Notes

Resolution of Diastereomeric Sulfoximines

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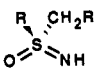
The sulfoximine functional group **1** has unexploited potential for useful incorporation into enzyme inhibitors. As shown previously, it successfully mimics the tetrahedral adduct **2** occurring as an intermediate in carboxamide addition reactions, notably with a metalloprotease.[1] Furthermore, the sulfoximine group represents a potential stereogenic center, in that the sulfur atom may bear four different substituents in a configurationally stable array. The resolution of sulfoximine-containing diastereomers is difficult; for example, only a partial preparative separation of the two isomers of the notoriously toxic sulfoximine from L-methionine could be achieved chromatographically.[2] This paper describes a tactic which has provided satisfactory diastereomeric resolution in such a case. Configuration of the resulting isomers is established crystallographically.



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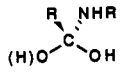
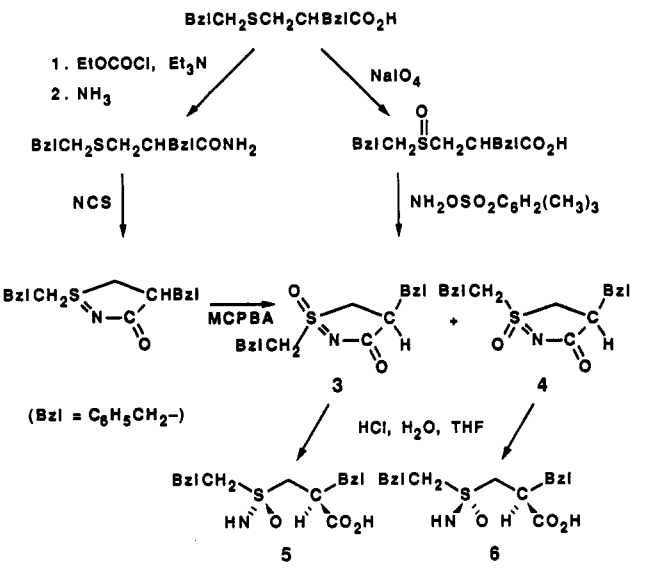


2

Scheme I summarizes two parallel paths for securing a β-sulfonimidoylpropionic acid. The 1,4 relationship between sulfoximine and carboxyl groups in the products **5** and **6** is particularly significant, because in a peptide the consecutive carbonyl moieties along the backbone have that spacing. Consequently, this unit may generally be incorporated into peptide analogues, with a sulfoximine group occupying a position which is ordinarily susceptible to enzymic scission. For these species, the key to diastereomeric discrimination is the spontaneous formation of cyclic intermediates (**3** and **4** in Scheme I). While the ring-opened final products appear to have identical solubilities and chromatographic R_f values, the conformational rigidity of the lactam rings of **3** and **4** not only renders the intermediates nicely crystalline, but also allows ready chromatographic separation.

The synthesis embodied in Scheme I (right-hand path) has been carried out with optically resolved materials, i.e., the starting carboxylic acid was separated into enantiomers by means of its chiral methylbenzylamine salt. Oxidation to sulfoxides followed by azotization gave **3** and **4** directly. Relative configuration between sulfoximine and carboxymethine centers has been unambiguously established by crystallography. The species designated as **3** has a trans orientation of aralkyl substituents, whereas **4** has the cis configuration. Moreover, anomalous scattering measurements in the refined structure for a single enantiomer of **4** yield an absolute configuration. Perspective depictions

Scheme I



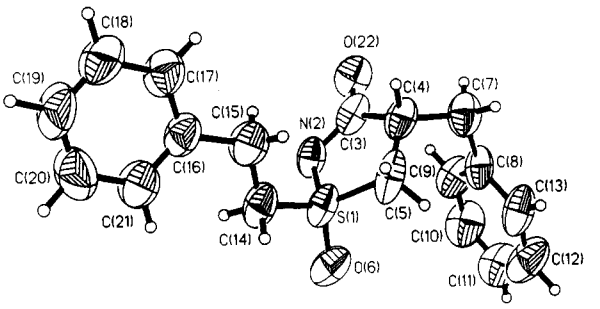


Figure 1. Perspective depiction of structure for **3**, as secured by crystallography.

