102. Absolute Conformation and Configuration of (2*S*, 3*S*)-3-Acetoxy-5-(dimethylaminoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one Chloride (Dilthiazem Hydrochloride)

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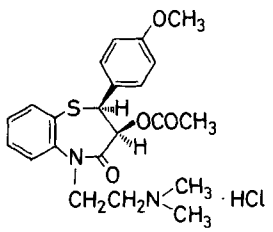
Summary

Resolution of racemic *cis*-3-(2-aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid (**2**) *via* the cinchonidine salt **3**, and brucine salt **4**, isolation of the calcium salts (+)- and (−)-**5**, as well as their cyclization to enantiomeric 1,5-benzothiazepines (+)- and (−)-**1**, are described. X-Ray single-crystal analysis reveals (2*S*, 3*S*) absolute configuration of (+)-**1**, and the existence of its 7-membered ring in a slightly twisted boat conformation in the solid state. *M*-absolute conformation in solution is assigned to (+)-**1** on the basis of tentative comparison of CD data with those for the 1,4-benzodiazepine derivative (+)-**8** of known absolute configuration.

1. Introduction. – Diltiazem [(+)-3-acetoxy-5-(2-dimethylaminoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one hydrochloride, **1**] belongs to a group of drugs commonly named «Ca antagonists» or «Ca channel blockers» [1–3]. They belong to quite diverse classes of organic compounds [4] [5]. As therapeutic agents they have proved effective in the treatment of cardiac arrhythmias and coronary diseases [6–8]. The detailed mechanism of action of these compounds is, however, largely unknown [9] [10].



(+)-**1**

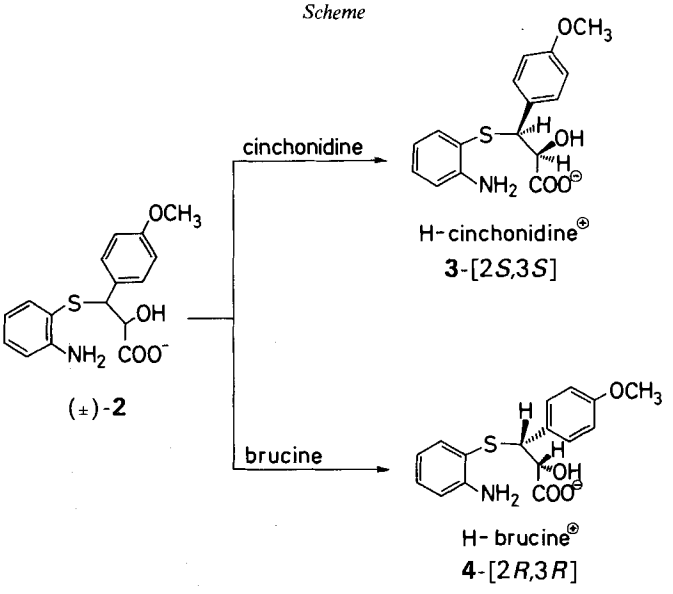
Diltiazem hydrochloride (**1**), like many other Ca channel blockers, is a chiral compound, and it was found that its (+)-form is more potent than the (−)-form [11] [12]. Its three-dimensional structure is mainly characterized by the following factors: a) absolute configuration at the chiral centers C(2) and C(3)[1]), b) absolute conformation (*M* or *P*) of the 7-membered ring, c) conformation of the dimethylaminoethyl side chain.

2. Results and Discussion. – 2.1. *Synthesis.* Preparation of diltiazem hydrochloride (**1**) has been repeatedly described in papers [14] [15] and patents [16–18]. Our own efforts in developing a new approach [19] to the optically pure derivatives of 2,3-disubstituted-5-alkylamino-1,5-benzothiazepin-4(5*H*)-ones, and improving some critical steps in the preparation of the known intermediates are described here.

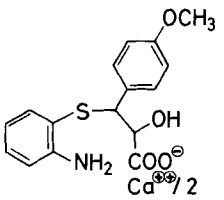
Starting from the racemic *cis*-α-hydroxy acid **2**, the two enantiomers were obtained from cinchonidine and brucine salts (*Scheme*). The cinchonidine salt **3** was crystallized from aqueous ethanol, while the brucine-salt **4** was crystallized first from acetonitrile, then from 2-butanone. They were quantitatively converted into the Ca(II)-salts, (+)-**5** and (−)-**5**, avoiding isolation of the free acids since this method affords resinous products and low chemical yields. Low solubility of (+)- and (−)-**5** could be ascribed to the chelating properties of Ca(II)-ions, already established, by X-ray analysis of some 2-hydroxycarboxylates [20] [21]. These salts were cyclised by heating in glacial acetic acid, affording the cyclic product (+)-**6** and its (−)-enantiomer. Their alkylation to (+)-**7** and (−)-**7**, and final acylation improving earlier procedures [14–16], furnished (+)- and (−)-**1**, respectively.

