Synthesis of 2-Phenylthiazolidine Derivatives as Cardiotonic Agents. III.\(^{1)}\)
Optically Active Isomers of N-Methyl-2-(2-(2-(4-phenylpiperazino)ethoxy)phenyl)thiazolidine-3-carboxamides

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Optically active isomers of N-methyl-2-(2-(2-(4-phenylpiperazino)ethoxy)phenyl)thiazolidine-3-carboxamides ((+)-2 and (-)-2) have been synthesized and tested for positive inotropic activity. The racemic thiocarboxamide ((±)-3) was resolved into the enantiomers ((+)-3 and (-)-3) via the L- and D-N-(2-naphthylsulfonyl)prolyl derivatives ((+)-4 and (-)-4). Conversion of the thio-carboxamides ((+)-3 and (-)-3) to the carboxamides ((+)-2 and (-)-2) was smoothly effected by treatment with the glycidic ester (7). The absolute stereochemistry of (-)-3 was determined to be 2S by X-ray crystallographic analysis. Hence, the absolute configuration of the carboxamide ((-)-2) is 2S. On i.v. administration to anesthetized dogs, the enantiomers of 2 showed only a threefold difference in positive inotropic activity, with the levo isomer ((-)-2) being the more active. In the isolated cat heart muscle, the enantiomers were nearly equipotent to each other. Thus, no significant difference between the positive inotropic activities of the optical isomers of 2 was observed.

Keywords—N-methyl-2-(2-(4-phenylpiperazino)ethoxy)phenyl)thiazolidine-3-carboxamide; urea; optical resolution; 2-phenylthiazolidine; N-(2-naphthylsulfonyl)prolyl chloride; absolute stereochemistry; absolute configuration; X-ray crystallographic analysis; positive inotropic activity; cardiotonic agent

The preceding paper\(^{1)}\) of this series disclosed the synthesis and cardiotonic activity of novel 2-phenylthiazolidine derivatives represented by general formula (1). Among the large number of derivatives synthesized, N-methyl-2-(2-(4-phenylpiperazino)ethoxy)-phenyl)thiazolidine-3-carboxamide (2) was found to produce a marked and sustained positive inotropic action without producing significant alteration in heart rate or blood pressure in anesthetized dogs. In view of the potential usefulness of 2 as a new cardiotonic agent, the effect of its optical resolution on the activity was examined. We describe here the synthesis of optically active isomers of 2, determination of their absolute stereochemistry by X-ray crystallographic analysis, and their cardiotonic activity.

![Chart 1](image-url)
Chemistry

Several attempts to resolve the racemate ((±)-2) with optically active acids were without success. Efforts were then turned to the resolution of the corresponding thiocarboxamide ((±)-3) via the optically active N-acyl derivative. The racemate ((±)-3) was allowed to react with N-(2-naphthylsulfonyl)-L-prolyl chloride (L-NSPCl) in the presence of NaH in dimethylformamide (DMF), giving a diastereoisomeric mixture of the N-acylthiocarboxamides ((+)-4 and 5 (2S)) together with the aldehyde (6). Chromatography of this mixture on silica gel gave (+)-4, mp 191–191.5 °C, in 24.1% yield.

The diastereoisomer (5 (2S)) could not be isolated in a pure state, since attempts to separate it from the aldehyde (6) were unsuccessful. Alkaline hydrolysis of (+)-4 at room temperature gave 93.3% yield of the thiocarboxamide ((+)-3), mp 144–144.5 °C, [α]D20 +145.7°. Similar treatment of the crude 5 (2S) gave (-)-3 in only low yield (4.1% from (±)-3). To obtain the levo isomer ((−)-3) in better yield, we carried out acylation of (±)-3

![Chart 2](image)

![Chart 3](image)
with N-(2-naphthylsulfonyl)-o-prolyl chloride (d-NSPCI), giving (-)-4, mp 191—192 °C, as a major product (24.6%). Alkaline hydrolysis of (-)-4 gave (-)-3, mp 144—145.5 °C, [\(\alpha\)]\(_D^{20}\) —145.3°, in 94.2% yield (Chart 2).

