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Synthesis of Optically Active Monothioimides with Chirality due to Sulphur Substitution

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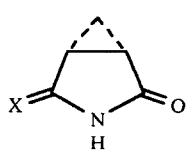
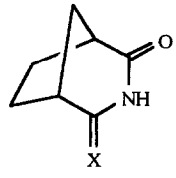
Abstract: Two optically active bicyclic monothioimides were prepared via chiral derivatives of *cis*-1,2-cyclopropanedicarboxylic and *cis*-1,3-cyclopentanedicarboxylic acids and their absolute configurations were assigned.

Thioamides, because of their reactivity have found wide applications as versatile synthetic intermediates in technology, medicine and laboratory practice.[1] The substitution of sulphur for oxygen in the amide group dramatically changes its spectroscopic properties.[1,2]

As a part of our project devoted to studies of the chiroptical spectra in connection with the stereochemistry of cyclic imides[3] and thioimides[4] we became interested in preparation of optically active thioimides with rigid skeletons and known absolute configurations. We designed and describe here the synthesis of the bicyclic monothioimides **1** and **3**, which besides their significance for theoretical and spectroscopic investigations might be potentially useful chiral building blocks. These small molecules owe their chirality to the presence of sulphur. The substitution of this atom for oxygen causes desymmetrization of the parent imides **2** and **4**, both of the C_s symmetry.



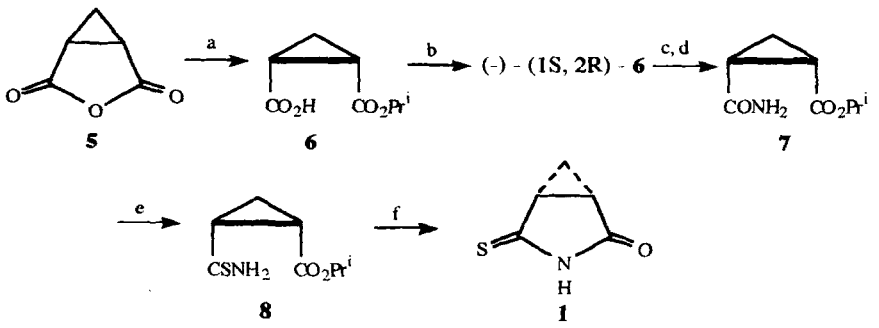
1, X = S
2, X = O



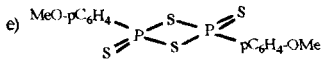
3, X = S
4, X = O

Cis-1,2-cyclopropanedicarboxylic anhydride (**5**), prepared according to the McCoy's procedure,[5] was reacted with PrⁱOH in pyridine to give the monoester **6**. It was resolved to enantiomers with quinine; two crystallizations of the salt from acetone-pentane gave nearly optically pure material. Optically active

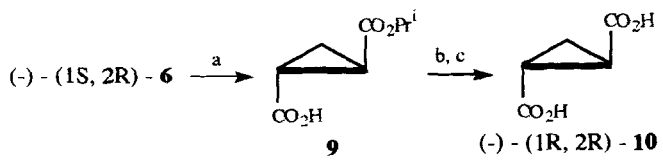
half-esters of *cis*-1,2-cyclopropanedicarboxylic acid represent attractive asymmetric synthons, which were accessible only from enzymatic hydrolysis of corresponding *meso*-diesters.[6] Conversion of the ester (-)-**6**[7] into the amide **7** followed by treatment with Lawesson's reagent[8] afforded the thioamide **8**, which without isolation, upon prolonged heating in C_6H_6, gave the thioimide **1**[9] in 45% overall yield.



5 6 7 8 1

a) Pr^iOH, pyridine, DMAP, 70°C; b) quinine; c) $(COCl)_2$; d) NH_3, C_6H_6;
e)  f) C_6H_6, reflux, 8h

The absolute configuration of (-)-**6** and thus **1** was assigned by conversion to the known *trans*-acid (-)-**10**; $[\alpha]_D^{21}$ -231 (*c* 2 in EtOH); lit.[10] enantiomer $[\alpha]_D^{22}$ +227.9 (*c* 2.34 in EtOH).