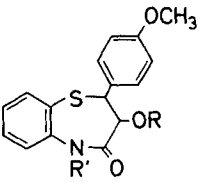
2.2. *^{1}H-NMR Spectroscopic Data.* ^{1}H-NMR characteristics of (+)-**1** have been studied in more detail to establish its conformational stability. Its spectrum in $CDCl_3$

Scheme



[1]) The assignment of the (2*S*,3*S*)-configuration by X-ray crystallographic analysis has been briefly mentioned by *Inoue et al.* [13]; on the other hand, no X-ray data of this compound could be found in the Cambridge Crystallographic Data Center, and Chemical Abstracts still refer to the substance as (+)-*cis*.





		R	R'
(+)- and (–)-**5**	(+)- and (–)-**6**	H	H
	(+)- and (–)-**7**	H	$CH_2CH_2N(CH_3)_2$
	(–)-1-[2*R*,3*R*]	CH_3CO	$CH_2CH_2N(CH_3)_2 \cdot HCl$

reveals two doublets centered at 5.00 and 5.12 ppm, corresponding to 2H, at C(2) and C(3), respectively. Two singlets at 2.86 and 2.93 ppm correspond to 3H each, *i.e.* for two CH_3-groups on the protonated N-atom. The signals of two non-equivalent protons at C(2) and C(3) remained unaltered on heating to 55°C ($J_{(2,3)} = 7.6$ Hz). On addition of D_2O the second of the two doublets changes into singlet. On the basis of the X-ray data (see *Sect. 2.4*) we propose that H-bonding of the ammonium group to the chloride, observed in the crystal, remains in solution, and the slow rotation of the bulky side chain renders the two CH_3 groups magnetically non-equivalent.

In the ^{1}H-NMR spectrum of (+)-**1** in (D_6)DMSO, however, two doublets at 4.99 and 5.17 ppm (for H at C(2) and C(3)) collapse into a singlet between 120–130°C *(Fig. 1)*, the doublet at 5.17 ppm being shifted 5.0 Hz upfield and the doublet at

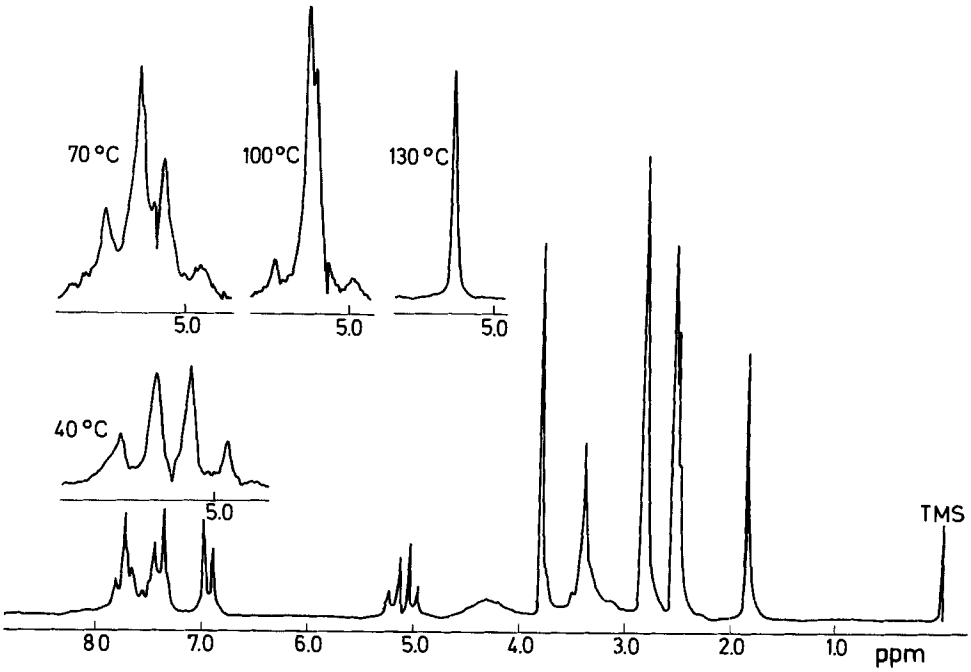
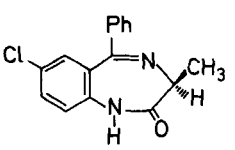


Fig. 1. *^{1}H-NMR spectrum of* (+)-**1** (90 MHz, (D_6)DMSO), *changes of double doublet for H–C(2) and H–C(3) with temperature*



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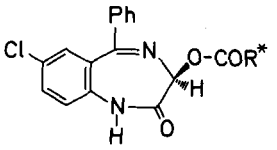

9 COR* = camphanoyl

4.99 ppm being shifted 11.6 Hz downfield. These results indicate a high energy barrier for the inversion of the 7-membered ring, *i.e.* its conformational stability at ambient temperature.

