans-15b)— NaBH_4 (0.3 g, 8 mmol) was added in small portions to an ice-cooled solution of **2b** (2.0 g, 6 mmol) in MeOH (15 ml) and THF (8 ml) with stirring. The mixture was stirred for 1 h, then poured into ice- H_2O and worked up (AcOEt; H_2O). The residue was subjected to column chromatography on silica gel (hexane: AcOEt = 2:1) to give *trans*-**15b** (0.5 g, 25%) from the first fraction, as colorless needles, mp 108–110 °C (recrystallized from AcOEt–hexane). *Anal.* Calcd for $\text{C}_{15}\text{H}_{19}\text{ClO}_5\text{S}$: C, 51.95; H, 5.52. Found: C, 51.63; H, 5.51. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3500 (OH), 1730 (ester). $^1\text{H-NMR}$ (CDCl_3) δ : 1.95 (4H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl}$), 3.48 (2H, t, $J=6.5$ Hz, CH_2Cl), 3.58 (3H, s), 3.70 (3H, s), 4.0–4.2 (3H, m).

The second fraction yielded *cis*-**15b** (1.25 g, 63%) as colorless prisms, mp 80–82 °C (recrystallized from EtOH). *Anal.* Calcd for $\text{C}_{15}\text{H}_{19}\text{ClO}_5\text{S}$: C, 51.95; H, 5.52. Found: C, 51.61; H, 5.48. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3540 (OH), 1735 (ester), 1600, 1485, 1440, 1250, 1210. $^1\text{H-NMR}$ (CDCl_3) δ : 1.4–2.4 (4H, m), 3.40 (2H, t, $J=4$ Hz, CH_2Cl), 3.75 (3H, s), 3.80

TABLE VIII. Physicochemical Properties of Methyl 4-Aminoalkyl-Substituted 3-Oxo-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (7—14)



Compd. No.	R ₁	n	N ₂ R ₂ R ₃	Meth- od	Yield (%)	mp (°C)	Formula	Analysis (%)		
								Calcd	Found	
								C	H	N
7a	H	3	N-Ph	B	18	176—178	C ₂₄ H ₂₈ N ₂ O ₅ S· HCl·1/2 H ₂ O	59.67 (59.49)	6.26 (6.33)	5.83 (5.79)
7b	7-OCH ₃	3	N-Ph	A	75	110—112	C ₂₅ H ₃₀ N ₂ O ₅ S	63.81 (63.50)	6.43 (6.37)	5.95 (5.71)
7c	8-OCH ₃	3	N-Ph	B	31	140—145	C ₂₅ H ₃₀ N ₂ O ₅ S· 2HCl·H ₂ O	53.47 (53.55)	6.10 (5.87)	4.99 (5.00)
7d	7-Cl	3	N-Ph	A	76	197—199	C ₂₄ H ₂₇ ClN ₂ O ₄ S· 2HCl·1/2 H ₂ O	51.76 (52.02)	5.43 (5.12)	5.03 (5.08)
7e	7-CH ₃	3	N-Ph	A	78	145—150	C ₂₅ H ₃₀ N ₂ O ₄ S· 2HCl·1/2 H ₂ O	55.96 (56.11)	6.20 (6.19)	5.22 (5.11)
8b	7-OCH ₃	3	N-(2-chlorophenyl)	A	73	153—156	C ₂₅ H ₂₉ N ₂ O ₅ S· 2HCl	51.95 (51.85)	5.41 (5.42)	4.85 (4.74)
9b	7-OCH ₃	3	N-(2-methoxyphenyl)	A	75	185—190	C ₂₆ H ₃₂ N ₂ O ₆ S· 2HCl	54.45 (54.46)	5.98 (5.94)	4.89 (4.83)
10b	7-OCH ₃	3	N-(3,4-dimethoxyphenyl)	A	76	133—135	C ₂₆ H ₃₂ N ₂ O ₅ S· 1/2 H ₂ O	61.27 (60.95)	6.26 (6.30)	5.50 (5.48)
11b	7-OCH ₃	3	N-(1-phenylethyl)	A	62	152—155	C ₃₂ H ₃₆ N ₂ O ₅ S· 2HCl·2 1/2 H ₂ O	56.63 (56.64)	6.39 (6.16)	4.13 (4.15)
12b	7-OCH ₃	3	N-(1-piperidyl)	A	58	158—162	C ₂₄ H ₂₉ N ₃ O ₅ S· 2HCl·1 1/2 H ₂ O	50.44 (50.69)	5.99 (5.81)	7.35 (7.30)
13b	7-OCH ₃	4	N-Ph	A	49	155—165	C ₂₆ H ₃₂ N ₂ O ₅ S· 2HCl·1/2 H ₂ O	55.12 (55.30)	6.22 (6.19)	4.95 (4.96)
14b	7-OCH ₃	5	N-Ph	A	44	130—150	C ₂₇ H ₃₄ N ₂ O ₅ S· 2HCl·1/2 H ₂ O	55.85 (56.00)	6.42 (6.41)	4.83 (4.81)

(3H, s), 3.7—4.4 (3H, m), 6.80 (1H, dd, $J=2, 4$ Hz, C₇-H), 6.9—7.1 (2H, m). Similar NaBH₄ reduction of **2f** gave *cis*- and *trans*-**15f**, respectively.

Methyl *cis*-7-Benzyloxy-4-(3-chloropropyl)-3-hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (*cis*-15f**)**—Yield 50%. Colorless oil. *Anal.* Calcd for C₂₁H₂₃ClO₅S: C, 59.64; H, 5.48. Found: C, 59.77; H, 5.39.

Methyl *trans*-7-Benzyloxy-4-(3-chloropropyl)-3-hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (*trans*-15f**)**—Yield 30%. Colorless prisms, mp 97—99°C (recrystallized from AcOEt-hexane). *Anal.* Calcd for C₂₁H₂₃ClO₅S: C, 59.64; H, 5.48. Found: C, 59.80; H, 5.51.

Methyl *cis*-3-Hydroxy-7-methoxy-4-[2-(4-phenyl-1-piperazinyl)ethyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (*cis*-16b**)**—AcOH (0.48 g, 8 mmol), was added to a suspension of NaBH₄ (0.30 g, 8 mmol) in THF (20 ml). The mixture was gently boiled for 0.5 h, and then *cis*-**6b** (0.5 g, 7 mmol) was added to the above mixture. The mixture was refluxed for 20 h. The reaction mixture was worked up (AcOEt; H₂O) and the residue was purified by column chromatography on silica gel (hexane:AcOEt=1:1) to give *cis*-**16b** (0.20 g, 42%) as a colorless oil, which was converted into the hydrochloride, *cis*-**16b**·2HCl, colorless crystals (from MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3520, 1740 (ester). ¹H-NMR (400 MHz) (DMSO-*d*₆-D₂O) δ : 4.022 (1H, dd, $J=2.7, 12.7$ Hz, C₂-H), 4.080 (1H, dd, $J=2.7, 6.1$ Hz, C₃-H), 4.168 (1H, dd, $J=6.1, 12.7$ Hz, C₂-H).

