Cyclophanes. 14. Synthesis, Structure Assignment, and Conformational Properties of [2.2](2,5)Oxazolo- and Thiazolophanes[1]

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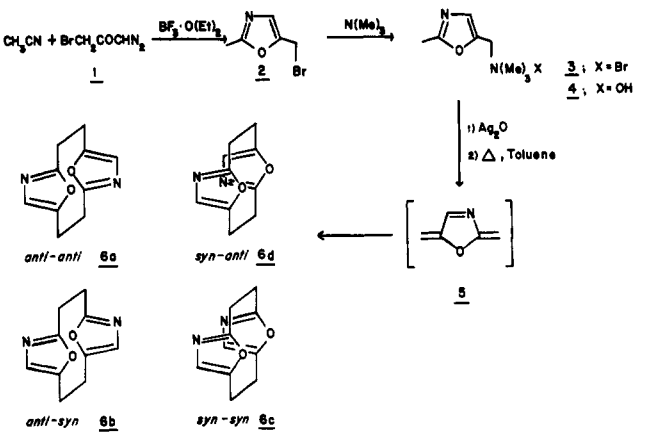
Abstract: The first synthesis of cyclophanes containing aromatic nuclei with two heteroatoms is described. A Hoffman pyrolytic route was used. Two isomeric [2.2](2,5)oxazolophanes (**6a** and **6b**) and two isomeric [2.2](2,5)thiazolophanes (**13a** and **13b**) were isolated. In both cases the isomers were found to have the anti-anti and the anti-syn structure. The assignments were made by spectral analysis and variable-temperature nuclear magnetic resonance spectroscopy in the oxazolophane case and on the basis of NMR spectral comparisons between normal (**13a** and **13b**) and deuterated derivatives (**14a** and **14b**) in the thiazolophane case. While the aromatic nuclei in the thiazolophanes were found to be conformationally rigid on the NMR time scale, those in the oxazolophanes were found to be conformationally mobile with a rotational barrier of 17.8 kcal/mol.

Though [2.2]heterocyclophanes containing one heteroatom in one or both aromatic nuclei have been synthesized and studied,[3] none containing two heteroatoms in a five-membered heterocycle have been reported.[4] Our interest in the synthesis of such cyclophanes has its origin in the fact that the oxazole, thiazole, and imidazole nuclei are a salient feature of a number of biologically active natural products, pharmaceuticals, and agrochemicals.[5] In addition, because of the 1,3 orientation of the heteroatoms in these nuclei, and subject to the conformational rigidity of the heteroaromatic nuclei, the potential exists for the introduction of chirality within a cyclophane macrocycle without the use of functional group vestiges.[6] Finally, the conformational behavior of these heteronuclei within the cyclophane is of interest for comparison with known heterocyclophanes.[7] In this paper we describe the synthesis, characterization, and conformational properties of the anti-anti and anti-syn isomers of [2.2](2,5)oxazolophane (**6a** and **6b**) and [2.2](2,5)thiazolophane (**13a** and **13b**).

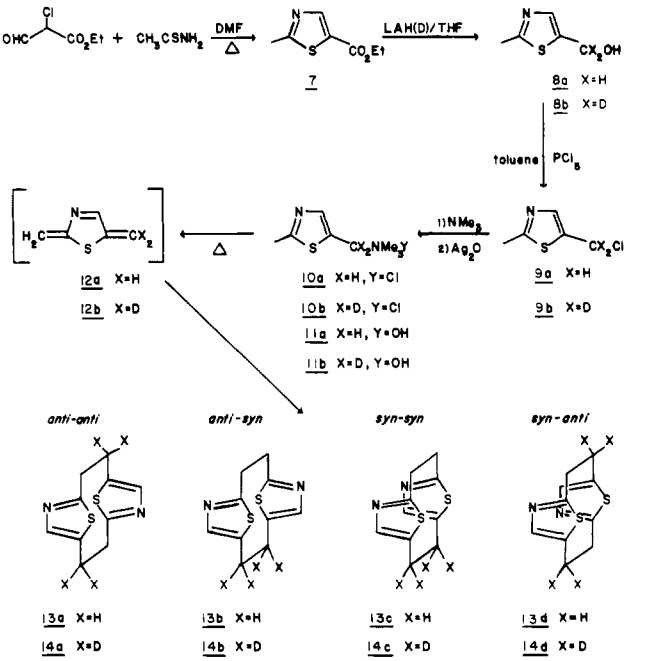
Synthesis

The syntheses utilize the known Hoffman pyrolytic route[3a] and are described for the oxazolophanes in Scheme I and the thiazolophanes in Scheme II. 2-Methyl-5-(bromomethyl)oxazole (**2**) was prepared in 30% yield by a 1,3-dipolar cycloaddition reaction[8] of acetonitrile on bromomethyl diazoketone (**1**).[9,10] Quaternization of **2** with trimethylamine afforded **3** in quantitative yield. Hydroxide **4**, prepared by the reaction of **3** with silver oxide, was then pyrolyzed in toluene[11] by high dilution techniques. After

Scheme I



Scheme II



(1) This paper is part 14 in a series. For the previous paper, see: Corson, M.; Foxman, B.; Keehn, P. M. *Tetrahedron* **1978**, *34*, 1641.