2.3. *UV and CD Spectroscopic Data.* Since X-ray structure analysis revealed the (2*S*, 3*S*) absolute configuration and a twisted-boat conformation of (+)-**1** in the solid state (see *Sect. 2.4*) it was of interest to see if this conformation remains in solution. To this aim the chiroptical properties of (+)-**1** were compared with X-ray conformational data, and with CD data of **8** and **9** as representatives of chiral 1,4-benzodiazepin-2-ones *(Fig. 2)*.

Cotton effect, strongly positive at 242 nm, and weakly negative at 224 nm for (+)-**1**, could be tentatively compared with the extrema at 221 nm and 210 nm for (+)-**8***[2]),

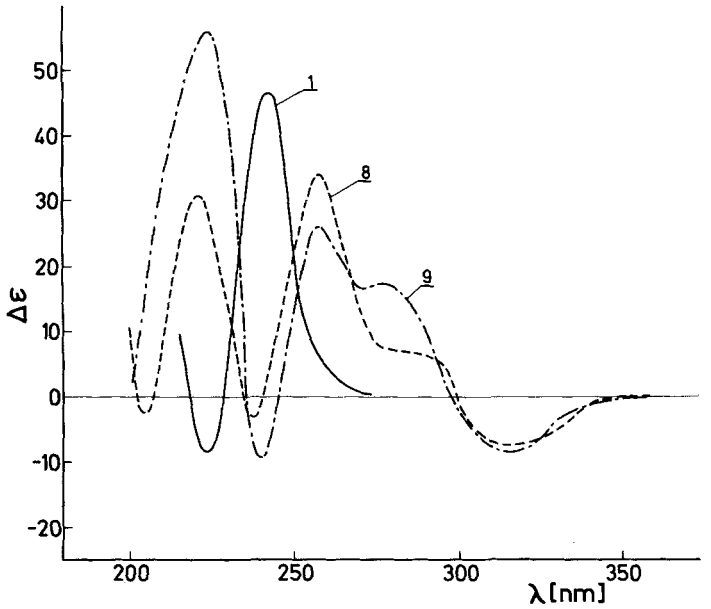

Fig. 2. *CD Spectra of* (+)-**1**, **8**, *and* **9** ($c = 1 \cdot 10^{-4}$ M, MeOH)

[2]) Compound (+)-**8** incorporates L-alanine [22], its chiroptical properties [23], conformation in solution [24] [25] and configuration of some congeners [26] were studied. Furthermore, it represents a configurationally chiral derivative of diazepam, a well-known psychopharmacological agent [27], which also acts as a coronary vasodilator [28].

and with strongly positive end of the same couplet at 226 nm for (+)-**9**. Chromophoric systems in (+)-**1** and (+)-**8** are not completely comparable. *N*-Acylaminophenyl subunit in (+)-**8** is cross-conjugated with the 5-phenyl ring *via* the azomethine double bond [23], the same subunit is isolated by alkylthio moiety in (+)-**1**. This results in different perturbations of the same chromophore in (+)-**1** and (+)-**8**, as reflected in their UV spectra. Thus, the 240-nm band in (+)-**1** corresponds to the shoulder at *ca.* 260 nm (+)-**8**. The short-wave band at 210 nm for (+)-**1** is then probably shifted to *ca.* 230 nm in (+)-**8**. In the spectra of (+)-**1**, both UV and CD maxima could be found at approximately the same wave-length, which is not the case for (+)-**8**. This is an additional indication that the transitions pertinent to these two bands are from a different origin. Since short-wavelength extrema of (+)-**1** cannot be unambiguously compared with the exciton-couplets assigned for chromophore A in (+)-**8** [23], they could only be used as an indication of *M*-absolute conformation of (+)-**1** in solution.

Thus, configurational chirality at C(3) in (+)-**1** (X-ray data), and (+)-**8** (chemical correlation [22]), being *S* in both cases, determines their *M*-conformational chirality. This conformation is favoured by adoption of the pseudo-equatorial position by the bulky substituent at C(3) *(Fig. 3)*.

2.4. *Crystal and Molecular Structure of* (+)-**1**. Interatomic distance and angles are listed in *Table 1*. The torsion angles describing the conformation of the benzothiazepine ring and relative orientations of the ring substituents are given in *Table 2*. Molecular packing and atom numbering are illustrated in *Fig. 4*.

Ineratomic distances and angles *(Table 1)* in the 1,5-benzothiazepine ring are in agreement with the given atom type, hybridization, and requirements of the 7-membered ring geometry. The S–C bond lengths are unequal [S(1)–C(10): 1.767(6), and S(1)–C(2): 1.845(6) Å]; one of them is affected by conjugation of the adjacent π-electron system. The bond lengths at C(sp^3) range from 1.518(7) to 1.539(6) Å. Interatomic distances in the phenyl rings are somewhat scattered [1.369(9)–1.406(8) Å]. Their angles range from 117.6(4) to 122.4(5)°. The carbonyl bonds are 1.190(6) and 1.221(7) Å. There are two more categories of C–O bonds: single C–O [C(3)–O(2): 1.440(6), and C(18)–O(1): 1.427(8) Å] and those adjacent to a C-atom involved in sp^2-bonding [C(15)–O(1): 1.365(6), and C(19)–O(2): 1.370(6) Å]. The C–N distances of N(5) and N(6) with different environment could not be compared. The C–N–C angles of protonated N(6) range from 109.8(5) to 112.1(4)°. The C–N(6) distances are from 1.484(9)