Conversion of the thioaspartic acids ((+)3 and (-)-3) to the corresponding carboxamides ((+)2 and (-)-2) was smoothly effected by treatment with methyl trans-3-(4-methoxyphenyl)glycidate (7). Reaction of thioureas with oxiranes has been reported to give episulfides or olefins together with ureas via isothiuronium salts. When heated with the glycidate (7) in EtOH, (+)-3 readily gave the carboxamide ((+)2), mp 151—152 C, [\(\alpha\)]\(_D^{20}\) +152.38°, in 75.7% yield after simple chromatographic separation from the methyl cinnamate (8) and elemental sulfur. Similarly, (-)-2, mp 151.5—152.5 C, [\(\alpha\)]\(_D^{20}\) —154.1°, was obtained from (-)-3 in 76.7% yield. Various methods for oxidative conversion of thioureas.

![Stereoscopic Drawing of (-)-3](chart2.png)

**Table I.** Fractional Coordinates and Isotropic Temperature Factors (Å\(^2\)) with e.s.d.’s in Parentheses

<table>
<thead>
<tr>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>(B_{eq})</th>
<th>Atom</th>
<th>x</th>
<th>y</th>
<th>z</th>
<th>(B_{eq})</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(1)</td>
<td>0.68920 (14)</td>
<td>0.54995 (6)</td>
<td>1.07069 (18)</td>
<td>5.61 (4)</td>
<td>C(16)</td>
<td>0.9153 (6)</td>
<td>0.8073 (3)</td>
<td>0.8987 (7)</td>
<td>6.6 (2)</td>
</tr>
<tr>
<td>C(2)</td>
<td>0.8504 (5)</td>
<td>0.5744 (2)</td>
<td>1.0420 (6)</td>
<td>4.6 (1)</td>
<td>C(17)</td>
<td>0.9813 (5)</td>
<td>0.8037 (3)</td>
<td>0.7506 (7)</td>
<td>7.1 (2)</td>
</tr>
<tr>
<td>N(3)</td>
<td>0.9129 (4)</td>
<td>0.5251 (1)</td>
<td>0.9825 (5)</td>
<td>4.7 (1)</td>
<td>N(18)</td>
<td>0.8987 (4)</td>
<td>0.8292 (2)</td>
<td>0.6400 (5)</td>
<td>5.3 (1)</td>
</tr>
<tr>
<td>C(4)</td>
<td>0.8519 (6)</td>
<td>0.4707 (2)</td>
<td>1.0125 (6)</td>
<td>5.4 (2)</td>
<td>C(19)</td>
<td>0.7811 (5)</td>
<td>0.8007 (3)</td>
<td>0.6342 (7)</td>
<td>6.3 (2)</td>
</tr>
<tr>
<td>C(5)</td>
<td>0.7465 (6)</td>
<td>0.4815 (2)</td>
<td>1.1191 (7)</td>
<td>5.6 (2)</td>
<td>C(20)</td>
<td>0.7192 (5)</td>
<td>0.8008 (2)</td>
<td>0.7854 (8)</td>
<td>6.2 (2)</td>
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<tr>
<td>C(6)</td>
<td>0.9035 (5)</td>
<td>0.5953 (2)</td>
<td>1.1852 (5)</td>
<td>4.4 (1)</td>
<td>C(21)</td>
<td>0.9526 (5)</td>
<td>0.8386 (2)</td>
<td>0.5009 (6)</td>
<td>4.9 (1)</td>
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<tr>
<td>C(7)</td>
<td>0.8789 (5)</td>
<td>0.6510 (2)</td>
<td>1.2287 (6)</td>
<td>4.6 (1)</td>
<td>C(22)</td>
<td>1.0769 (5)</td>
<td>0.8520 (2)</td>
<td>0.4679 (7)</td>
<td>5.3 (2)</td>
</tr>
<tr>
<td>C(8)</td>
<td>0.9195 (5)</td>
<td>0.6699 (2)</td>
<td>1.3661 (6)</td>
<td>5.3 (2)</td>
<td>C(23)</td>
<td>1.1270 (6)</td>
<td>0.8382 (2)</td>
<td>0.3328 (7)</td>
<td>6.2 (2)</td>
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<tr>
<td>C(9)</td>
<td>0.9845 (6)</td>
<td>0.6344 (3)</td>
<td>1.4576 (6)</td>
<td>6.1 (2)</td>
<td>C(24)</td>
<td>1.0556 (7)</td>
<td>0.8635 (2)</td>
<td>0.2255 (7)</td>
<td>6.8 (2)</td>
</tr>
<tr>
<td>C(10)</td>
<td>1.0116 (5)</td>
<td>0.5803 (2)</td>
<td>1.4156 (7)</td>
<td>5.9 (2)</td>
<td>C(25)</td>
<td>0.9346 (7)</td>
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<td>0.2573 (7)</td>
<td>6.8 (2)</td>
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<tr>
<td>C(11)</td>
<td>0.9718 (5)</td>
<td>0.5618 (2)</td>
<td>1.2792 (6)</td>
<td>5.3 (2)</td>
<td>C(26)</td>
<td>0.8827 (6)</td>
<td>0.8660 (2)</td>
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<tr>
<td>C(12)</td>
<td>0.8137 (3)</td>
<td>0.6829 (1)</td>
<td>1.1311 (4)</td>
<td>5.3 (1)</td>
<td>C(27)</td>
<td>1.0149 (6)</td>
<td>0.5304 (2)</td>
<td>0.8965 (6)</td>
<td>5.3 (2)</td>
</tr>
<tr>
<td>C(13)</td>
<td>0.8062 (6)</td>
<td>0.7422 (2)</td>
<td>1.1591 (7)</td>
<td>5.5 (2)</td>
<td>C(28)</td>
<td>1.0769 (18)</td>
<td>0.59330 (6)</td>
<td>0.85690 (21)</td>
<td>7.10 (5)</td>
</tr>
<tr>
<td>C(14)</td>
<td>0.7380 (5)</td>
<td>0.7704 (2)</td>
<td>1.0367 (7)</td>
<td>5.6 (2)</td>
<td>C(29)</td>
<td>1.0629 (5)</td>
<td>0.4822 (2)</td>
<td>0.8430 (6)</td>
<td>6.3 (2)</td>
</tr>
<tr>
<td>N(15)</td>
<td>0.6021 (4)</td>
<td>0.7740 (2)</td>
<td>0.8971 (6)</td>
<td>5.6 (1)</td>
<td>C(30)</td>
<td>1.1740 (8)</td>
<td>0.4785 (3)</td>
<td>0.7530 (9)</td>
<td>8.8 (3)</td>
</tr>
</tbody>
</table>