(2) Dreyfus Teacher-Scholar, 1979–1984.

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(4) A cyclophane containg two heteratoms in a six-membered ring has been recently reported. Staab, H. A.; Apple, W. K. *Liebigs Ann. Chem.* **1981**, 1065.

(5) (a) Wiley, R. H. *Chem. Rev.* **1945**, *37*, 401. (b) Turchi, I. J.; Dewar, M. J. S. *Ibid.* **1975**, *75*, 389. (c) Lakhan, R.; Ternai, B. *Adv. Heterocycl. Chem.* **1974**, *17*, 99. (d) Metzger, J. V. *Chem. Heterocycl. Compd.* **1979**, *34*, pt. 1–3.

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(7) (a) Gault, I.; Price, B. J.; Sutherland, I. O. *J. Chem. Soc. Chem. Commun.* **1967**, 540. (b) Whiteside, G. M.; Pawson, B. A.; Cope, A. C. *J. Am. Chem. Soc.* **1968**, *90*, 639. (c) Mizogami, S.; Osaka, N.; Otsubo, T.; Sakata, Y.; Misumi, s. *Tetrahedron Lett.* **1974**, 799. (d) Rosenfeld, S. M.; Keehn, P. M. *Ibid.* **1973**, 4021. (e) Sherrod, S. A.; daCosta, R. I.; Barnes, R. A.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1565.

(8) Ibata, T.; Sato, R. *Bull. Chem. Soc. Jpn.* **1979**, *3597*.

(9) Compound **1** was prepared by reacting bormoacetyl chloride with diazomethane (90% yield) by a modification of the procedure reported by Arndt: Arndt, F. *Ber.* **1928**, *61*, 1122.

(10) 2-(Chloromethyl)-5-methyloxazole was also prepared by treating chloroacetonitrile with diazoacetone. Pyrolysis of the corresponding quaternary ammonium salt gave lower yields of the [2.2](2,5)oxazolophanes.

(11) Phenothiazine was used as a polymerization inhibitor.

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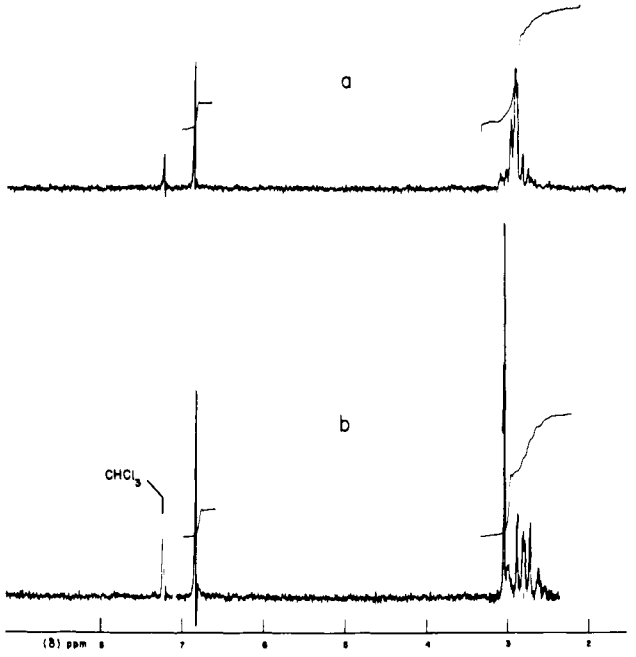

Figure 1. Proton NMR spectra of **6a** (a) and **6b** (b).

azeotropic removal of water and evaporation of the toluene, the crude mixture was chromatographed on silica gel, and the middle fractions were subjected to high-pressure liquid chromatography. This gave two crystalline solids in equal amounts, with a combined yield from **3** of 10.3%. The low-melting solid (mp 128–130 °C) was designated B and the high-melting one (mp 191–192 °C) A. Both A and B were identified as isomeric oxazolophanes by elemental analysis and fragmentation pattern in their mass spectra (*m/e* 190, 95).[3g]

The known precursor, 2-methyl-5-(chloromethyl)thiazole (**9a**) was prepared in 33.3% yield in three steps by condensing ethyl α-chloro-α-formylacetate with thioacetamide in DMF at 90–100 °C for 4 h and treating the resulting ester **7** successively with $LiAlH_4$/THF and PCl_5/toluene.[12] Quaternization of **9a** with trimethylamine in dry DMF afforded salt **10a** in quantitative yield. The chloride salt was converted to the hydroxide salt **11a** with Ag_2O, and the latter was pyrolyzed by high dilution methods in refluxing toluene with azeotropic removal of water.[11] After completion of the reaction, the solvent was removed and the crude reaction mixture was chromatographed on silica gel. The middle fractions were then subjected to HPLC. Two crystalline compounds were isolated in equal quantities in a combined yield of 33.3% from salt **10a**. The low-melting compound (mp 222–225 °C dec) was designated D and the high-melting compound (mp 240–245 °C dec) C. Combustion analysis and mass spectral data (*m/e* 222, 111) indicated that both compounds were isomeric [2.2](2,5)thiazolophanes.