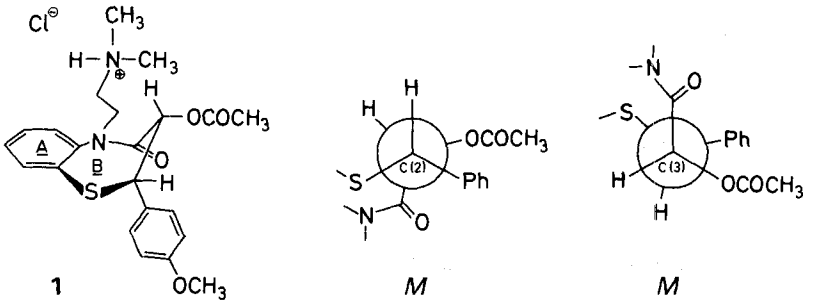

Fig. 3. *Absolute* M-*conformation of* (+)-**1**, *as predicted from the sign of the* Cotton *effect in* Fig. 2

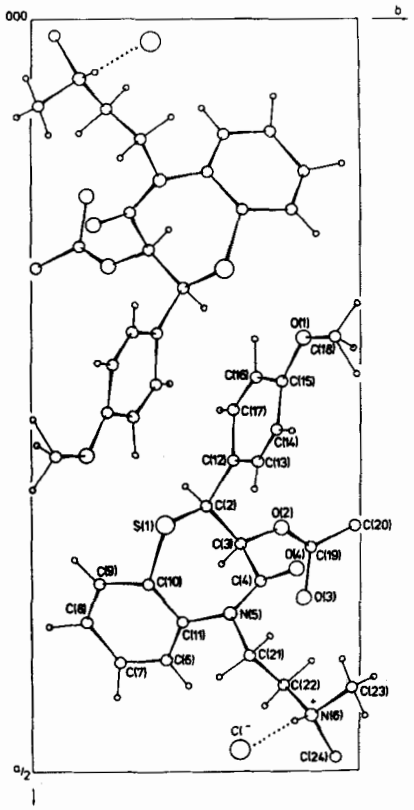

Fig. 4. *Atom numbering, and molecular packing of* (+)-**1** *showing N(6)...Cl contact*

to 1.517(8) Å. The N(5)-configuration is dictated by the ring geometry and hybridization; the C–N–C angles are from 118.3(4) to 123.0(4)°. The C–N bond lengths are unequal [1.432(7) and 1.351(6) Å]. Bond lengths and angles of the title compound could not be compared with those of two 2,4-benzothiazepine derivatives [29] and of one 1,4-benzothiazepine analogue [30], the only example described in the literature.

The substituents at C(2) and C(3) are *cis*-oriented exhibiting the (2*S*, 3*S*) absolute configuration[3]). Thus the absolute conformation of a benzothiazepine ring in (+)-**1** is determined with C(10), C(11) lying above the S(1), C(2), C(3) plane and C(4), N(5) below it. On the basis of UV and CD spectroscopic data a distinction between boat and twisted-boat conformation cannot be made. However, the X-ray analysis clearly revealed a twisted-boat conformation *(Table 2)*. The values of torsion angles of (+)-**1** and 3-methyl-3,5-dihydro-1,4-benzothiazepin-2(1*H*)-one 4-oxide [30] are very close, showing a twisted-boat conformation. The known absolute configuration at C(3) (being *S*) determines the absolute conformation of 7-membered ring as *M*.

[3]) This finding determines the absolute configurations at C(2) and C(3) atoms in the (+)-series of the open chain intermediates, **5**, **6** and **7**, as (2*S*,3*S*).

Table 1. *Interatomic Distances* (Å) *and Angles* (°)

For non-H-atoms		For non-H-atoms	
S(1)–C(2)	1.845 (6)	C(10)–C(11)	1.396 (7)
S(1)–C(10)	1.767 (6)	C(12)–C(13)	1.392 (8)
C(2)–C(3)	1.532 (7)	C(12)–C(17)	1.383 (7)
C(2)–C(12)	1.518 (7)	C(13)–C(14)	1.385 (8)
C(3)–C(4)	1.539 (7)	C(14)–C(15)	1.373 (7)
C(3)–O(2)	1.439 (6)	C(15)–C(16)	1.404 (8)
C(4)–N(5)	1.350 (6)	C(15)–O(1)	1.365 (6)
C(4)–O(4)	1.223 (6)	C(16)–C(17)	1.375 (7)
N(5)–C(11)	1.434 (7)	C(18)–O(1)	1.426 (8)
N(5)–C(21)	1.470 (7)	C(19)–O(2)	1.369 (6)
C(6)–C(7)	1.394 (9)	C(19)–O(3)	1.191 (6)
C(6)–C(11)	1.387 (8)	C(21)–C(22)	1.533 (8)
C(7)–C(8)	1.391 (9)	C(22)–N(6)	1.498 (7)
C(8)–C(9)	1.371 (9)	C(23)–N(6)	1.482 (9)
C(9)–C(10)	1.397 (8)	C(24)–N(6)	1.514 (8)