Methyl 4-Aminoalkyl-Substituted 3-Hydroxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylates (17—36, Table I)—Method C) NaBH₄ (0.51 g, 13.5 mmol) was added in small portions to an ice-cooled solution of **7b** (12.6 g, 27 mmol) in MeOH (100 ml) and THF (30 ml) with stirring. The mixture was stirred for 3 h. The reaction mixture was poured into ice-H₂O and extracted with AcOEt. The organic layer was worked up. The residue obtained was subjected to column chromatography on silica gel (hexane:AcOEt=2:1—1:3). *trans*-**17b** was obtained from the

first fraction as a pale yellow oil, which was isolated as the hydrochloride, *trans*-**17b**·HCl (4.6 g), colorless prisms (recrystallized from 50% EtOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3530, 3500—3200, 2700—2300, 1720, 1600, 1485, 1255, 1235, 1205, 1035. $^1\text{H-NMR}$ (400 MHz) (DMSO- d_6 - D_2O) δ : 3.667 (3H, s), 3.746 (3H, s), 3.794 (1H, dd, $J=8.4, 12.7$ Hz, $\text{C}_2\text{-H}$), 4.107 (1H, dd, $J=3.8, 12.7$ Hz, $\text{C}_2\text{-H}$), 4.383 (1H, dd, $J=3.8, 8.4$ Hz, $\text{C}_3\text{-H}$).

The second fraction yielded *cis*-**17b** as a colorless oil, which was converted into the hydrochloride, *cis*-**17b**·HCl (6.9 g), colorless prisms (recrystallized from 50% EtOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3600—3300, 1735, 1720, 1595, 1480, 1250. $^1\text{H-NMR}$ (400 MHz) (DMSO- d_6 - D_2O) δ : 3.693 (3H, s), 3.758 (3H, s), 3.873 (1H, dd, $J=0-1, 13.1$ Hz, $\text{C}_2\text{-H}$), 3.999 (1H, dd, $J=0-1, 4.6$ Hz, $\text{C}_3\text{-H}$), 4.155 (1H, dd, $J=4.6, 13.1$ Hz, $\text{C}_2\text{-H}$). Method D) A mixture of *cis*-**15b** (95 g, 0.20 mol), *N*-phenylpiperazine (50 g, 0.33 mol), K_2CO_3 (42 g, 0.31 mol) and DMF (400 ml) was stirred at 70 °C for 8 h. The reaction mixture was worked up (AcOEt; H_2O). The residue was purified by column chromatography on silica gel (hexane: AcOEt = 2:3) to give *cis*-**17b**, which was isolated as the hydrochloride (83.7 g, 56%).

Compounds **17**—**36** were similarly prepared by method C or method D, and their physicochemical properties are listed in Table I.

Methyl *cis*-3,7-Dihydroxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (*cis*-17g**, Table I)**—Method E) Pd black (1.0 g) was added to a solution of *cis*-**17f** (2.45 g), conc. HCl (1.1 ml), and MeOH (200 ml). The mixture was hydrogenated under atmospheric pressure of H_2 for 20 h. After filtration of the catalyst, the filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane: AcOEt: MeOH = 30:30:1), followed by recrystallization from AcOEt to give *cis*-**17g** (1.31 g, 64%) as colorless crystals. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3450 (OH), 1730 (ester). $^1\text{H-NMR}$ (CDCl_3) δ : 1.1—3.4 (14H, m), 3.72 (3H, s, COOCH_3), 4.0—4.1 (3H, m), 6.6—7.4 (8H, m). MS m/z : 458 (M^+).

Similarly, catalytic hydrogenation of *cis*-**36f** and *cis*-**37f** gave *cis*-**38g** and *cis*-**39g** (Table I), respectively.

Methyl *cis*-7-Benzyloxy-3-hydroxy-4-(3-piperazinylpropyl)-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (*cis*-37f**, Table I)**—A mixture of *cis*-**15f** (2.0 g, 4.7 mmol), *N*-*tert*-butyloxycarbonylpiperazine (1.76 g, 9.5 mmol), K_2CO_3 (0.98 g, 7 mmol), KI (0.4 g, 2.4 mmol) and CH_3CN (20 ml) was refluxed for 6 h. The reaction mixture was worked up (AcOEt; H_2O) and the residue was purified by column chromatography on silica gel (hexane: AcOEt = 3:2) to give the *tert*-butyloxycarbonyl derivative of *cis*-**37f** (1.8 g, 69%) as a colorless oil. MS m/z : 572 (M^+), which was treated with HCl-AcOEt to give *cis*-**37f** (1.6 g) as colorless prisms (recrystallized from MeOH). IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3400 (OH), 1730 (ester). $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.2—2.4 (6H, m), 3.40—3.60 (8H, m), 3.68 (3H, s, COOCH_3), 3.9—4.1 (3H, m), 5.16 (2H, s, CH_2Ph), 6.7—7.5 (8H, m).

Methyl *cis*- and *trans*-3-(3-Hydroxy-7-methoxy-3,4-dihydro)2H-1,5-benzoxathiepin-2-yl)propionate (*cis*- and *trans*-41b**)**— NaBH_4 (0.2 g, 5.3 mmol) was added in small portions to a solution of **40b**¹⁾ (2.0 g, 6.7 mmol) in MeOH (20 ml) and THF (20 ml) with stirring. The mixture was stirred for 3 h. The reaction mixture was poured into ice- H_2O and extracted with AcOEt. The organic layer was worked up. The residue was subjected to column chromatography on silica gel (hexane: CH_2Cl_2 : AcOEt = 3:3:1) to give *cis*-**41b** (0.94 g, 47%) from the first fraction, as colorless crystals, mp 88—89 °C (recrystallized from Et_2O -petroleum ether). *Anal.* Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_5\text{S}$: C, 56.36; H, 6.08. Found: C, 56.50; H, 6.04. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3490 (OH), 1730 (ester). $^1\text{H-NMR}$ (400 MHz) (CDCl_3) δ : 2.950 (1H, dd, $J=2.0, 14.3$ Hz, $\text{C}_4\text{-H}$), 3.000 (1H, dd, $J=5.0, 14.3$ Hz, $\text{C}_4\text{-H}$), 3.574 (1H, ddd, $J=0-1, 3.3, 10.4$ Hz, $\text{C}_2\text{-H}$), 3.966 (1H, ddd, $J=0-1, 2.0, 5.0$ Hz, $\text{C}_3\text{-H}$).

From the second fraction, *trans*-**41b** (0.72 g, 36%) was obtained as colorless crystals, mp 65—66 °C (recrystallized from Et_2O -petroleum ether). *Anal.* Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_5\text{S}$: C, 56.36; H, 6.08. Found: C, 56.48; H, 6.10. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3450 (OH), 1725 (ester). $^1\text{H-NMR}$ (400 MHz) (CDCl_3) δ : 2.739 (1H, dd, $J=4.6, 14.6$ Hz, $\text{C}_4\text{-H}$), 3.558 (1H, dd, $J=2.6, 14.6$ Hz, $\text{C}_4\text{-H}$), 3.910 (1H, ddd, $J=2.4, 6.0, 8.0$ Hz, $\text{C}_2\text{-H}$), 3.950 (1H, ddd, $J=2.6, 4.6, 8.0$ Hz, $\text{C}_3\text{-H}$).