\[B_{eq} = 4 \sum \sum_j \beta_{ij} a_i a_j\]
into ureas have been reported recently. The above procedure, however, appears to be of practical use in view of the mild and neutral reaction conditions (Chart 3).

The absolute stereochemistry of the thiocarboxamide ((−)-3) was determined to be 2S by X-ray crystallographic analysis, and a stereoscopic drawing of the molecule is shown in Fig. 1. It follows from this fact that the absolute configurations of the carboxamides ((−)-2 and (+)-2) are 2S and 2R, respectively.

**Pharmacology**

The optically active isomers of the carboxamide (2) were tested for positive inotropic activity by measuring the increase in the maximum derivative of left ventricular pressure (LVdP/dt\text{max}) after i.v. administration to anesthetized dogs by the method reported previously. The results are summarized in Table V together with comparative data for the
The positive inotropic activity of 2 was not significantly changed by optical resolution. Its enantiomers showed only an approximately threefold difference in activity, with the levo isomer ((−)-2) being the more active. The levo isomer ((−)-2) was nearly equipotent to the racemate. In the isolated cat heart muscle,8 the optical isomers of 2 produced a dose-dependent increase in contractile force from $4 \times 10^{-7}$ M. The enantiomers, however, were nearly equipotent to each other in this test also. The rather uniform activity of the enantiomers of 2 appears to suggest that the positive inotropic activity of 2 is largely conferred by the phenylpiperazinoethoxy moiety1) and that the change in the chirality at C2 of the thiazolidine ring, which is remote from this moiety, does not significantly alter the activity.

Further studies on 2-phenylthiazolidine derivatives as new cardiotonic agents are being continued.