For non-H-atoms		For non-H-atoms	
C(2)–S(1)–C(10)	101.3 (3)	C(2)–C(12)–C(17)	120.1 (5)
S(1)–C(2)–C(3)	108.6 (3)	C(13)–C(12)–C(17)	117.6 (5)
S(1)–C(2)–C(12)	107.3 (4)	C(12)–C(13)–C(14)	121.1 (5)
C(2)–C(3)–C(4)	113.9 (4)	C(13)–C(14)–C(15)	120.2 (5)
C(2)–C(3)–O(2)	108.3 (4)	C(14)–C(15)–C(16)	119.7 (5)
C(3)–C(4)–N(5)	115.8 (4)	C(14)–C(15)–O(1)	125.2 (5)
C(3)–C(4)–O(4)	121.3 (4)	C(14)–C(15)–C(16)	119.7 (5)
N(5)–C(4)–O(4)	122.7 (5)	C(14)–C(15)–O(1)	125.2 (5)
C(4)–N(5)–C(11)	123.0 (4)	C(16)–C(15)–O(1)	115.0 (4)
C(4)–N(5)–C(21)	118.2 (4)	C(15)–C(16)–C(17)	118.9 (5)
C(11)–N(5)–C(21)	118.5 (4)	C(12)–C(17)–C(16)	122.4 (5)
C(7)–C(6)–C(11)	120.1 (5)	C(15)–O(1)–C(18)	118.2 (4)
C(6)–C(7)–C(8)	119.5 (6)	C(3)–O(2)–C(19)	113.2 (3)
C(7)–C(8)–C(9)	120.2 (6)	O(2)–C(19)–O(3)	122.8 (5)
C(8)–C(9)–C(10)	121.1 (5)	O(2)–C(11)–C(20)	111.7 (4)
S(1)–C(10)–C(9)	119.7 (4)	O(3)–C(19)–C(20)	125.5 (5)
S(1)–C(10)–C(11)	121.7 (4)	N(5)–C(21)–C(22)	108.9 (5)
C(9)–C(10)–C(11)	118.5 (5)	C(21)–C(22)–N(6)	110.7 (5)
N(5)–C(11)–C(6)	119.1 (4)	C(22)–N(6)–C(23)	112.7 (4)
N(5)–C(11)–C(10)	120.4 (4)	C(22)–N(6)–C(24)	110.1 (5)
C(6)–C(11)–C(10)	120.4 (5)	C(23)–N(6)–C(24)	110.6 (5)
C(2)–C(12)–C(13)	122.3 (4)		

Table 2. *Torsion Angles*

Benzothiazepine ring		Substituents	
S(1)–C(2)–C(3)–C(4)	– 42.1 (5)	S(1)–C(2)–C(12)–C(13)	49.5 (6)
C(2)–C(3)–C(4)–N(5)	90.6 (5)	S(1)–C(2)–C(3)–O(2)	– 163.7 (3)
C(3)–C(4)–N(5)–C(11)	– 13.3 (7)	C(2)–C(3)–O(2)–C(19)	– 175.6 (4)
C(4)–N(5)–C(11)–C(10)	– 48.0 (6)	C(3)–O(2)–C(19)–C(20)	– 179.6 (4)
N(5)–C(11)–C(10)–S(1)	0.6 (8)	C(3)–O(2)–C(19)–O(3)	– 0.2 (5)
C(11)–C(10)–S(1)–C(2)	69.4 (5)	C(4)–N(5)–C(21)–C(22)	– 79.6 (5)
C(10)–S(1)–C(2)–C(3)	– 42.0 (4)	N(5)–C(21)–C(22)–N(6)	169.7 (4)
		C(21)–C(22)–N(6)–C(23)	– 76.6 (6)
		C(21)–C(22)–N(6)–C(24)	159.3 (4)

Molecules of (+)-**1** are involved in the N(6)...Cl 3.001(5) Å contact forming an infinite chain along *c (Fig. 4)*. Molecular packing is completed by *van der Waals* interactions [C(8)...O(3), 3.487(8), C(13)...O(2), 3.393(7), C(19)...O(4), 3.203(7), C(20)...O(1), 3.263(7) Å].