Methyl *cis*-(3-Hydroxy-8-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin-2-yl)propionate (*cis*-41c**)**— NaBH_4 reduction of **40c** as described for **40b** gave *cis*-**41c** (86% yield) as a colorless oil. *Anal.* Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_5\text{S}$: C, 56.36; H, 6.08. Found: C, 56.55; H, 6.19. IR $\nu_{\text{max}}^{\text{neat}}$ cm^{-1} : 3480 (OH), 1730 (ester).

***cis*-7-Methoxy-2-[3-oxo-3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*cis*-**42b**)**—A mixture of *cis*-**41b** (300 mg, 1 mmol) and *N*-phenylpiperazine (1 ml) was stirred at 90 °C for 3 h. The reaction mixture was worked up (AcOEt; H_2O). The residue was recrystallized from AcOEt- Et_2O to yield *cis*-**42b** (320 mg, 74%) as colorless crystals, mp 110—111 °C. *Anal.* Calcd for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_4\text{S}$: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.62; H, 6.51; N, 6.52. IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3400 (OH), 1645 (amide).

Similar amidation of *trans*-**41b** and *cis*-**41c** gave *trans*-**42b** and *cis*-**42c**, respectively.

***trans*-7-Methoxy-2-[3-oxo-3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*trans*-**42b**)**—Yield 75%. Recrystallization from AcOEt gave colorless crystals, mp 139—140 °C. *Anal.* Calcd for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_4\text{S}$: C, 64.46; H, 6.59; N, 6.54. Found: C, 64.52; H, 6.31; N, 6.61.

***cis*-8-Methoxy-2-[3-oxo-3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*cis*-**42c**)**—Yield 71%. Colorless prisms, mp 126—127 °C (recrystallized from AcOEt). *Anal.* Calcd for $\text{C}_{23}\text{H}_{28}\text{N}_2\text{O}_4\text{S}$: C, 64.46; H, 6.31; N, 6.61. Found: C, 64.30; H, 6.60; N, 6.43.

***cis*-7-Methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*cis*-**43b**)**—A solution of *cis*-**42b** (350 mg, 0.8 mmol) in THF (10 ml) was added dropwise to a suspension of LiAlH_4 (100 mg, 2.6 mmol)

in dry Et₂O (20 ml) with stirring under an atmosphere of dry N₂. The mixture was refluxed for 3 h. The reaction mixture was diluted with 20% NaOH and filtered off. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane:AcOEt:MeOH = 10:10:1) to give *cis*-**43b** (270 mg, 80%) as colorless crystals, mp 107–109 °C (recrystallized from AcOEt). *Anal.* Calcd for C₂₃H₃₀N₂O₃S: C, 66.64; H, 7.29; N, 6.76. Found: C, 66.59; H, 7.22; N, 6.90. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3450–3300 (OH), 1585, 1475, 1230, 1030, 915. ¹H-NMR (400 MHz) (CDCl₃) δ : 2.953 (1H, dd, *J* = 2.1, 14.2 Hz, C₄-H), 3.039 (1H, dd, *J* = 5.4, 14.2 Hz, C₄-H), 3.609 (1H, ddd, *J* = 0–1, 4.0, 9.6 Hz, C₂-H), 3.975 (1H, ddd, *J* = 0–1, 2.1, 5.4 Hz, C₃-H).

Similar LiAlH₄ reduction of *trans*-**42b** and *cis*-**42c** gave *trans*-**43b** and *cis*-**43c**, respectively.

trans-7-Methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*trans*-**43b**)—Yield 77%. Recrystallization from AcOEt gave colorless crystals, mp 128–130 °C. *Anal.* Calcd for C₂₃H₃₀N₂O₃S: C, 66.64; H, 7.29; N, 6.76. Found: C, 66.50; H, 6.94; N, 6.56. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3450–3000 (OH), 1585, 1490, 1235, 1035. ¹H-NMR (400 MHz) (CDCl₃) δ : 2.735 (1H, dd, *J* = 4.8, 14.5 Hz, C₄-H), 3.534 (1H, dd, *J* = 2.3, 14.5 Hz, C₄-H), 3.96 (2H, m, C₂-H, C₃-H).

cis-8-Methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*cis*-**43c**)—Yield 76%. Recrystallization from AcOEt gave colorless prisms, mp 149–150 °C. *Anal.* Calcd for C₂₃H₃₀N₂O₃S: C, 66.64; H, 7.29; N, 6.76. Found: C, 66.71; H, 7.26; N, 6.79. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3400–3200 (OH), 1595, 1475, 1290, 1240, 1160, 1005. ¹H-NMR (400 MHz) (CDCl₃) δ : 2.886 (1H, dd, *J* = 2.1, 14.2 Hz, C₄-H), 2.966 (1H, dd, *J* = 5.4, 14.2 Hz, C₄-H), 3.668 (1H, ddd, *J* = 0–1, 4.0, 9.4 Hz, C₂-H), 3.970 (1H, dd, *J* = 0–1, 2.1, 5.4 Hz, C₃-H).

3-[2-(1,3-Dioxolan-2-yl)ethyl]-7-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (**45**)—A solution of **44**¹⁾ (2.0 g, 9.5 mmol) in THF (10 ml) was added dropwise to a solution of Grignard reagent prepared from Mg (350 mg, 14 mmol), 2-(1,3-dioxolan-2-yl)ethyl bromide (2.6 g, 14 mmol) and THF (30 ml) with stirring. The mixture was stirred for 1 h. The reaction mixture was diluted with 1N NaOH (20 ml) and worked up (AcOEt; H₂O). The residue was purified by column chromatography on silica gel (CH₂Cl₂:Et₂O = 5:1) to give **45** (2.44 g, 82%) as a colorless oil. *Anal.* Calcd for C₁₅H₂₀O₅S: 57.67; H, 6.45. Found: C, 57.41; H, 6.52. IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 3230 (OH), 1595, 1490, 1475, 1195. ¹H-NMR (90 MHz) (CDCl₃) δ : 1.6–1.8 (4H, m), 2.83 (2H, s, C₄-H), 3.75 (3H, s, OCH₃), 3.6–4.2 (6H, m), 5.93 (1H, t, *J* = 3 Hz, CH₂^o). MS *m/z*: 312 (M⁺).