Structure Assignments

By analogy with similar pyrolytic routes[3a-c] we believe that dimethides **5** and **12a** are the intermediates formed upon pyrolysis of **4** and **11a**, respectively. Dimerization, however, can occur in both symmetrical and unsymmetrical modes,[3h] affording isomers **6a–d** and **13a–d**.[13] These are designated by anti and syn nomenclature to describe both the orientation of the rings (first designation) and the orientation of the nitrogen atoms (second designation) with respect to one another. Thus, structures **6a** and **13a** have both rings and both nitrogen atoms facing away from one another, and these compounds are designated anti-anti. As in similar dimethide dimerizations the syn orientation of the rings in the transition state leading to **6c**, **6d**, **13c**, and **13d** would be energetically unfavored due to increased π–π repulsion[14] and would thus tend to minimize the formation of these isomers.

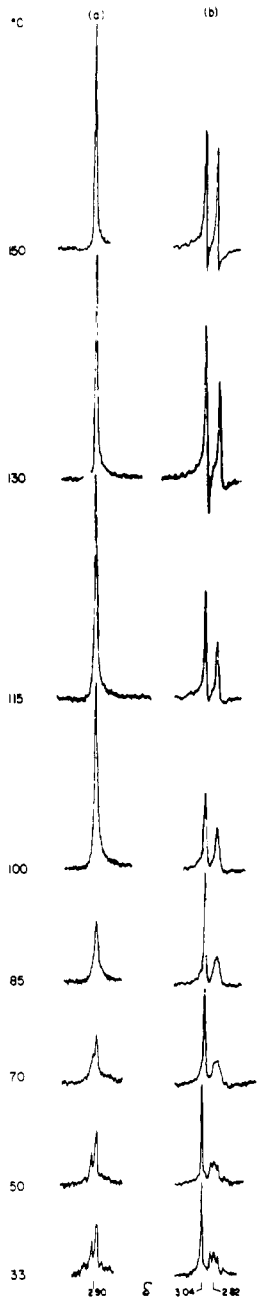

Figure 2. Variable-temperature ^1H NMR spectra of [2.2](2,5)oxazolophanes **6a** (a) and **6b** (b).

The infrared and ultraviolet spectra of the isolated oxazolophanes and thiazolophanes were of little value in structure assignment, but careful analysis of their NMR spectra (Figures 1–3) allowed tentative assignments to be made (A to **6a**, B to **6b**, C to **13a**, and D to **13b**).

The syn forms, **6c**, **6d**, **13c**, and **13d** (syn with respect to the rings), could be ruled out on the bais of the following considerations. The aromatic protons in A and B (Figure 1) resonate as sharp singlets at δ 6.85 and 6.82, respectively. These values are about 0.3 ppm downfield compared to the analogous proton in 2,5-dimethyloxazole.[15] The aromatic photons in C and D resonate

(12) (a) Takata, Y.; Yamamoto, K.; Takatei, Y. *J. Pharm. Soc. Jpn* **1953**, *73*, 126. (b) Zubarovskii, V. M.; Moskaleva, R. N. *Zh. Obshch. Khim.* **1962**, *32*, 570.

(13) The isomer problem is further complicated because structures **6b**, **6d**, **13b**, and **13d** are chiral. This problem vanishes only in the oxazolophane system because of the conformational mobility of the oxazole rings.

(14) Shana, C. B.; Rosenfeld, S. M.; Keehn, P. M. *Tetrahedron* **1977**, 1081 and the references cited therein.

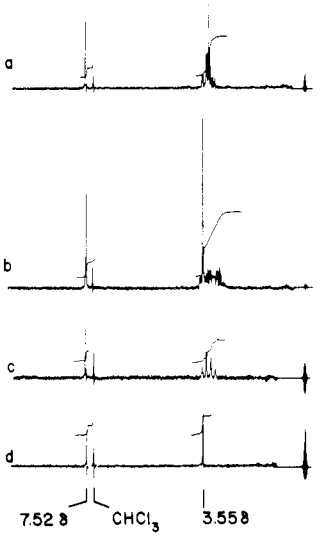

Figure 3. Proton NMR spectra of **13a** (a), **13b** (b), **14** (c), and **14b** (d).

at δ 7.55 and 7.52, respectively. These values are also downfield compared with the analogous proton in 5-ethylthiazole (δ 7.39)[16a] and 2,5-dimethylthiazole (δ 7.03).[16b] A syn orientation of the rings in the isolated compounds should give rise to an upfield shift of these protons relative to the model compounds due to the anisotropic shielding effects of the proximate aromatic rings. The syn isomers are therefore ruled out.

In the aliphatic portion of the NMR spectra of A and B, compound B (**6b**) (Figure 1b) exhibits two distinct absorptions. A four-proton singlet is observed at δ 3.04 and a symmetrical four-proton multiplet appears at δ 2.80. The occurrence of a singlet for the bridge protons in a cyclophane in which the aromatic ring is unsymmetrical is somewhat surprising but could be due to accidental shift coincidence of all four protons on the bridging carbons bound to the 2-position of the oxazole ring.[17] This is likely only if compound B has the syn orientation of the nitrogen atoms as in **6b**. (The assignment of the lower field aliphatic absorptions to the protons on the bridging carbons adjacent to the 2-position of the oxazole ring is also substantiated by the fact that the methyl protons at the 2-position in 2,5-dimethyloxazole absorb at a lower field than those at the 5-position.[15]) Compound A on the other hand exhibits an eight-proton multiplet for the bridging protons centered at δ 2.88, indicating the anti-anti assignment **6a** for A (see Figure 1a).