**Experimental**

All melting points are uncorrected. Infrared (IR) spectra were recorded in Nujol mulls on a Hitachi IR-215 spectrometer. Proton nuclear magnetic resonance (1H-NMR) spectra were taken in CDC1₃ at 60 MHz on a JEOL PMX-60 spectrometer with tetramethylsilane (TMS) as an internal reference. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Mass spectra (MS) were measured with a Hitachi RMU-6M instrument. Optical rotations were determined for solutions in CHC1₃ or MeOH on a Union PM-201 automatic digital polarimeter.

**Reaction of ((+)3 with L-NSPCI**—The racemate ((+)3, 5.33 g, 0.012 mol) was added to a stirred suspension of NaH (0.64 g, 50% oil dispersion, 0.013 mol) in DMF (55 ml) under ice-cooling, and the mixture was stirred for 0.5 h. A solution of L-NSPCI13) (4 g, 0.0124 mol) in DMF (40 ml) was added dropwise to the mixture under ice-cooling, and the whole was stirred at room temperature for 2 h. The mixture was diluted with ice-water and extracted with AcOEt. The AcOEt extracts were washed with sat. NaHCO₃ and water, dried, and evaporated to give an oil. The oil was chromatographed over SiO₂ and eluted with benzene—AcOEt (3 : 2). (R)-N-Methyl-N-(N-(2-naphthylsulfonyl)-L-propyl)-2-(2-(2-(4-phenylpiperazino)ethoxy)phenyl)thiazolidine-3-thiocarboxamide ((+)-4, 0.94 g, mp 191–191.5 °C from AcOEt-hexane) was obtained as needles from the first eluate. $[\alpha]_{D}^{20} + 26.4^\circ$ (c = 0.417, CHCl₃). IR $\nu_{max}$ cm⁻¹: 1690, 1600, 1490, 1354, 1150, 760. MS m/z: 729 (M⁺), 597, 538, 469, 412, 368, 326, 292, 260 (base peak), 212, 191. 189, 175, 130, 132, 128, 127. NMR (CDCl₃) δ: 1.5–2.4 (4H, m), 2.4–3.8 (17H, m), 4.0–4.2 (4H, m), 4.9 (1H, br), 6.7–7.4 (10H, m), 7.5–8.6 (6H, m), 8.44–8.55 (1H, m). Anal. Calcd for C₃₈H₃₃N₅O₄S₃: C, 62.53; H, 5.94; N, 9.59; S, 13.18. Found: C, 62.64; H, 5.99; N, 9.48; S, 13.02.

**TABLE V. N-Methyl-2-(2-(2-(4-phenylpiperazino)ethoxy)phenyl)thiazolidine-3-carboxamide ((+)2, (−)2, and (+)2)**

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Dose (mg/kg) i.v.</th>
<th>$LVdP/dt_{max}$ (Δ %)</th>
<th>Duration (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-2 (2R) Oxalate</td>
<td>0.01</td>
<td>20</td>
<td>30</td>
</tr>
<tr>
<td>(−)-2 (2S) Oxalate</td>
<td>0.003</td>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td>(±)-2 Oxalate</td>
<td>0.003</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>

a) For methodology, see reference 7.
The residue was chromatographed over SiO₂ and eluted with CHC₁₃-EtOH (40:1). Elemental sulfur (23 mg (66%)) was worked up as described above, and the crude product was purified by column chromatography (SiO₂, benzene-AcOEt-hexane and had mp 138-144 °C (dec.). 

Reaction of (+)-3 with d-NSPCI—A mixture of (+)-3 (5.33 g, 0.012 mol), d-NSPCI (4 g, 0.0124 mol), and NaOH (0.12 g) in H₂O (3 ml), MeOH (40 ml), and tetrahydrofuran (THF) (40 ml) was stirred at room temperature for 15.5 h and concentrated in vacuo.