7-Methoxy-3-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (**46**)—A 50% H₂SO₄ solution (2 ml) was added to a solution of **45** (2.9 g, 9.3 mmol) in acetone (20 ml) and H₂O (10 ml). The mixture was stirred for 3 h. The reaction mixture was concentrated to ca. 10 ml *in vacuo* and extracted with CH₂Cl₂. The organic layer was worked up and the residue was dissolved in CH₃CN (20 ml). *N*-Phenylpiperazine (1.6 g, 10 mmol) was added to the above solution, the mixture was stirred for 10 h, and then NaBH₃CN (130 mg, 20 mmol) and MeOH were added. The reaction mixture was stirred for 3 h, then diluted with 3N HCl (10 ml) and stirred for 2 h. The mixture was washed with AcOEt. The aqueous layer was made alkaline with 3N NaOH (20 ml) and extracted with AcOEt. The organic layer was worked up and the residue was purified by column chromatography on silica gel (hexane:AcOEt:MeOH = 10:10:1) to give **46** as a colorless oil, which was converted into the hydrochloride, **46**·HCl (2.4 g, 57%), colorless plates, mp 216–219 °C (recrystallized from 50% EtOH). *Anal.* Calcd for C₂₃H₃₀N₂O₃S·HCl: C, 61.25; H, 6.93; N, 6.21. Found: C, 61.43; H, 6.70; N, 6.27. IR $\nu_{\text{max}}^{\text{KBr}}$ cm⁻¹: 3500–3200 (OH), 1595, 1485. ¹H-NMR (90 MHz) (DMSO-*d*₆) δ : 1.6–2.1 (4H, m), 2.90 (2H, s, C₄-H), 3.2–4.0 (10H, m), 3.67 (3H, s, OCH₃), 3.93 (2H, s, C₂-H).

4-(3-Chloropropyl)-7-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin-3-one (**47b**)—A mixture of **2b** (5.0 g, 14.5 mmol), LiCl (1.5 g, 35 mmol), H₂O (0.3 ml) and DMSO (30 ml) was stirred at 100 °C for 5 h. The reaction mixture was poured into ice-H₂O and extracted with AcOEt. The organic layer was washed with H₂O, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane:AcOEt = 2:1) to give **47b** (2.0 g, 48%) as a colorless oil. *Anal.* Calcd for C₁₃H₁₅ClO₃S: C, 54.45; H, 5.27. Found: C, 54.90; H, 5.24. IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1730, 1595, 1490, 1205. ¹H-NMR (CDCl₃) δ : 1.7–2.4 (4H, m), 3.4–4.0 (3H, m), 3.68 (3H, s, OCH₃), 4.43 (1H, d, *J* = 17 Hz, C₂-H), 4.75 (1H, d, *J* = 17 Hz, C₂-H).

cis-4-(3-Chloropropyl)-7-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*cis*-**48b**)—NaBH₄ reduction of **47b** in MeOH and THF (5:1) and usual work up gave *cis*-**48b** (84% yield) as a colorless oil. *Anal.* Calcd for C₁₃H₁₇ClO₃S: C, 54.07; H, 5.93. Found: C, 54.46; H, 6.11. IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 3450 (OH), 1580, 1485. ¹H-NMR (400 MHz) (CDCl₃) δ : 3.044 (1H, ddd, *J* = 1.2, 5.6, 8.8 Hz, C₄-H), 3.659 (1H, dd, *J* = 0.7, 12.5 Hz, C₂-H), 3.903 (1H, ddd, *J* = 0.7, 1.2, 4.0 Hz, C₃-H), 4.367 (1H, dd, *J* = 4.0, 12.5 Hz, C₂-H).

7-Methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-one (**49b**)—A mixture of **47b** (1.8 g) and *N*-phenylpiperazine (2.4 g) was heated at 100 °C for 1 h. The reaction mixture was worked up (AcOEt; H₂O). The residue was purified by column chromatography on silica gel (hexane:AcOEt = 1:1) to give **49b** (1.68 g, 65%) as a colorless oil. *Anal.* Calcd for C₂₃H₂₈N₂O₃S: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.62; H, 6.73; N, 6.68. IR $\nu_{\text{max}}^{\text{neat}}$ cm⁻¹: 1725 (CO), 1595. ¹H-NMR (CDCl₃) δ : 1.5–2.0 (4H, m), 2.3–2.8 (4H, m), 3.65 (3H, s, OCH₃), 4.42 (1H, d, *J* = 8 Hz, C₄-H), 4.73 (1H, d, *J* = 18 Hz, C₂-H), 4.80 (1H, d, *J* = 18 Hz, C₂-H).

cis-7-Methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (*cis*-**50b**)—a Substitution reaction of *cis*-**48b** with *N*-phenylpiperazine, as described for *cis*-**17b** (method D), gave *cis*-**50b** (42% yield) as

colorless prisms, mp 112–113 °C (recrystallized from AcOEt). *Anal.* Calcd for $C_{23}H_{30}N_2O_3S$: C, 66.64; H, 7.29; N, 6.76. Found: C, 66.95; H, 7.34; N, 6.92. IR ν_{\max}^{KBr} cm^{-1} : 3500–3000, 1595, 1490, 1440, 1200, 1035. 1H -NMR (400 MHz) (DMSO- d_6 - D_2O) δ : 3.206 (1H, ddd, $J=3.8, 4.6, 8.1$ Hz, C_4 -H), 3.776 (1H, dd, $J=8.5, 12.2$ Hz, C_2 -H), 4.017 (1H, dd, $J=3.8, 12.2$ Hz, C_2 -H), 4.152 (1H, dt, $J=3.8, 8.5$ Hz, C_3 -H).

b) $NaBH_4$ reduction of **49b** in a solution of THF and MeOH (10:1) gave *cis*-**50b** (93% yield). The structure of *cis*-**50b** was determined by X-ray crystallographic analysis (Fig. 1).

cis-4-(3-Chloropropyl)-3-hydroxy-7-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylic Acid (cis-51b)—

A 1 N NaOH solution (8 ml, 8 mmol) was added to a solution of *cis*-**16b** (2.0 g, 5.8 mmol) in MeOH (20 ml). The mixture was stirred for 14 h, then poured into ice- H_2O containing conc. HCl (5 ml). The resulting precipitates were collected by filtration and recrystallized from AcOEt to give *cis*-**51b** (1.25 g, 75%) as colorless prisms, mp 174–176 °C. *Anal.* Calcd for $C_{14}H_{17}ClO_5S$: C, 50.53; H, 5.15. Found: C, 50.60; H, 5.12. IR ν_{\max}^{KBr} cm^{-1} : 3430, 1740, 1485, 1205, 1035. 1H -NMR (DMSO- d_6) δ : 1.2–2.3 (4H, m), 3.43 (2H, t, $J=4$ Hz, CH_2Cl), 3.75 (3H, s, OCH_3), 3.7–4.4 (3H, m).

trans-4-(3-Chloropropyl)-7-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (trans-48b)—*cis*-**51b** (700 mg) was heated at 180 °C for 0.5 h under atmosphere of dry N_2 . After cooling, the residue was subjected to column chromatography on silica gel (hexane: CH_2Cl_2 : AcOEt = 3:3:1) to give *trans*-**48b** (101 mg, 16%) as a colorless oil. *Anal.* Calcd for $C_{13}H_{17}ClO_3S$: C, 54.07; H, 5.93. Found: C, 54.33; H, 6.06. IR ν_{\max}^{neat} cm^{-1} : 3450 (OH), 1600, 1485, 1200, 1035.

trans-7-Methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (trans-50b)—A mixture of *trans*-**48b** (100 mg) and *N*-phenylpiperazine (200 mg) was heated at 90 °C for 2 h. The reaction mixture was subjected to column chromatography on silica gel (hexane: AcOEt: MeOH = 10:10:1) to give *trans*-**50b** as a colorless oil, which was converted into the hydrochloride, *trans*-**50b**·2HCl (50 mg, 29%), amorphous powder. *Anal.* Calcd for $C_{23}H_{28}N_2O_3S \cdot 2HCl \cdot H_2O$: C, 56.42; H, 6.85; N, 5.51. Found: C, 56.32; H, 6.75; N, 5.44. IR ν_{\max}^{KBr} cm^{-1} : 3400, 2800–2200, 1595, 1490, 1440, 1200, 1035. 1H -NMR (400 MHz) (DMSO- d_6 - D_2O) δ : 3.031 (1H, ddd, $J=3.4, 7.7, 9.3$ Hz, C_4 -H), 3.785 (1H, ddd, $J=2.7, 4.9, 7.7$ Hz, C_3 -H), 3.855 (1H, dd, $J=5.0, 12.6$ Hz, C_2 -H), 4.329 (1H, dd, $J=2.8, 12.6$ Hz, C_2 -H).