In order to substantiate our conclusions about the above assignments, we carried out a variable-temperature NMR study on **6a** and **6b**. We reasoned that should the oxazole ring in **6b** undergo ring flipping, then the four protons (m, δ 2.80) of the bridge connecting the C-5 positions of the two oxazole rings would become equivalent and give rise to a singlet. Since the flipping process exchanges all the protons on a given bridge but does not exchange the protons on the C-5 linking bridge with those on the C-2 linking bridge, the high-temperature NMR spectrum for **6b** should consist of two singlets for the aliphatic protons. On the other hand, oxazole ring flipping in **6a** averages the protons of the two bridges but does not average all the protons on a given bridge. Thus, one would not expect to observe two singlets for the protons on the aliphatic bridge **6a** under conditions of fast chemical exchange.

The variable-temperture NMR spectra for **6a** and **6b** are given in Figure 2. For compound B (Figure 2b), as the temperature is raised the aromatic singlet at δ 6.82 and the aliphatic singlet at δ 3.04 remain unchanged. The multiplet at δ 2.80, however, broadens and coalesces at about 80 °C. Continued heating to 150 °C gives rise to a singlet at δ 2.82. Thus, the high-temperature NMR spectrum of B exhibits two singlets for the bridging protons (δ 2.82 and 3.04), and this compound is unequivocally assigned structure **6b**.

For compound A (Figure 2a), the aromatic absorption at δ 6.85 maintains its singlet character even at high temperatures. However, the multiplet at δ 2.88 due to the bridge protons broadens as the temperature is raised. Coalescence takes place at about 80 °C, and continued heating to 150 °C gives rise to a singlet at δ 2.92.[18] With the above data on the conformational properties of the oxazolophanes, the four-isomer problem is reduced to two and A and B are unequivocally assigned structures **6a** and **6b**, respectively.

Assignment, in the thiazolophane series, of the high-melting isomer to **13a** and the low-melting isomer to **13b** is also based on the position and multiplicity of the absorption of the hydrogen atoms on the ethylene bridges (Figure 3a,b). Thus, the high-melting isomer (C) exhibits an 8-H multiplet at δ 3.33 while the low-melting isomer (D) exhibits a 4-H multiplet at δ 3.23 and a 4-H singlet at δ 3.55.[19] Again, the singlet in isomer D could be accounted for if all the protons on a given bridge are accidentally coincident in shift. Such a situation is likely to arise for structure **13b** in which the two thiazole rings are linked to one another through one C^5–CH_2–CH_2–C^5 and one C^2–CH_2–CH_2–C^2 linkage. Since two C^5–CH_2–CH_2–C^2 linkages are found in **13a**, the two bridges are identical, each should give rise to the same absorption, and a multiplet, not a singlet, is to be expected for **13a**, as is observed.[20]

Unequivocal assignments for the thiazolophanes were made after synthesis of the tetradeuterated derivatives **14a** and **14b**, as shown in Scheme II. Reduction of **7** with $LiAlD_4$, followed by chlorination, quaternization, ion exchange, pyrolysis, and chromatographic separation, as used for the undeuterated series, afforded 29% yield of isomers **14a** (mp 239–244 °C) and **14b** (mp 222–225 °C) in the pyrolysis step. A correct mass spectrum was obtained for the deuterated alcohol **8b** ($C_5H_5D_2ONS$, *m/e* 131), and those for **14a** and **14b** indicated incorporation of four deuterium atoms, two in each half of the molecule (*m/e* 226 and 113).

The ^1H NMR spectrum of the high-melting isomer is given in Figure 3c, and that of the low-melting isomer is shown in Figure 3d. As is evident by virtue of the synthetic route, deuterium can only be present at the carbons bound to the C-5 positions of the thiazole ring, and thus verification of the chemical shift position and multiplicity of the bridge protons in **13a** and **13b** can be made. Since the two protons on the bridge carbons adjacent to the C-2 carbon atoms of the thiazole rings in **14a** cannot be equivalent, they are expected to give rise to an AB quartet centered at the same chemical shift position as those protons found in the undeuterated isomer **13a**. This is indeed observed. On the other hand, the two protons adjacent to the C-2 carbon atoms in the thiazole rings in **14b** should, by our previous assignment involving equivalency in **13b**, give rise to a singlet at δ 3.55. Again, this is observed, and the relationship of **14b** to **13b** and of **14a** to **13a**

(15) $CDCl_3$: δ 2.25 (s, 3 H), 2.37 (s, 3 H), 6.53 (s, 1 H). These values are slightly upfield in CCl_4. See: Brown, D. J.; Ghosh, P. B. *J. Chem. Soc. B* **1969**, 270. CCl_4: δ 2.22 (s, 3 H), 2.29 (s, 3 H), 6.43 (s, 1 H).