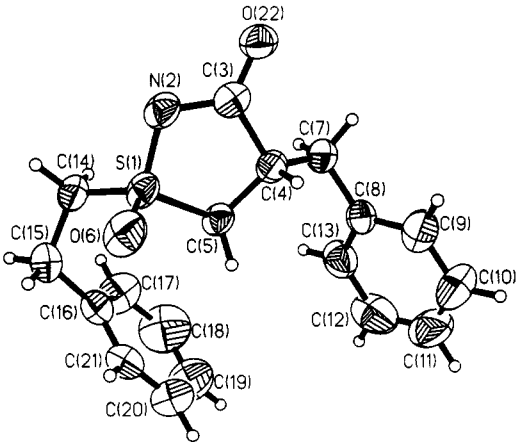


Figure 2. Perspective depiction of structure for **4**, as secured by crystallography.

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(1) Mock, W. L.; Tsay, J.-T. *J. Am. Chem. Soc.* **1989**, *111*, 4467–4472.

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of the lactams are provided in Figures 1 and 2, with crystallographic details available as supplementary material.

Ring opening of **3** and **4** can be achieved by acidic hydrolysis, which should not invert the stereogenic centers (N–CO bond cleavage). By employing chiral intermediates in the sequence, all four possible isomeric sulfoximinecarboxylic acids **5** and **6** have been secured. Absolute configurational assignments may then be confirmed biochemically. The enzyme bovine pancreatic carboxypeptidase A (EC 3.4.17.1) has high specificity for C-terminal phenylalanine substrates of the natural L-configuration. The 3-phenylpropionate portion ($BzlCHRCO_2H$) of **5** and **6** resembles that amino acid, providing a basis for inhibitor recognition by the enzyme. The isomer L-**5** (actually dextrorotatory) is the most firmly bound to carboxypeptidase A of all four epimers (competitive K_i value of 0.3 μM at a pH of 7), and its enzymic affinity is at least 47 times greater than for its enantiomer. Accordingly, it has the 2*R*,4*S* configuration (numbering from carboxylic acid to sulfoximine). However, there is reason to suspect that the acidic hydrolysis of **4** is not entirely stereospecific; D-**6** seems to be contaminated with L-**5**, such as would be produced by a small amount of acid-induced epimerization next to the carbonyl group of optically resolved **4** in the course of ring opening. Indicative evidence is that D-**6** appears to bind to the enzyme only 12-fold more poorly than does L-**6**, and it also exhibits a pH profile for K_i similar to that observed for L-**5** (and not at all like that of L-**6**). Consequently, the situation might exist that the true level of inhibition by D-**6** is masked by a few percent of L-**5**. A full comparison of the inhibition characteristics of **5** and **6** for carboxypeptidase A will be provided elsewhere.