Methyl 5-(4-Phenyl-1-piperazinyl)-2-(6-methoxy-1,4-benzoxathian-3-yl)pentanoates (52 and 53)—a) A mixture of TsCl (3.0 g, 16 mmol) in pyridine (3 ml) was added dropwise to an ice-cooled solution of *cis*-**17b** (5.0 g, 11 mmol) in pyridine (15 ml). The mixture was stirred at 0–5 °C for 6 h and then poured into ice- H_2O . The supernatant was removed by decantation and the residue was worked up (AcOEt; H_2O). The residue was subjected to column chromatography on silica gel (hexane: AcOEt = 1:1) to give a gummy residue [2.0 g, MS m/z : 454 (M^+)]. Catalytic hydrogenation of the product obtained (2.0 g) in AcOEt (20 ml) was carried out in the presence of 5% Pd-C (100 mg) under atmospheric pressure of H_2 . After hydrogen absorption had ceased (100 ml), the catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residue was subjected to column chromatography on silica gel (hexane: AcOEt: MeOH = 10:10:1) to give **52** from the first fraction as a colorless oil, which was converted into the hydrochloride, **52**·HCl (360 mg, 7% from *cis*-**17b**), colorless prisms, mp 121–123 °C (recrystallized from 50% EtOH). *Anal.* Calcd for $C_{25}H_{32}N_2O_4S \cdot HCl \cdot H_2O$: C, 58.75; H, 6.90; N, 5.48. Found: C, 58.39; H, 6.79; N, 5.30. IR ν_{\max}^{KBr} cm^{-1} : 3500, 3430, 2700–2300 (ester), 1595, 1485, 1260, 1205, 1195. 1H -NMR (400 MHz) (DMSO- d_6 - D_2O) δ : 2.730 (1H, ddd, $J=3.4, 9.5, 10.0$ Hz, $-CHCOOCH_3$), 3.612 (1H, ddd, $J=2.1, 5.4, 9.5$ Hz, C_3 -H), 4.115 (1H, dd, $J=5.4, 12.0$ Hz, C_2 -H), 4.263 (1H, dd, $J=2.1, 12.0$ Hz, C_2 -H).

The second fraction gave **53** as a colorless oil, which was isolated as the hydrochloride **53**·HCl (320 mg, 6% from *cis*-**17b**). Recrystallization from 50% EtOH gave colorless prisms, mp 152–154 °C. *Anal.* Calcd for $C_{25}H_{32}N_2O_4S \cdot HCl$: C, 60.90; H, 6.75; N, 5.68. Found: C, 60.53; H, 6.83; N, 5.70. IR ν_{\max}^{KBr} cm^{-1} : 3520, 3450, 2700–2300, 1725, 1595, 1490, 1440, 1260, 1245, 1200. 1H -NMR (400 MHz) (DMSO- d_6 - D_2O) δ : 2.805 (1H, ddd, $J=3.4, 9.8, 10.5$ Hz, $-CHCOOCH_3$), 3.599 (1H, ddd, $J=2.0, 4.2, 9.8$ Hz, C_3 -H), 4.184 (1H, dd, $J=2.0, 12.2$ Hz, C_2 -H), 4.439 (1H, dd, $J=4.2, 12.2$ Hz, C_2 -H).

b) A mixture of red P (300 mg, 10 mmol), I_2 (90 mg) and AcOH (6 ml) was stirred for 0.5 h. *cis*-**16b** (3.0 g, 8.7 mmol) and H_2O (0.1 ml) were added to the above mixture and the mixture was refluxed for 1 h. The reaction mixture was worked up (AcOEt; H_2O) and the residue was subjected to column chromatography on silica gel (hexane: AcOEt = 2:1) to give a colorless oil [1.38 g, MS m/z : 330, 332 (M^+)], which was heated with *N*-phenylpiperazine (4 ml) at 90 °C for 2 h. The mixture obtained was subjected to column chromatography on silica gel (hexane: AcOEt: MeOH = 10:10:1) to give first **52** (isolated as **52**·HCl; 0.46 g, 11% from *cis*-**15b**) and then **53** (isolated as **53**·HCl; 0.38 g, 9% from *cis*-**15b**).

1-Chloro-5-(1,3-dioxolan-2-yl)pentan-3-ol (54)—A solution of 3-chloropropanal (3.3 g, 36 mmol) in THF (10 ml) was added to a solution of 2-(1,3-dioxolan-2-yl)ethylmagnesium bromide prepared from Mg (1.0 g, 41 mmol), 2-(1,3-dioxolan-2-yl)ethyl bromide (7.5 g, 41 mmol) and THF (20 ml). The mixture was stirred for 2 h, then diluted with 1 N NaOH (20 ml) and worked up (AcOEt; H_2O). The residue was purified by column chromatography on silica gel (CH_2Cl_2 : Et $_2O$ = 5:1) to give **54** (2.6 g, 73%) as a colorless oil. *Anal.* Calcd for $C_8H_{15}ClO_3$: C, 49.36; H, 7.77. Found: C, 49.55; H, 7.51. IR ν_{\max}^{neat} cm^{-1} : 3400 (OH), 1450, 1415, 1345, 1210, 1040. 1H -NMR ($CDCl_3$) δ : 1.2–2.2 (6H, m), 3.4–4.2 (7H, m), 4.91 (1H, t, $J=4$ Hz, O-CH-O).

5-(1,3-Dioxolan-2-yl)-3-mesyloxypropyl Benzoate (55)—A mixture of **54** (3.0 g, 15 mmol), sodium benzoate (3.0 g, 21 mmol), KI (1.0 g, 6 mmol), CH₃CN (30 ml) and DMF (20 ml) was stirred at 80 °C for 5 h. The reaction mixture was worked up (AcOEt; H₂O) and the residue was purified by column chromatography on silica gel (CH₂Cl₂:Et₂O=5:1) to give 5-(1,3-dioxolan-2-yl)-3-hydroxypropyl benzoate (1.8 g, 42%) as a colorless oil [MS *m/z*: 280 (M⁺)]. MsCl (1.8 g, 6.4 mmol) was added to the alcohol obtained above (1.8 g) in pyridine (10 ml). The mixture was stirred for 2 h, poured into ice-H₂O containing conc. HCl (20 ml) and extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (CH₂Cl₂:Et₂O=5:1) to give **55** (0.9 g, 54%) as a colorless oil. MS *m/z*: 358 (M⁺), 357. High-resolution MS Calcd for C₁₆H₂₂O₅S: 358.1085. Found: 358.1088. IR ν_{\max}^{neat} cm⁻¹: 1725, 1710, 1595, 1445, 1350, 1280, 1270, 1175. ¹H-NMR (CDCl₃) δ : 1.7–2.4 (6H, m), 3.08(3H, s, OSO₂CH₃), 3.2–4.2 (4H, m), 4.2–4.6 (3H, m), 4.9–5.1 (1H, t, J=4 Hz, O-CH-O).