(16) (a) Dou, H. J. M.; Metzger, *J. Bull. Soc. Chim. Fr.* **1966**, 2395. (b) Spillance, W. J.; Dou, H. J. M.; Metzer, J. *Tetrahedron Lett.* **1976**, 2269.

(17) A similar NMR absorption pattern for the bridge protons (a 4 H singlet and a 4 H multiplet) was observed for [2.2](2,5)pyridinophane. See: Bruhin, J.; Jenny, W. *Chemia* **1971**, *25*, 288. In the thiazole series the anti-syn isomer **13b** shows a similar pattern for the bridge protons and also gives a singlet for the protons bound to the bridge carbons linking the C-2 positions of the thiazole rings (see Figure 3b).

(18) Theoretically one would expect to see an A_2B_2 (AA'BB') pattern for the protons on the aliphatic bridges in **6a**. However, if the chemical shift difference between the A and B protons is small, as can be inferred from the position of corresponding protons in **6b** at high temperature (δ 3.04 and δ 2.82), then a multiplicity wherein the central lines are heavily weighted and observed as a single absorption is reasonable. If this is so, then the position of this line in **6a** should be centered between the low-field (δ 3.04) and the high-field (δ 2.82) absorption for the corresponding protons in **6b**. This is the case for **6a**. At high temperature the bridge protons absorb at δ 2.92.

(19) The lower field absorption is assigned to the protons on the bridging carbon atoms adjacent to the C-2 position of the thiazole ring while the higher field absorption is assigned to the protons on the carbon atoms adjacent to the C-5 position of the thiazole ring. This assignment is based on the different chemical shifts of the two methyl group protons in 2,5-dimethylthiazole.[16b] The C-2 methyl protons appear at a lower field than the C-5 methyl protons.

(20) An AA'BB' multiplet is expected.

is unambiguous. The above conclusions are also corrobrated by the structural assignments made above with variable-temperature nuclear magnetic resonance spectroscopy of the *anti-anti-* and *anti-syn*-[2.2](2,5)oxazolophanes (**6a**, and **6b**). As in **13b**, **6b** gives rise to two absorptions for the protons on the bridging carbons, one that is observed as a multiplet and the other (assigned to bridge carbon protons linking the C-2 positions of the oxazole rings) that is observed as a singlet.

Conformational Behavior

The conformational behavior of **6a** and **6b** is consistent with the known behavior of [2.2](2,5)furanophane whose energy barrier for ring flipping is 16.8 kcal/mol.[7a] On the basis of coalescence temperatures of 80 °C, approximate exchange rates (K) of 66 s^{-1} were calculated, giving rise to an Arrhenius energy of activation of ca. 17.8 kcal/mol for **6a** and **6b**.[21] Apparently the nitrogen atom of the oxazole ring in these cyclophanes has a minimal influence on the ring-flipping process, since the energy barriers are similar to that of [2.2](2,5)furanophane.

Variable-temperature NMR experiments were also carried out on both thiazolophanes **13a** and **13b**, with no coalescence of the bridge protons occurring up to temperatures of 150 °C. This is to be expected, however, since the [2.2](2,5)thiazolophanes are related to the [2.2](2,5)thiophenophanes, whose rings are also conformationally rigid on the NMR time scale.[7a]

The synthesis of a number of mixed thiazolophanes incorporating the benzene, naphthalene, thiophene, and furan nuclei, as well as the corresponding thiazolium salts of the above will be the subject of a forthcoming paper.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus. Boiling points and melting points are uncorrected. Ultraviolet and visible spectra were recorded on a Perkin-Elmer Model 323 spectrophotometer. Infrared spectra were recorded on Perkin-Elmer Models 567 and 683 grating spectrophotometers. Mass spectra were obtained on a A.E.I. Model MS-12 mass spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian Model EM-390 spectrometer. Chemical shifts are reported in δ units, using tetramethylsilane as an internal standard. Variable-temperature spectra were recorded on a Perkin-Elmer Model R-32 spectrometer, using hexachloro-1,3-butadiene as the solvent and hexamethyldisiloxane as an internal standard. THF and ether were distilled from sodium benzophenone ketyl. Microanalysis were performed by Galbraith Laboratories, Knoxville, TN.

Bromomethyl Diazomethyl Ketone (1). An ethereal solution (250 mL) of diazomethane (~4.46 g, ~106 mmol), generated from 32 g of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide by standard procedure,[22] was cooled to −20 °C, and freshly distilled bromoacetyl bromide (7.2 g, 35.66 mmol) in dry ether (20 mL) was added with stirring over 30 min. The reaction was allowed to warm to ambient temperature over a period of 5 h. Ether was removed by careful distillation using a bath temperature of 50 °C until the volume was reduced to about 40 mL. After the solution was dried over $MgSO_4$, the remaining ether was removed under vacuum (water aspirator). The residual oil was distilled (bp 55–60 °C (5mm)) and afforded 6.7 g of **1**; NMR ($CDCl_3$) δ 3.83 (s, 2 H), 5.72 (s, 1 H). NMR analysis also indicated 15% of an unidentified impurity. This material was used as such without further purification.