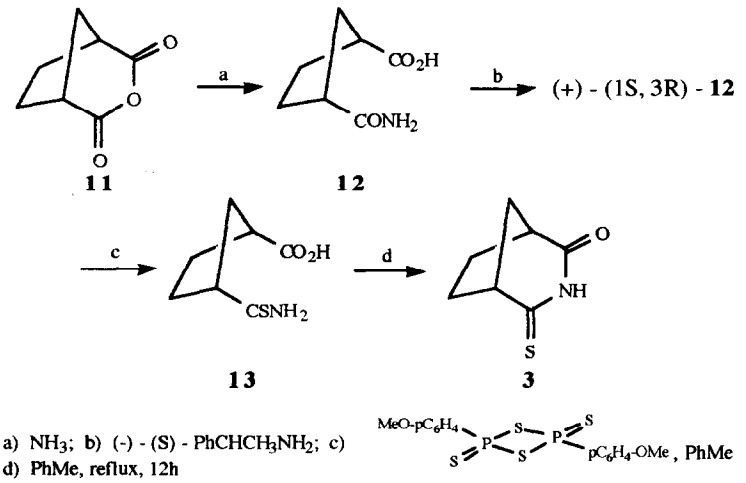


9 (-) - (1R, 2R) - **10**

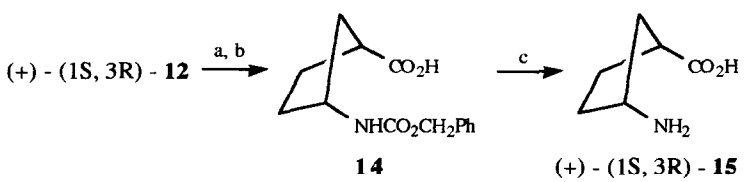
a) Pr^iONa, Pr^iOH, reflux, 6h; b) NaOH; c) HCl

The ammonolysis of *cis*-1,3-cyclopentanedicarboxylic anhydride (**11**)[11] afforded the racemic monoamide **12**, which was resolved to enantiomers with (-)-(S)-1-phenylethylamine (two crystallizations of the salt from EtOH-Et_2O). The enantiomer (+)-**12**[12] treated with Lawesson's reagent in boiling

toluene provided monothioimide **3**[13] (yield 43%) via corresponding thioamide **13**.



The absolute configuration of the amide (+)-**12** and thus **3** was assigned by the Hoffmann's degradation to the known amino acid (+)-**15**[14,15] isolated from the reaction mixture as the N-benzyloxycarbonyl derivative **14** followed by cleavage of the protective group.[16]



The above procedure appears to be a relatively simple and efficient source of optically active *cis*-3-aminocyclopentanecarboxylic acid (**15**) obtained as a degradation product of the antiviral antibiotic amidomycin.[17] This amino acid, being a conformationally restricted analog of of γ-aminobutyric acid (GABA), have a potent inhibitory action on neuronal firing in the mammalian central nervous system.[15]

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References and Notes

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7. (-)-**6**: crystallizing oil (racemate m.p. 48°C); $[\alpha]_D^{22}$ -9.7 (*c* 10 in $CHCl_3$); e.e. > 97%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.64 (br s, 1 H), 5.01 (q, *J* = 6.3 Hz, 1 H), 2.08 (m, 2 H), 1.66 (m, 1 H), 1.34 (m, 1 H), 1.22 (d, *J* = 6.2 Hz, 3 H), 1.21 (d, *J* = 6.2 Hz, 3 H).
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9. **1**: m. p. 91-92°C (toluene); $[\alpha]_{578}^{21}$ + 201; $[\alpha]_{546}^{21}$ + 312 (*c* 1 in C_6H_6); e.e. > 97%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.86 (br s, 1 H), 3.03 (m, 1 H), 2.54 (m, 1 H), 1.67 (m, 1 H), 1.57 (m, 1 H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 209.01 (CS), 176.82 (CO), 32.00, 24.22, 23.45; IR (CCl_4) 3420, 1755, 1425, 1175, 970 cm^{-1}.
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12. (+)-**12**: m.p. 135°C (EtOH-AcOEt) (lit.[11] racemate m.p. 164°C); $[\alpha]_{578}^{21}$ +6.4; $[\alpha]_{546}^{21}$ +7.3 (*c* 3 in EtOH); e.e. > 97%.
13. **3**: m.p. 104-106°C (toluene-hexane); $[\alpha]_{578}^{20}$ -179; $[\alpha]_{546}^{20}$ -242 (*c* 1.4 in C_6H_6); e.e. > 97%; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 9.04 (br s, 1 H), 3.70 (m, 1 H), 3.13 (m, 1 H), 2.25-1.90 (complex m, 5 H), 1.75 (m, 1 H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 214.19 (CS), 174.52 (CO), 52.95, 43.73, 33.89, 30.24, 27.89; IR (CCl_4) 3370, 1730, 1715, 1440, 1125 cm^{-1}.
14. (+)-**15**: m.p. 245-250°C (dec.); $[\alpha]_{578}^{21}$ +7.0; $[\alpha]_{546}^{21}$ +8.0 (*c* 2 in H_2O) {lit.[15] m.p. 240-250°C (dec.); $[\alpha]_{578}^{20}$ +6.5; $[\alpha]_{546}^{20}$ +8.0 (*c* 1 in H_2O)}.
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