2-[1-(1,3-Dioxolan-2-yl)-5-hydroxy-3-pentyl]thio-4-methoxyphenol (56)—A mixture of **55** (1.4 g, 3.9 mmol), 2-mercapto-4-methoxyphenol (0.8 g, 5 mmol), K₂CO₃ (0.6 g, 4.4 mmol) and acetone (20 ml) was stirred for 15 h and then filtered, and the filtrate was concentrated *in vacuo*. A 1 N NaOH solution (10 ml) was added to a solution of the above residue in MeOH (30 ml). The resulting mixture was stirred for 5 h, neutralized with 1 N HCl and worked up (AcOEt; H₂O). The residue was purified by column chromatography on silica gel (hexane:AcOEt=1:1) to give **56** (0.7 g, 43%) as a colorless oil. Anal. Calcd for C₁₅H₂₂O₄S: C, 57.30; H, 7.05. Found: C, 57.51; H, 7.21. IR ν_{\max}^{neat} cm⁻¹: 3450–3200 (OH), 1600, 1480, 1275, 1250, 1220, 1205. ¹H-NMR (CDCl₃) δ : 1.6–2.2 (6H, m), 2.8–3.2 (1H, m), 3.77 (3H, s, OCH₃), 3.6–4.2 (6H, m), 4.90 (1H, t, J=4 Hz, O-CH-O). MS *m/z*: 314 (M⁺), 252, 213, 200, 183.

4-[2-(1,3-Dioxolan-2-yl)ethyl]-7-methoxy-3,4-dihydro-2H-1,5-benzoxathiepin (57)—Ph₃P (0.85 g, 3.2 mmol) was added to a solution of **56** (0.9 g, 2.9 mmol) and toluene (10 ml) with stirring. Then, a solution of ethyl azodiformate (0.55 g, 3.2 mmol) in toluene (1 ml) was added dropwise to the above mixture. The whole was stirred for 2 h and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane:AcOEt=2:1) to give **57** (0.61 g, 71%) as a colorless oil. Anal. Calcd for C₁₅H₂₀O₄S: C, 60.79; H, 6.80. Found: C, 60.88; H, 6.71. IR ν_{\max}^{neat} cm⁻¹: 1595, 1485, 1435, 1280, 1265, 1200. ¹H-NMR (CDCl₃) δ : 1.5–2.4 (6H, m), 2.9–3.1 (1H, m, C₄-H), 3.75 (3H, s, OCH₃), 3.7–4.6 (6H, m), 4.88 (1H, t, J=4 Hz, O-CH-O).

7-Methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin (58)—A mixture of **57** (680 mg, 2.3 mmol), 50% H₂SO₄ (0.5 ml), H₂O (2 ml) and acetone (10 ml) was stirred for 2 h, then the reaction mixture was worked up (AcOEt; H₂O). *N*-Phenylpiperazine (0.4 g, 2.5 mmol) was added to a solution of the residual oil in CH₃CN (10 ml) and the mixture was stirred for 4 h. Then, NaBH₃CN (190 mg, 3 mmol) was added. The reaction mixture was stirred for 4 h and then worked up (AcOEt; H₂O). The resulting residue was purified by column chromatography on silica gel (hexane:AcOEt=1:1) to give **58** as a colorless oil, which was converted into the hydrochloride, **58**·2HCl (550 mg, 51%), white crystals, mp 150–153 °C (recrystallized from 50% EtOH). Anal. Calcd for C₂₃H₃₀N₂O₃S·2HCl: C, 58.59; H, 6.84; N, 5.94. Found: C, 58.48; H, 6.75; N, 5.64. IR ν_{\max}^{KBr} cm⁻¹: 3500–3400, 2600–2200, 1595, 1480.

Methyl *cis*-3-Acetoxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (*cis*-59b)—Acetylation of *cis*-**17b** with Ac₂O in pyridine gave *cis*-**59b** as colorless prisms, mp 168–170 °C (recrystallized from AcOEt) in 83% yield. Anal. Calcd for C₂₇H₃₄N₂O₆S: C, 63.01; H, 6.66; N, 5.44. Found: C, 63.01; H, 6.69; N, 5.40. IR ν_{\max}^{KBr} cm⁻¹: 1740 (ester). ¹H-NMR (CDCl₃) δ : 2.08 (3H, s, OCOCH₃), 3.62 (3H, s), 3.63 (3H, s).

Methyl *cis*-7-Methoxy-3-*N*-methylcarbamoyloxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (*cis*-60b)—*cis*-**60b** was prepared by the reaction of *cis*-**17b** with CH₃NCO in DMF and isolated as the hydrochloride in 89% yield. Recrystallization from EtOH gave *cis*-**60b**·2HCl as colorless prisms, mp 167–172 °C. Anal. Calcd for C₂₇H₃₅N₃O₆S·2HCl: C, 53.82; H, 6.19; N, 6.97. Found: C, 53.56; H, 6.42; N, 6.71. IR ν_{\max}^{KBr} cm⁻¹: 3400, 1720 (ester). ¹H-NMR (DMSO-*d*₆-D₂O) δ : 2.75 (3H, s, NHCH₃), 3.73 (6H, s, 7-OCH₃+COOCH₃), 5.25 (1H, m, C₃-H).

***cis*-3-Hydroxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylic Acid (*cis*-61b)**—A mixture of *cis*-**17b** (3.0 g, 6.3 mmol), 1 N NaOH (12 ml) and MeOH (40 ml) was stirred at 60 °C for 5 h. After evaporation of the MeOH, the residual mixture was acidified with 1 N HCl. The resulting precipitates were collected by filtration and recrystallized from EtOH to give *cis*-**61b** (2.4 g, 95%) as colorless crystals, mp 250–260 °C (dec.). Anal. Calcd for C₂₄H₃₀N₂O₅S·H₂O: C, 60.48; 6.77; N, 5.88. Found: C, 60.27; H, 6.73; N, 5.66. IR ν_{\max}^{KBr} cm⁻¹: 3600, 3510–3300, 2600–2200, 1640–1590, 1485, 1370, 1210.