2-Methyl-5-(bromomethyl)oxazole (2). Freshly distilled boron trifluoride etherate (5 mL, 40.65 mmol) was added via syringe, with stirring, under nitrogen and at room temperature to dry acetonitrile (10 mL, distilled from calcium hydride). After 2–3 min the reaction was cooled to −25 °C and the aforementioned diazo ketone, **1** (6.62 g), in dry acetonitrile (10 mL) was added over a period of 10 min. A vigorous evolution of nitrogen was observed. The reaction was removed from the cooling bath and allowed to stand at room temperature for 30 min. After this time, it was poured into a mixture of ice (100 g) and ether (100 mL) and basified by adding solid sodium bicarbonate. The ether layer was separated and the aqueous layer extracted with ether (2 × 50 mL). The combined ether extract was washed with brine, dried over Na_2SO_4, and concentrated to give a light red oil. Purification was effected by chromatography on silica gel (eluent, 2% methanol in methylene chloride) to furnish **2** (2.05 g, 29.4%) as a light yellow oil. Attempted purification by vacuum distillation led to extensive decomposition: IR (CH_2Cl_2) 3105, 2960, 1740, 1605, 1570, 1430, 1385, 1337, 1276, 1220, 1015, 970, 845 cm^{-1}; NMR ($CDCl_3$) δ 2.46 (s, 3 H), 4.42 (s, 2 H), 6.90 (s, 1 H); MS; (m/e) 175.

Trimethyl(2-methyl-5-oxazolyl)ammonium Bromide (3). Through a stirred solution of bromide **2** (1.42 g, 8.07 mmol) in dry dimethylformamide (5 mL) was bubbled trimethylamine. After 20 min a crystalline solid began to separate out. Amine was passed through the solution for an additional 30 min. After this time the reaction mixture was allowed to settle for 3 h. Dry ether was added with stirring to complete the precipitation of the salt. The supernatant clear liquid was removed by decantation and the solid washed several times with dry ether under nitrogen. Vacuum drying for several hours afforded crystalline but hygroscopic salt **3** (1.86 g, 98.5%): mp 199–204 °C dec; NMR (Me_2SO-d_6) δ 2.45 (s, 3 H), 3.13 (s, 9 H), 4.76 (s, 2 H), 7.36 (s, 1 H).

***anti-anti-* and *anti-syn*-[2.2](2,5)Oxazolophane (6a and 6b).** Bromide salt **3** (1.82 g, 7.74 mmol) was dissolved in distilled water (25 mL) and stirred with freshly prepared silver oxide (1.80 g, 14.53 mmol). The reaction was kept in a nitrogen atmosphere and protected from light for 14 h. The reaction mixture was then filtered through Celite and the insoluble residue washed with water (10 mL). The filtrates containing hydroxide **4** was diluted with water to a volume of 75 mL and added dropwise over a period of 5 h to a stirred solution of refluxing toluene (300 mL) containing phenothiazine (50 mg). The water was continuously removed by azeotropic distillation. After the addition was over, the reaction was refluxed for 30 min more and then allowed to cool somewhat. Insoluble polymeric material was removed by filtration. The filtrate was concentrated and afforded a crude semisolid (650 mg). Initial purification was done by chromatography on silica gel (30 g, 5% methanol in chloroform as eluant) and afforded a mixture of **6a** and **6b** (~1:1 by HPLC analysis). These compounds were separated by using preparative high-pressure liquid chromatography (Waters Prep LC; normal phase Partisil M9 10/50 column; 5% methanol in chloroform as solvent) to furnish **6a** (39 mg, 5.3%) and **6b** (37 mg, 5.0%). An analytical sample of **6a** was prepared by crystallization from ethyl acetate: mp 191–192 °C; UV λ_{max} (95% EtOH) (log ϵ) 243 (3.20), 215 (4.08), 228 (sh) nm; IR (KBr) 3100, 2930, 1589, 1550, 1425, 1350, 1335, 1165, 1110, 1084, 980, 970, 884, 835 cm^{-1}; NMR ($CDCl_3$) δ 2.88 (m, 8 H), 6.85 (s, 2 H); MS, m/e 190 (m+), 95. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.26; N, 14.73. Found: C, 63.09; H, 5.34; N, 14.54.

An analytical sample of **6b** was obtained by sublimation (110–125 °C (0.2 mm)): mp 128–130 °C; UV λ_{max} (95% EtOH) (log ϵ) 243 (3.29), 215 (4.21), 228 (sh) nm; IR (KBr) 3100, 2930, 1589, 1550, 1425, 1350, 1335, 1165, 1110, 1084, 980, 970, 884, 835 cm^{-1}; NMR ($CDCl_3$) δ 2.80 (m, 4 H), 3.04 (s, 4 H), 6.82 (s, 2 H); MS; m/e 190 (m^+), 95. Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.26; N, 14.73. Found C, 63.0; H, 5.34; N, 14.52).