Experimental Part

X-Ray Data. The crystals of (+)-**1** suitable for X-ray analysis were prepared in methanol/acetone (1:3), after chilling at −6° for 48 h. Preliminary cell dimensions and the space group ($P\,2_12_12_1$) were determined from oscillation and *Weissenberg* photographs recorded with Cu*Ka* radiation; final cell dimensions ($a = 42.18(1)$, $b = 9.079(1)$, $c = 6.035(2)$ Å) were refined from diffractometer measurements using 20 reflexions. Intensities were collected on a *Philips PW 1100* computer-controlled four-circle diffractometer in the ω-scan mode [scan width 1.20° (θ), scan speed 0.04° (θ) s^{-1}] with graphite-monochromated Cu*Ka* radiation. Dimensions of crystal were $0.57 \cdot 0.13 \cdot 0.40$ mm. 2068 independent reflexions $I \geq 3\sigma(I)$ in the range $4 < \theta < 68°$ were used in calculations; three standard reflexions were measured every 2 h. The structure was solved by combination of *Patterson* and direct methods, MULTAN 80 [31]. A subsequent difference synthesis located the H-atoms except those of two terminal CH_3-groups [C(2) and C(24)]. Full-matrix least-squares refinement, minimized $\Sigma\, w(|F_o|-|F_c|)^2$ with $w = w_1 \cdot w_2$ where $w_1 = 1$ for $F_o \leq 25$ and $25|F_o|$ for $|F_o| > 25$; $w_2 = 1$ for $\sin\theta \geq 0.40$ and $\sin\theta/0.40$ for $\sin\theta < 0.40$. A scale factor, atomic coordinates, and anisotropic thermal parameters (337 variables in all) were refined; atomic coordinates and isotropic thermal parameters of the H-atoms were refined, but coordinates of H(6), H(14), H(18)1, H(18)2, H(18)3 and H(N6) kept constant. The isotropic thermal parameter of H(N6), 0.12 $Å^2$ is high but the difference synthesis clearly located its position. Anisotropic thermal parameters are in the usual range: the maximum value is U_{33} for C(8) 0.083(5) $Å^2$. The final $R = 0.052$, $R_w = 0.061$ for 2068 observed reflexions ($S = 1.24$). An $R = 0.062$, $R_w = 0.072$ for the (2*R*, 3*R*)-enantiomer was obtained. The absolute configuration was assigned as (2*S*, 3*S*) on the basis of the *R*-factor difference although the *Bijvoet* pairs were not measured. The ratio of maximum least-squares shift to error on coordinates in the final refinement cycle was 1.264 [for *x* of Cl]. Scattering factors from *Cromer & Mann* [32] and (for H) *Stewart et al.* [33] were used. Anomalous-dispersion corrections were included for S and Cl [34].

Calculations were carried out on the *Univac 1110* computer at the University Computing Centre in Zagreb with the XRAY system [35]. Final atomic coordinates with U_{eq} are listed in *Table 3*.

Chemistry. The melting points (m.p.), determined with a *Kofler* microheating stage (*Boetius*), are uncorrected. Optical rotations were measured on a *Perkin-Elmer 141*. UV spectra [λ_{max} nm ($\log\varepsilon$)] were recorded with a *PYE Unicam SP 8-100* instrument. Following UV data for (+)-**8** were recorded ($c = 3 \cdot 10^{-3}$M, MeOH) 204 (4.51), 224 (4.53), 253 (sh, 4.15), 320 (3.30). IR spectra (for KBr pellets, cm^{-1}) were recorded on a *Perkin-Elmer M 297* spectrometer, ^{1}H-NMR spectra were determined on a *Perkin-Elmer R 12*, and a *Varian FX 90Q* instruments. Chemical shifts are reported in δ values relative to TMS as a standard.

Cinchonidine Salt of (2S,3S)3-(2-Aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic Acid (**3**). Racemic *cis*-3-(2-Aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid (**2**) (9.58 g, 30.0 mmol) was added to a solution of cinchonidine (8.83 g, 30.0 mmol) in aq. EtOH (500 ml). After brief heating (70°), the resulting, clear solution was set aside for crystallization at r.t. for 48 h. The resulting crystalline salt **3** was collected, affording 7.87 g (85%) of the optically pure salt, m.p. 132–135°; $[\alpha]_D^{25} = +158°$ ($c = 1.0$, EtOH). IR: 3450, 3330, 1580, 1510, 1480, 1375, 1250, 1010, 760. Anal. calc. for $C_{35}H_{39}N_3O_5S$ (613.80): C 68.48, H 6.40, N 6.85; found: C 68.24, H 6.58, N 6.60.

Brucine Salt of (2R,3R)-3-(2-Aminophenylthio)-2-hydroxy-3(4-methoxyphenyl)propionic Acid (**4**). Propionic acid **2** (9.58 g, 30.0 mmol) and brucine (11.83 g, 30.0 mmol) were dissolved in CH_3CN (500 ml) and the mixture was heated at 50–60° for 30 min; then the clear solution was left for crystallization at r.t. for 24 h. The resulting brucine salt (22.0 g) was filtered off and recrystallized from 2-butanone to afford 6.9 g (64.5%) of the optically pure salt, m.p. 140–142°. $[\alpha]_D^{25} = -208°$ ($c = 3.0$; MeOH). IR: 3420, 3330, 2980, 1680, 1610, 1500, 1440, 1400, 1300, 1110, 1025, 750.