The residue was purified by SiO₂ chromatography (benzene-AcOEt = 3:2) and recrystallized from Me₂CO-hexane and had mp 170-172 °C (dec.). [α]₀ +88.63° (c = 0.102, MeOH). Anal. Calcd for C₂₃H₃₀N₄O₂S₂.C₄H₄O₄.H₂O: C, 57.12; H, 6.21; N, 9.87; S, 11.29. Found: C, 56.91; H, 6.12; N, 9.74; S, 11.52. From the aqueous layer, 0.4 g (90.2%) of (S)-2 was recovered. Its spectral data were identical to those of (+)-3. Anal. Calcd for C₂₃H₃₀N₄OS₂: C, 62.41; H, 6.83; N, 12.66; S, 14.35. The fumarate was crystallized from Me₂CO-hexane and NaOH (0.12 g) in H₂O (3 ml), MeOH (30 ml), and THF (30 ml) was hydrolyzed in the same manner as described for (+)-3 to give 0.6 g (94.2%) of (-)-3, mp 144-145.5 °C (from AcOEt-hexane). [α]₀ -145.37° (c = 0.216, CHC₁₃). The spectral data were identical to those of (+)-3. Anal. Calcd for C₂₃H₃₀N₄O₂S: C, 64.76; H, 7.09; N, 13.13; S, 7.52. Found: C, 64.60; H, 7.05; N, 13.20; S, 7.57. The oxalate was crystallized from Me₂CO and had mp 135-135 °C (dec.). [α]₀ +141.74° (c = 0.206, CHC₁₃). Its spectral data were identical to those of (+)-3 obtained from (+)-4.

b) Hydrolysis of Crude 5 (2Æ): A solution of the crude mixture (1.04 g) of 5 (2Æ) and 6 was evaporated and chromatographed over SiO₂, benzene-AcOEt = 3:2. The first eluate gave an additional amount of (+)-4 (0.12 g, total yield 24.1%), mp 190.5-191.5 °C after recrystallization from AcOEt-hexane. From the second eluate, a mixture (0.2 g) of (+)-4 and 5 (2Æ) was obtained. The third eluate gave a mixture (0.88 g) of 5 (2Æ) and the aldehyde (6) (see below). The starting material ((±)-3, 2.0 g (37.5%)) was recovered from the fourth eluate after recrystallization from AcOEt-hexane.
of (−)-2, mp 151.5–152.5 °C (from AcOEt-hexane). \([\alpha]_D^{20} = -154.11\) (c = 0.23, CHCl₃). The spectral data were identical to those of (+)-2. The oxalate crystallized from Me₂CO had mp 170–172 °C (dec.). \([\alpha]_D^{20} = -90.87\) (c = 0.130, MeOH). Anal. Calcd for C₂₃H₃₀N₄O₂S·C₂H₂O₄·0.33H₂O: C, 57.46; H, 6.30; N, 10.72; S, 6.13. Found: C, 57.64; H, 6.37; N, 10.54; S, 5.94.

Crystal Data for (−)-3 C₂₃H₃₀N₄O₂S, M₀ = 442.65, orthorhombic, P2₁2₁2₁, a = 10.722 (1), b = 23.749 (2), c = 9.104 (1) Å, V = 2318.1 (3) Å³, Dᵣ = 1.268 g/cm³, Z = 4.

X-Ray Analysis — Colorless, plate-like crystals of (−)-3 were obtained from ethanol solution by slow evaporation. Intensity data were measured on an automated diffractometer (Rigaku AFC-5) with graphite-monochromated CuKα radiation. In total, 2272 reflections were measured, of which 1972 were judged significant (|Fₒ| ≥ 2.67σ(Fₒ)). The structure was solved by the direct method using MULTAN 80⁰ and refined by the block-diagonal least-squares with anisotropic temperature factors for all non-hydrogen atoms and with isotropic ones for all hydrogen atoms. The final R value was 0.058. The final atomic parameters, bond angles, and bond distances are listed in Tables I, II, and III, respectively.

Absolute Configuration — The absolute configuration was determined by the use of the anomalous dispersion term in the atomic scattering factor of the sulfur atom (‡+ = 0.319, ‡− = 0.557; International Tables for X-Ray Crystallography).¹⁰ The observed and calculated intensity ratios for some Bijvoet pairs are listed in Table IV. The results in Table IV indicate that the absolute configuration of the molecule is 2S.

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References and Notes

2) Attempts to acylate the carboxamide ((−)-2) with L-NSPCl under various conditions were unsuccessful.