2-Methyl-5-(carbethoxy)thiazole (7).[12a] This compound was prepared by modifying the literature method as follows: Ethyl α-chloro-α-formylacetate[12a] (29.5 g, 0.214 mol), thioacetamide (20.5 g, 0.35 mol), and dry dimethylformamide (150 mL) were stirred at room temperature until a clear solution resulted. The reaction flask was then immersed in an oil bath maintained at 85 °C. After a short induction period, a mildly exothermic reaction was noted. The reaction was removed from the oil bath and allowed to cool somewhat. It was then heated at 90–100 °C for 4 h. After this time, the reaction was cooled in ice and 400 mL of cold water was added. The reaction was basified by adding solid sodium bicarbonate until pH 8 and extracted with ether (3 × 250 mL). The combined ether extract was washed with water and brine and dried over Na_2SO_4. After concentration, the residual oil was vacuum distilled (bp 90–105 °C (12 mm)) and afforded a light yellow oil (23.5 g, 64%): IR (neat film) 2967, 1715, 1520, 1365, 1300, 1175, 1090, 1010, 965, 860 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7 Hz), 2.65 (s, 3 H), 4.28 (q 2H, J = 7 Hz), 8.15 (s, 1 H).

2-Methyl-5-(hydroxymethyl)thiazole (8a).[12b] This compound was prepared by adaptation of the literature procedure as follows: To a slurry of lithium aluminum hydride (2.5 g, 65.8 mmol) in dry THF (500 mL), was added dropwise with stirring over a period of 1 h ester **7** (11.7 g, 58.4 mmol) dissolved in THF (50 mL). After the solution was stirred for 24 h, the reaction was cooled in an ice–salt bath and hydrolyzed by successive addition, with stirring, of water (2.5 mL), 15% sodium hydroxide (2.5 mL), and water (7.5 mL). The precipitated hydroxides were allowed to settle for 1 h. This was removed by filtration, and the filtered cake was washed thoroughly with THF and finally with chloroform. The total filtrate was dried over magnesium sulfate and concentrated to give a brown oil. Distillation under reduced pressure (bp 95–110 °C (10 mm)) furnished **8a** as light yellow pungent-smelling oil (6.75 g, 76.5%): IR (neat film) 3370, 2930, 1530, 1465, 1378, 1160, 1010, 853 cm^{-1}; NMR

(21) Calculations based on the equations $K = \pi\Delta\nu/(2)^{1/2}$ and $G^* = 2.303RT_c(10.319 - \log K + \log T_c)$. See Akabori, S.; Hayashi, S.; Nawa, M.; Shiomi, K. *Tetrahedron Lett.* **1969**, 3737.

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($CDCl_3$) δ 2.61 (s, 3 H), 4.63 (bs, 1 H), 4.73 (s, 2 H), 7.33 (s, 1 H); MS, m/e 129 (m^+).

2-Methyl-5-(chloromethyl)thiazole (9a).[12b] This compound was prepared according to the literature procedure. Starting with 1.8 g (13.95 mmol) of **8a**, we obtained 1.62 g (78.7%) of **9a** as a colorless solid on sublimation: mp 43–45 °C; IR (CH_2Cl_2) 2965, 1528, 1462, 1160, 965, 860 cm^{-1}; NMR ($CDCl_3$) δ 2.70 (s, 3 H), 4.75 (s, 2 H), 7.55 (s, 1 H).

Trimethyl(2-methyl-5-thiazolyl)ammonium Chloride (10a). This was prepared as described for **3**. Thus chloride **9a** (1.2 g, 8.13 mmol) afforded, after drying in vacuo, 1.5 g (89.3%) of **10a** as a crystalline hygroscopic solid: mp 176–183 °C dec; NMR (Me_2SO-d_6) δ 2.70 (s, 3 H), 3.46 (s, 9 H), 5.50 (s, 2 H), 8.05 (s, 1 H).

***anti-anti-* and *anti-syn*-[2.2](2,5)Thiazolophane (13a and 13b).** The chloride salt **10a** (1.35 g, 6.54 mmol) was converted with Ag_2O (1.1 g, 8.88 mmol) to the corresponding hydroxide **11a** and pyrolyzed as described for **6a** and **6b**. After removal of the solvent, the crude residue (435 mg) was chromatographed on silica gel (20 g). Elution with 10% methanol in $CHCl_3$ afforded a solid, which was found to be a mixture (1:1) of **13a** and **13b** by HPLC analysis. The two compounds were separated by preparative high-pressure liquid chromatography (Waters Prep LC, reverse phase, Partisil M9 10/50 ODS-3 column, acetonitrile solvent system), which afforded **13a** (123 mg, 17%) and **13b** (118 mg, 16.3%). An analytical sample of **13a**, was obtained by crystallization from hexane–chloroform: mp 240–245 °C dec; UV λ_{max} (95% EtOH) (log ϵ) 275 (3.84), 243.5 (3.95) nm; IR (KBr) 3050, 2960, 1500, 1420, 1270, 1110, 1090, 1076, 975, 842 cm^{-1}; NMR ($CDCl_3$) δ 3.33 (m, 8 H), 7.55 (s, 2 H); MS, m/e 222 (m^+), 111. Anal. Calcd for $C_{10}H_{10}N_2S_2$: C, 54.05; H, 4.50; N, 12.52; S, 28.82. Found: C, 53.89; H, 4.64; N, 12.45; S, 29.03.

An analytical sample of **13b** was prepared by crystallization from ethyl acetate: mp 222–225 °C dec; λ_{max} (95% EtOH) (log ϵ) 263.4 (3.97), 230 (3.82) nm; IR (KBr) 3050, 2910, 1590, 1500, 1430, 1285, 1110, 1160, 853, 825 cm^{-1}; NMR ($CDCl_3$) δ 3.23 (m, 4 H) 3.55 (s, 4 H), 7.52 (s, 2 H); MS m/e 222 (m^+), 111.