Ca(II)-Salt of (2S,3S)-3-(2-Aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic Acid ((+)-**5**). The cinchonidine salt **3** (3.07 g, 5.0 mmol) was dissolved in $CHCl_3$ (15 ml) and treated with 5% NaOH (20 ml). The aq. phase was acidified (pH ≈ 2), and treated with an aq. $CaCl_2$. After 30 min stirring, the precipitated Ca-salt was collected and dried at 100° to give 1.04 g (85%) of **5**, a sample recrystallized from acetone/water had m.p.

Table 3. *Final Atomic Coordinates* ($\times 10^5$) *and Isotropic Thermal Parameters* ($\times 10^2$) *for Non-H-Atoms*

	x	*y*	*z*	*U* (Å)^2
Cl	48683 (2)	65144 (16)	22044 (26)	3.93 (4)
S(1)	33713 (2)	41478 (14)	76687 (29)	3.66 (4)

Final Atomic Coordinates ($\times 10^4$) *and Isotropic Thermal Parameters* ($\times 10^2$) *for Non-H-Atoms*

	x	*y*	*z*	*U* (Å)^2
C(2)	3200 (1)	5415 (6)	5599 (9)	3.0 (2)
C(3)	3465 (1)	6402 (5)	4700 (8)	2.7 (2)
C(4)	3695 (1)	6966 (5)	6491 (8)	2.6 (2)
N(5)	3951 (1)	6113 (4)	6885 (7)	2.6 (2)
C(6)	4256 (1)	4201 (6)	5034 (11)	3.7 (3)
C(7)	4295 (1)	2745 (7)	4356 (13)	4.7 (3)
C(8)	4050 (1)	1740 (6)	4687 (13)	4.7 (4)
C(9)	3773 (1)	2181 (6)	5669 (12)	4.1 (3)
C(10)	3729 (1)	3635 (6)	6361 (10)	3.2 (3)
C(11)	3978 (1)	4631 (5)	6085 (9)	2.8 (2)
C(12)	2922 (1)	6191 (5)	6693 (9)	2.7 (2)
C(14)	2691 (1)	7579 (6)	9706 (9)	3.2 (2)
C(13)	2947 (1)	6859 (6)	8762 (9)	3.0 (2)
C(15)	2405 (1)	7634 (5)	8615 (9)	2.7 (2)
C(16)	2373 (1)	6939 (6)	6550 (9)	2.9 (2)
C(17)	2630 (1)	6232 (5)	5649 (9)	2.9 (2)
O(1)	2139 (1)	8318 (4)	9380 (7)	3.8 (3)
C(18)	2169 (1)	9291 (7)	11224 (11)	4.3 (3)
O(2)	3322 (1)	7640 (4)	3599 (6)	2.9 (1)
C(19)	3538 (1)	8545 (5)	2589 (9)	2.9 (2)
O(3)	3816 (1)	8320 (4)	2634 (6)	3.4 (1)
C(20)	3378 (1)	9841 (6)	1464 (10)	3.9 (3)
O(4)	3656 (1)	8163 (3)	7379 (6)	3.0 (1)
C(21)	4196 (1)	6675 (6)	8393 (9)	2.8 (2)
C(22)	4407 (1)	7768 (6)	7131 (10)	3.0 (2)
N(6)	4622 (1)	8573 (5)	8691 (7)	2.8 (2)
C(23)	4455 (1)	9743 (8)	9950 (14)	4.4 (3)
C(24)	4902 (1)	9204 (8)	7441 (13)	4.9 (3)

232–234° (dec.); $[\alpha]_D^{25} = +540°$ (c = 1.0, DMF). IR: 3500–3100, 2840, 1610, 1510, 1480, 1440, 1420, 1305, 1250, 1180, 1110, 1095, 1030, 830, 750. Anal. calc. for $C_{16}H_{16}NO_4SCa_{1/2} \cdot 2H_2O$ (374.43): C 51.32, H 5.38, N 3.74; found: C 51.23, H 5.35, N 3.68.

*Ca(II)-Salt of (2*R*,3*R*)-3-(2-Aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic Acid* ((−)-**5**). The brucine salt (3.6 g, 5.0 mmol) was treated according to the above procedure for the corresponding cinchonidine salt, to afford 1.5 g, (89%) of (−)-**5**. $[\alpha]_D^{25} = -537°$ (c = 1.0, DMF).