Ethyl *cis*-3-Hydroxy-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-4-carboxylate (*cis*-62b)—A mixture of *cis*-**61b** (1.2 g, 2.5 mmol), Et₂SO₄ (0.5 g, 3.2 mmol), NaHCO₃ (1.0 g, 12 mmol) and EtOH (25 ml) was refluxed for 3 h, then worked up (AcOEt; H₂O). The residue was purified by column chromatography on silica gel (hexane:AcOEt=1:1) to give *cis*-**62b** as colorless oil, which was isolated as the hydrochloride *cis*-**62b**·2HCl (0.5 g, 42%), colorless prisms, mp 186–188 °C (from EtOH). Anal. Calcd for C₂₆H₃₄N₂O₅S·2HCl: C, 55.81; H, 6.49; N, 5.01. Found: C, 55.74; H, 6.56; N, 5.03. IR ν_{\max}^{KBr} cm⁻¹: 3540 (OH), 1740 (ester). ¹H-NMR (DMSO-*d*₆-D₂O) δ : 1.30 (3H, t, J=7 Hz, OCH₂CH₃), 3.72 (3H, s, 7-OCH₃), 4.1–4.2 (3H, m, C₂-H+C₃-H), 4.28 (2H, t, J=7 Hz, OCH₂CH₃).

cis-4-Hydroxymethyl-7-methoxy-4-[3-(4-phenyl-1-piperazinyl)propyl]-3,4-dihydro-2H-1,5-benzoxathiepin-3-ol (cis-63b)—A solution of *cis-17b* (400 mg, 0.8 mmol) in dry Et₂O (10 ml) was added dropwise to a suspension of LiAlH₄ (90 mg, 2.4 mmol) and dry Et₂O (20 ml) with stirring. The mixture was refluxed for 0.5 h. Excess LiAlH₄ was decomposed by adding H₂O and 15% NaOH. The inorganic deposit was filtered and the filtrate was concentrated *in vacuo*. The residue was recrystallized from AcOEt to give *cis-62* (300 mg, 80%) as colorless needles, mp 163–165 °C. *Anal.* Calcd for C₂₄H₃₂N₂O₄S: C, 64.84; H, 7.25; N, 6.30. Found: C, 64.76; H, 7.31; N, 6.39. IR ν_{\max}^{KBr} cm⁻¹: 3540 (OH). ¹H-NMR (400 MHz) (CDCl₃-D₂O) δ : 3.923 (1H, dd, *J* = 1.0, 4.9 Hz, C₃-H), 3.995 (1H, dd, *J* = 1.0, 12.8 Hz, C₂-H), 4.138 (1H, dd, *J* = 4.9, 12.8 Hz, C₂-H).

Methyl 8-Methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (64)—A solution of methyl 3-(4-methoxy-2-methoxycarbonylmethoxyphenyl)propionate (15 g, 53 mmol) in toluene (200 ml) was added dropwise to a gently boiling suspension of 60% NaH (5.6 g, 140 mmol), *tert*-BuOH (0.4 ml) and toluene (200 ml) (8 h). After refluxing for 0.5 h, the reaction mixture was allowed to stand overnight and then poured into ice-H₂O containing AcOH (10 ml). The organic layer was separated, washed with H₂O, dried and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (hexane:AcOEt = 4:1) to give **64** (9.5 g, 71%) as a colorless oil. *Anal.* Calcd for C₁₃H₁₄O₅S: C, 62.39; H, 5.64. Found: C, 62.18; H, 5.86. IR ν_{\max}^{neat} cm⁻¹: 1760, 1720. ¹H-NMR (CDCl₃) δ : 2.9–3.1 (4H, m), 3.72 (3H, s), 3.80 (3H, s), 5.00 (1H, s, C₂-H), 6.5–7.2 (3H, m).

Methyl 3-Oxo-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (65)—**65** was prepared in 81% yield by Dieckmann reaction of methyl 3-(2-methoxycarbonylmethylthiophenyl)propionate, as described for **64**. The starting methyl 3-(2-methoxycarbonylmethylthiophenyl)propionate was prepared in 5 steps from methyl 3-(2-hydroxyphenyl)propionate *via* the route involving thiocarbonylation with dimethylthiocarbonyl chloride (74% yield), thermal rearrangement at 260–270 °C (70% yield), alkaline hydrolysis, *S*-alkylation with methyl bromoacetate and esterification with dimethyl sulfate (55% yield). Chromatographic purification of the crude product gave **65** as a colorless oil. *Anal.* Calcd for C₁₂H₁₂O₃S: C, 61.00; H, 5.12. Found: C, 61.23; H, 5.28. MS *m/z*: 236 (M⁺). IR ν_{\max}^{neat} cm⁻¹: 1740, (ester), 1700 (CO). ¹H-NMR (CDCl₃) δ : 2.6–3.4 (4H, m), 3.62 (3H, s, COOCH₃), 4.20 (1H, s, C₂-H), 6.9–7.7 (4H, m).

Methyl 8-Methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (66)—**66** was similarly prepared by Dieckmann reaction of methyl 3-(4-methoxy-2-methoxycarbonylmethylthiophenyl)propionate in 80% yield. Recrystallization from AcOEt-hexane gave **66** as colorless prisms, mp 76–78 °C. *Anal.* Calcd for C₁₃H₁₄O₄S: C, 58.68; H, 5.30. Found: C, 58.59; H, 5.26. IR ν_{\max}^{KBr} cm⁻¹: 1740 (ester), 1710 (CO). ¹H-NMR (CDCl₃) δ : 2.9–3.1 (4H, m), 3.68 (3H, s), 3.78 (3H, s), 4.22 (1H, s, C₂-H), 6.7–7.4 (3H, m).

Methyl 2-(3-Chloropropyl)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (67)—**67** was prepared by alkylation of **64** with 3-bromo-1-chloropropane, as described for **2**. Chromatographic purification gave a colorless oil. MS *m/z*: 326, 328 (M⁺). High-resolution MS Calcd for C₁₆H₁₉ClO₅: 326.0919. Found: 326.0925. IR ν_{\max}^{neat} cm⁻¹: 1750 (ester), 1720 (CO). ¹H-NMR (CDCl₃) δ : 2.0–2.2 (4H, m), 2.92 (4H, s, C₄-H + C₅-H), 3.52 (2H, t, *J* = 6 Hz, CH₂Cl), 3.64 (3H, s), 3.72 (3H, s), 6.4–7.1 (3H, m). Compound **67** thus obtained was found to contain a small amount of enol ether (2–3%) as a by-product, but was used for the following step without further purification. **68** and **69** were similarly prepared by alkylation of **65** and **66**, respectively.

Methyl 2-(3-Chloropropyl)-3-oxo-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (68)—A colorless oil (41% yield). MS *m/z*: 312, 314 (M⁺). High-resolution MS Calcd for C₁₅H₁₇ClO₃S: 312.0586. Found: 312.0582. IR ν_{\max}^{neat} cm⁻¹: 1720 (ester, CO). ¹H-NMR (CDCl₃) δ : 1.7–3.6 (10H, m), 3.65 (3H, s, COOCH₃), 7.1–7.8 (4H, m).