Experimental Section

2-Benzyl-3-((2-phenylethyl)thio)propionic Acid. Chloromethyl 2-phenylethyl sulfide, bp 80 °C (5 mm), was prepared in 71% yield from 2-phenylethanethiol, paraformaldehyde, and anhydrous hydrogen chloride.[3] It was allowed to react with sodium diethyl benzylmalonate in ethanolic solution (80 °C, 30 min) in a previously employed manner.[4] The crude diester product was isolated by extraction (Et_2O–H_2O) and was directly hydrolyzed with aqueous potassium hydroxide. Acidification and extraction (CH_2Cl_2) yielded 54% of 2-(((2-phenylethyl)thio)-methyl)-2-benzylmalonic acid: mp 145–147 °C dec; 400-MHz ^{1}H NMR ($CDCl_3$) δ 7.15–7.30 (m, 10 H), 3.33 (s, 2 H), 3.15 (s, 2 H), and 2.85 (m, 4 H); IR (KBr) 1710 cm^{-1}. Preparative thermal decarboxylation was achieved by melting this material, quantitatively yielding 2-benzyl-3-((2-phenylethyl)thio)propionic acid as an oil which eventually solidified: 400-MHz ^{1}H NMR ($CDCl_3$) δ 12.0 (s, 1 H), 7.15–7.30 (m, 10 H), 3.07 (dd, J = 9.8, 16.3 Hz, 1 H), 2.93 (m, 2 H), 2.74–2.87 (m, 5 H), and 2.66 (dd, J = 4.9, 13.2 Hz, 1 H); IR ($CHCl_3$) 1700 cm^{-1}. Resolution into L- and D-enantiomers was accomplished by repeated recrystallization from methanol of the salts formed with enantiomerically pure methylbenzylamine (Aldrich Chemical Co). To a solution of 29.59 g (0.1 mol) of racemic 2-benzyl-3-((2-phenylethyl)thio)propionic acid in a minimum volume of methanol was added dropwise with stirring 11.95 g (0.1 mol) of (*S*)-(−)-α-methylbenzylamine; a white precipitate formed upon standing. Repeated recrystallization of the solid from methanol to constant melting point yielded 13.03 g of a pure (*S*)-(−)-α-methylbenzylamine salt of 2-benzyl-3-((2-phenylethyl)thio)propionic acid: mp 136–138 °C; $[\alpha]_D$ = −11.4° (c = 10.0, MeOH). From the supernatants was obtained, by recovery of the acid and addition of the enantiomeric amine, 12.85 g of a pure (*R*)-(+)-α-methylbenzylamine salt of 2-benzyl-3-((2-phenylethyl)thio)propionic acid: mp 136–138 °C; $[\alpha]_D$ = +11.2° (c = 10.0, MeOH).

L-4,5-Dihydro-1-(2-phenylethyl)-4-(phenylmethyl)-3*H*-1λ^4-isothiazol-3-one 1-Oxides. A solution containing 8.59 g (0.02 mol) of the (*S*)-(−)-α-methylbenzylamine salt previously obtained in 640 mL of chloroform was washed with 4 × 310 mL of 2 M sulfuric acid solution and then with 2 × 310 mL of water. The chloroform layer was separated, dried, filtered, and concentrated to give as an oil 6.65 g of L-2-benzyl-3-((2-phenylethyl)thio)-propionic acid, $[\alpha]_D$ = −24.3° (c = 10.22, MeOH). The configurational designation is on the basis of homology to L-phenylalanine, and only coincidentally by intrinsic rotation. Oxidation of this material with 1 equiv of sodium metaperiodate in aqueous methanol gave an 86% yield of sulfinyl epimers of L-2-benzyl-3-((2-phenylethyl)sulfinyl)propionic acid, which were subsequently used without separation: IR (KBr) 995 (S=O), 1705 (CO_2H) cm^{-1}. To a solution of this material in dry methylene chloride was added 1.5 equiv of *O*-mesitylenesulfonylhydroxylamine[5] and the reaction mixture was stirred for 24 h under nitrogen at 25 °C. It was then poured into 50 mL of cold 10% sodium hydroxide solution and stirred for 10 min. The aqueous layer was washed with methylene chloride (2 × 25 mL), and the organic extracts were dried and evaporated. The products were obtained by silica preparative plate chromatography ($CHCl_3$–*i*-PrOH, 15:1). A band with an R_f value of 0.39 was extracted with acetone, giving a solid which was recrystallized from chloroform and hexanes to provide *trans*-L-(+)-4,5-dihydro-1-(2-phenylethyl)-4-(phenylmethyl)-3*H*-1λ^4-isothiazol-3-one 1-oxide (L-**3**, homologous to L-phenylalanine) in 16% yield: mp 144–145 °C; $[\alpha]_D$ = +18° (c = 10.0, $CHCl_3$); 400-MHz ^{1}H NMR ($CDCl_3$) δ 7.15–7.40 (m, 10 H), 3.72 (m, 1 H), 3.55 (m, 1 H), 3.40 (dd, J = 3.9, 14.0 Hz, 1 H), 3.19 (m, 3 H), 3.08 (m, 1 H), 3.00 (dd, J = 4.3, 14.8 Hz, 1 H), and 2.87 (dd, J = 10.1, 14.0 Hz, 1 H); 100-MHz ^{13}C NMR ($CDCl_3$) δ 28.92, 30.96, 37.96, 47.68, 53.08, 56.37, 127.10, 127.69, 128.59, 128.91, 128.95, 129.24, 136.05, 137.73, and 181.62; IR (KBr) 1220 (S=O?) and 1660 (C=O) cm^{-1}; MS (CI) m/e 314.0 (MH^+). A band from the chromatography with an R_f value of 0.45 was also extracted with acetone, giving a solid which was recrystallized from chloroform and hexanes to provide *cis*-L-(−)-4,5-dihydro-1-(2-phenylethyl)-4-(phenylmethyl)-3*H*-1λ^4-isothiazol-3-one 1-oxide (L-**4**) in 28% yield: mp 187–187.5 °C; $[\alpha]_D$ = −91° (c = 10.0, $CHCl_3$); 400-MHz ^{1}H NMR ($CDCl_3$) δ 7.10–7.40 (m, 10 H), 3.46 (m, 1 H), 3.27 (dd, J = 5.3, 13.8 Hz, 1 H) 3.15 (m, 2 H), 2.95 (m, 2 H), 2.87 (m, 2 H), 2.58 (m, 1 H); 100-MHz NMR ($CDCl_3$) δ 28.83, 35.67, 45.95, 52.12, 56.28, 127.44, 127.68, 128.76, 129.04, 129.12, 129.86, 136.01, 136.56, and 181.46; IR (KBr) 1220 (S=O?) and 1680 (C=O) cm^{-1}; MS (CI), m/e 314.0 (MH^+). The same procedure was followed to obtain the D-series isomers: D-**3**, mp 142–144 °C, $[\alpha]_D$ = −19° (c = 10.0, $CHCl_3$); D-**4**, mp 179–181 °C, $[\alpha]_D$ = +86° (c = 10.0, $CHCl_3$).