*(2*S*,3*S*)-3-Hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one* ((+)-**6**). The Ca-salt (+)-**5** (3.4 g, 10.0 mmol) was dissolved in AcOH (50 ml) and the mixture was heated at reflux for 5 h. After evaporation of the solvent, the oily residue was dissolved in $CHCl_3$, the org. phase was washed first with H_2O (50 ml), then with aq. 5% NaOH (2 × 50 ml), dried (Na_2SO_4), and evaporated to give 1.1 g of crude (+)-**6**. On recrystallization from 2-propanol (0.75 g, 25% yield) of (+)-**6** was obtained, m.p. 208–210°; $[\alpha]_D^{25} = +55°$ (c = 1.0, $CHCl_3$). IR: 3350, 3190, 1680, 1640, 1610, 1510, 1480, 1305, 1250, 1180, 1100, 1025, 765. ^{1}H-NMR ((D$_7$)DMF): 3.8 (*s*, 3H); 4.45 (*d*, 1H); 4.8 (br., 1H); 5.18 (*d*, 1H); 6.8–7.8 (*m*, 8H); 10.3 (br., 1H). Anal. calc for $C_{16}H_{15}NO_3S$ (301.35): C 63.75, H 5.02, N 4.65; found: C 63.43, H 5.04, N 4.47.

*(2*R*,3*R*)-3-Hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-one* ((−)-**6**). Starting from the Ca-salt (−)-**5**, compound (−)-**6** was obtained as described for (+)-enantiomer, m.p. 207–208°. $[\alpha]_D^{25} = -54.5°$ (c = 1.0, $CHCl_3$).

*(2*S*,3*S*)-5-(2-Dimethylaminoethyl)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5*H*)-*

one ((+)-**7**). A suspension of NaH (0.26 g of 55–60% dispersion in the mineral oil, 6.0 mmol) in abs. DMF (30 ml) under N_2 was added to solution of (+)-**6** (1.8 g, 6.0 mmol) in abs. DMF (15 ml). After 15 min stirring, the mixture was treated with a solution of 2-dimethylaminoethyl chloride (0.77 g, 7.2 mmol) in Et_2O (30 ml), then heated at 70–80° for 3 h. The solvents were distilled off, and oily residue treated with diluted aq. HCl. Unreacted starting material was collected, and the cooled solution was made alkaline (pH 12) with NaOH (5%), and extracted with Et_2O (3 × 100 ml). Dried (Na_2SO_4) org. extracts were evaporated to give 1.5 g (67%) of (+)-**7** as a gummy oil, $[\alpha]_D^{25} = +134.4°$ ($c = 1.0$, $CHCl_3$). Analytical sample was purified on silica gel column with AcOEt/$CHCl_3$ (3:1). IR (film): 3500–3400, 2960, 1665, 1610, 1510, 1470, 1375, 1305, 1255, 1180, 1100, 1035, 765. ^{1}H-NMR ($CDCl_2$): 2.25 (*s*, 6H); 2.4–2.8 (*m*, 2H); 2.9 (br., 1H, OH); 3.8 (*s*, 3H); 3.5–4.8 (*m*, 2H); 4.3 (*d*, 1H); 4.9 (*d*, 1H); 6.7–7.9 (*m*, 8H). Anal calc. for $C_{20}H_{24}N_2O_3S$ (372.47): C 64.49, H 6.49, N 7.52; found: C 64.34, H 6.55, N 7.61.

(2R,3R)-5-(2-Dimethylaminoethyl)-3-hydroxy-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one ((−)-**7**). Compound (−)-**6** was treated as (+)-**6** to afford the title compound, $[\alpha]_D^{25} = -135.1°$ ($c = 1.0$, $CHCl_3$).

(2S,3S)-3-Acetoxy-5-(2-dimethylaminoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one ((+)-**1**). A solution of (+)-**7** (3.0 g, 8.0 mmol) in Ac_2O (50 ml) was heated at 90–100° for 1 h. The excess Ac_2O was removed under reduced pressure, residue was dissolved in 2-butanone and treated with ethanolic HCl to afford crystalline (+)-**1** (2.89 g, 80%) m.p. 210–215°. $[\alpha]_D^{25} = +99$ ($c = 3.0$, MeOH). UV ($c = 3 \cdot 10^{-3}$M, MeOH): 210 (4.41), 239 (4.26), 280 (3.26). IR: 2600–2350, 1750, 1685, 1612, 1590, 1515, 1480, 1260, 1220, 1065, 1030, 842, 785. ^{1}H–NMR ((D$_6$)DMSO) 1.8 (*s*, 3H); 2.8 (*s*, 6H); 2.9–3.5 (*m*, 2H); 3.8 (*s*, 3H); 4.0–4.7 (*m*, 2H); 4.98 (*d*, 1H); 5.18 (*d*, 1H); 6.9–7.9 (*m*, 8H). Anal. calc. for $C_{22}H_{26}N_2O_4S \cdot HCl$ (451.05): C 58.59, N 6.03, N 6.21; found: C 58.53, N 6.10, N 6.18.

(2R,3R)-3-Acetoxy-5-(2-dimethylaminoethyl)-2-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepin-4(5H)-one ((−)-**1**). Compound (−)-**7** was acetylated as for (+)-**1** to give (−)-**1**, $[\alpha]_D^{25} = -99°$ ($c = 3.0$, MeOH).

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