Methyl 2-(3-Chloropropyl)-8-methoxy-3-oxo-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (69)—A colorless oil (50% yield). MS *m/z*: 342, 344 (M⁺). High-resolution MS Calcd for C₁₆H₁₉ClO₄S: 342.0692. Found: 342.0693. IR ν_{\max}^{neat} cm⁻¹: 1740 (ester), 1700 (CO). ¹H-NMR (CDCl₃) δ : 1.8–2.0 (4H, m), 2.8–3.0 (4H, m), 3.42 (2H, t, *J* = 7 Hz, CH₂Cl), 3.62 (3H, s), 3.72 (3H, s), 6.7–7.4 (3H, m).

Methyl cis- and trans-2-(3-Chloropropyl)-3-hydroxy-8-methoxy-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (cis- and trans-70)—NaBH₄ reduction of **67** in an ice-cooled solution of THF and MeOH (1:4) and subsequent column chromatography on silica gel (hexane:AcOEt = 3:1) gave *cis-70* (from the first fraction) and *trans-70* (from the second fraction).

cis-70: A colorless oil (46% yield). *Anal.* Calcd for C₁₆H₂₁ClO₅: C, 58.45; H, 6.44. Found: C, 58.66; H, 6.59. IR ν_{\max}^{neat} cm⁻¹: 3500 (OH), 1740 (ester). ¹H-NMR (CDCl₃) δ : 1.8–2.0 (4H, m), 2.4–3.5 (6H, m), 3.72 (3H, s), 3.75 (3H, s), 6.5–7.2 (3H, m).

trans-70: A colorless oil (44% yield). *Anal.* Calcd for C₁₆H₂₁ClO₅: C, 58.45; H, 6.44. Found: C, 58.78; H, 6.21. IR ν_{\max}^{neat} cm⁻¹: 3500 (OH), 1740 (ester). ¹H-NMR (CDCl₃) δ : 1.9–2.0 (4H, m), 2.4–3.2 (4H, m), 3.48 (2H, t, *J* = 7 Hz, CH₂Cl), 3.66 (3H, s), 3.72 (3H, s), 4.0–4.2 (1H, m), 6.46–7.02 (3H, m).

Methyl cis-2-(3-Chloropropyl)-3-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (cis-71)—NaBH₄ reduction of **68** gave *cis-71* (80% yield) as colorless prisms, mp 108–110 °C (recrystallized from AcOEt). *Anal.* Calcd for C₁₅H₁₉ClO₃S: C, 57.23; H, 6.08. Found: C, 57.27; H, 6.11. IR ν_{\max}^{KBr} cm⁻¹: 3500 (OH), 1730 (ester). ¹H-NMR (400 MHz) (DMSO-*d*₆-D₂O) δ : 4.051 (1H, dd, *J* = 2.7, 5.4 Hz, C₃-H).

Methyl cis-2-(3-Chloropropyl)-3-hydroxy-8-methoxy-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (cis-72)—NaBH₄ reduction of **69** gave *cis-72* (74% yield) as a colorless oil. *Anal.* Calcd for C₁₆H₂₁ClO₄S: C, 55.73; H, 6.14.

Found: C, 55.98; H, 6.00. IR ν_{\max}^{neat} cm^{-1} : 3530 (OH), 1740. $^1\text{H-NMR}$ (400 MHz) ($\text{DMSO-}d_6\text{-D}_2\text{O}$) δ : 4.056 (1H, dd, $J=2.7, 5.4$ Hz, $\text{C}_3\text{-H}$).

Methyl *cis*-3-Hydroxy-8-methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (*cis*-73, Table II)—A mixture of *cis*-70 (1.0 g, 3.1 mmol), *N*-phenylpiperazine (1.1 g, 6.8 mmol), and KI (0.25 g, 1.5 mmol) was stirred at 90 °C for 3 h. The reaction mixture was subjected to column chromatography on silica gel (hexane: AcOEt: MeOH = 30:20:1) to give *cis*-73 (0.65 g, 47%) as colorless prisms (recrystallized from AcOEt). IR ν_{\max}^{KBr} cm^{-1} : 3400 (OH), 1760, 1730. $^1\text{H-NMR}$ (400 MHz) of *cis*-73·2HCl ($\text{DMSO-}d_6\text{-D}_2\text{O}$) δ : 4.064 (1H, dd, $J=3.4, 3.9$ Hz, $\text{C}_3\text{-H}$).

Similar treatment of *trans*-70, *cis*-71 and *cis*-72 gave *trans*-73, *cis*-74 and *cis*-75, respectively (Table II).

Methyl *trans*-3-Hydroxy-8-methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzoxepin-2-carboxylate (*trans*-73)—Recrystallization of the hydrochloride from MeOH-Et₂O gave *trans*-73·2HCl as colorless crystals. $^1\text{H-NMR}$ (400 MHz) ($\text{DMSO-}d_6\text{-D}_2\text{O}$) δ : 4.070 (1H, dd, $J=2.7, 7.3$ Hz, $\text{C}_3\text{-H}$).

Methyl *cis*-3-Hydroxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (*cis*-74)—Recrystallization from AcOEt gave *cis*-74 as colorless prisms. IR ν_{\max}^{KBr} cm^{-1} : 3450—3100 (OH), 1720 (ester).

Methyl *cis*-3-Hydroxy-8-methoxy-2-[3-(4-phenyl-1-piperazinyl)propyl]-2,3,4,5-tetrahydro-1-benzothiepin-2-carboxylate (*cis*-75)—Recrystallization of the hydrochloride from 30% EtOH gave *cis*-75·HCl as colorless crystals. $^1\text{H-NMR}$ (400 MHz) ($\text{DMSO-}d_6\text{-D}_2\text{O}$) δ : 4.056 (1H, dd, $J=2.2, 5.1$ Hz, $\text{C}_3\text{-H}$).

X-Ray Analyses of *cis*-17b, *cis*-50b, *cis*-58b, *cis*-71 and *cis*-73—All single-crystal measurements were made with a Rigaku AFC-5 automatic diffractometer. The structures were solved by the direct method²⁷⁾ and refined by a block-diagonal least-squares method²⁸⁾ using unit weight. In the final refinement, non-hydrogen and hydrogen atoms were refined with anisotropic and isotropic temperature factors, respectively. Details of the X-ray analyses will be published elsewhere.

Serotonin S₂-Receptor-Blocking Activity and Adrenergic α_1 -Receptor-Blocking Activity *in Vitro*—Pig hearts were obtained from a slaughterhouse under ice-cooling and the left circumflex or anterior descending coronary artery was dissected out within 3 h after death. The coronary artery was cut into a ring preparation of 3 mm in width. On the other hand, the thoracic aorta was dissected out from albino rabbits (2—3 kg body weight, male) after exsanguination. The rabbit aorta was cut into a spiral preparation of about 2 mm in width and about 2 cm in length. These blood vessel preparations were suspended in organ baths containing 20 ml of Krebs–Henseleit solution with a pair of suspending hooks. One of the hooks was fixed to the bottom of the organ bath, while the other was connected to a strain-gauge transducer, and the tension developed by these preparations was isometrically measured. The organ bath was maintained at 37 °C, and the Krebs–Henseleit solution was saturated with a gas mixture of 97% O₂ + 3% CO₂. As agonists, serotonin (10⁻⁶ M) and norepinephrine (10⁻⁷ M) were used in the porcine coronary and rabbit aortic preparations, respectively.

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