2-Methyl-5-(hydroxymethyl-d_2)thiazole (8b). Ester **7** (4.1 g, 23.97 mmol) was reduced with lithium aluminum deuteride[23] (1.0 g, 23.81 mmol) in dry tetrahydrofuran as described for the preparation of **8a**. After Kugelrohr distillation (bp 85–95 °C (2mm)) carbinol **8b** was obtained (2.4 g, 76.5%) as a light yellow oil: IR (CH_2Cl_2) 3595, 3260, 2914, 1535, 1460, 1300, 1180, 1162, 1086, 1047, 960, 868, 820 cm^{-1}; NMR ($CDCl_3$) δ 2.64 (s, 3 H), 3.83 (bs, 1 H), 7.35 (s, 1 H); MS; m/e 131 (m^+).

2-Methyl-5-(chloromethyl-d_2)thiazole (9b). Carbinol **8b** (2.3 g, 17.55 mmol) was converted to the corresponding deuterated chloro derivative **9b** as described.[12b] A colorless oil (2.47 g, 93%, bp 85–95 °C (10 mm)) was obtained. The oil solidified on standing for a day: mp 43–45 °C; IR (CH_2Cl_2) 2985, 1530, 1460, 1402, 1375, 1182, 1165, 1052, 964, 870 cm^{-1}; NMR ($CDCl_3$) δ 2.64 (s, 3 H), 7.51 (s, 1 H).

Trimethyl(2-(methyl-d_2)-5-thiazolyl)ammonium Chloride (10b). This was prepared as described for **3**. Thus, starting with 2.25 g (15.05 mmol) of chloride **9b**, we obtained 2.7 g (86%) of the crystalline hygroscopic salt **10b** mp 181–184 °C dec; NMR (M_2SO-d_6) δ 2.73 (s, 3 H), 3.40 (s, 9 H), 7.90 (s, 1 H).

***anti-anti-* and *anti-syn*-[2.2](2,5)Thiazolophane-d_4 (14a and 14b).** Chloride **10b** (2.3 g, 11.03 mmol) was treated with Ag_2O (2.2 g, 17.76 mmol) to generate the corresponding hydroxide **11b**, which was pyrolyzed as detailed for **6a** and **6b**. Purification of the crude reaction mixture was effected as described for **13a** and **13b** and afforded **14a** (193 mg, 15.5%) and **14b** (164 mg, 13.3%). **13a**: mp 239–244 °C dec (hexane–chloroform); IR (KBr) 2930, 1500, 1428, 1285, 1215, 1155, 994, 955, 840, 742, 719 cm^{-1}; NMR ($CDCl_3$) δ 3.33 (AB, q, 4 H, J = 15 Hz), 7.55 (s, 2 H); MS; m/e 226 (m^+), 113. **14b**: mp 222–225 °C dec (ethyl acetate); IR (KBr) 2925, 1500, 1430, 1315, 1270, 1145, 1108, 1062, 880, 847, 750, 715 cm^{-1}; NMR ($CDCl_3$) δ 3.55 (s, 4 H), 7.52 (s, 2 H); MS, m/e 226 (m^+), 113.

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Crystal Structure of *cyclo*-(Gly-L-Pro-L-Pro-Gly-L-Pro-L-Pro) Trihydrate. Unusual Conformational Characteristics of a Cyclic Hexapeptide

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Abstract: The crystal structure of *cyclo*-(Gly-L-Pro-L-Pro-Gly-L-Pro-L-Pro) trihydrate, $C_{24}H_{34}O_6N_6 \cdot 3H_2O$, has been determined from single-crystal X-ray diffraction data. The phase problem was solved by direct methods. The space group is $P2_12_12_1$ with the dimensions a = 9.237 (4) Å, b = 13.972 (3) Å, c = 20.851 (3) Å, and Z = 4. The synthetic hexapeptide contains one transannular intramolecular C=O···NH hydrogen bond. In combination with three molecules of water, a coherent system of hydrogen bonds is formed in which also an intermolecular bifurcated hydrogen bond is present. Thus in the lattice parallel to the b axis, linear molecular chains are formed. The peptide backbone contains one cis Gly–Pro and one cis Pro–Pro linkage in consecutive positions. The most striking feature of the asymmetric conformation is, however, the occurrence of a hydrogen-bonded type I β-turn encompassing two trans-configured proline residues in the other half of the molecule. Concerning these linkages, the conformation of the cyclic hexapeptide in the present crystal differs from that in its Mg^{2+} complex.

As a part of systematic investigations into the biological activity, conformation, and complexing ability of antamanid analogues, Wieland and Hollósi have synthesized a series of cyclic peptides consisting of glycine and two pairs of L-proline only.[2] One of these model peptides, *cyclo*-(Gly-Pro-Pro-Gly-Pro-Pro) (thereafter GPPGPP), proved to be of particular interest for its CD spectrum does not show solvent dependence. The high selectivity of the cyclic hexapeptide for alkaline earth ions over alkali metal ions

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