An alternate route to **3** and **4** (left-hand portion of Scheme I, conversion to carboxamide and sequential oxidations with *N*-chlorosuccinimide and *m*-chloroperbenzoic acid) was also investigated with racemic materials, following a previously devised procedure;[4] equivalent results were obtained.

2-Benzyl-3-((2-phenylethyl)sulfonimidoyl)propionic Acid (L-5 and L-6). To a solution of 175 mg (0.56 mmol) of L-**3** in 6.8 mL of tetrahydrofuran was slowly added 1.5 mL of concentrated hydrochloric acid. After the mixture was stirred at room temperature for 24 h, the solvent was rotary evaporated to give a green solid residue. Recrystallization from ethyl acetate and hexanes (containing a trace of anhydrous HCl), yielded 120 mg (59%) of (2*R*,4*S*)-2-benzyl-3-((2-phenylethyl)sulfonimidoyl)propionic acid (L-**5**, homologous to L-phenylalanine) as the hydrochloride: mp 146–148 °C; $[\alpha]_D$ = +11° (c = 10.0, MeOH); 400-MHz ^{1}H NMR (CD_3OD) δ 7.15–7.30 (m, 10 H), 3.68 (dd, J = 10.1, 14.7 Hz, 1 H), 3.2–3.33 (m, 3 H), 3.15 (dd, J = 5.3, 13.5 Hz, 1 H), 2.92–3.08 (m, 3 H), 2.83 (m, 1 H), and 2.70 (dd, J = 9.4, 13.3 Hz, 1 H); 100-MHz ^{13}C NMR (CD_3OD) δ 29.83, 40.07, 47.19, 56.14, 56.87, 127.56, 127.72, 129.58, 129.63, 129.69, 130.32, 139.45, 140.39, and 180.36;

(2) Manning, J. M.; Moore, S.; Rowe, W. B.; Meister, A. *Biochemistry* **1969**, *8*, 2681–2685. However, see: Christensen, B. W.; Kjaer, A.; Neidle, S.; Rogers, D. *J. Chem. Soc., Chem. Commun.* **1969**, 169–170. Johnson, C. R.; Kirchhoff, R. A.; Corkins, H. G. *J. Org. Chem.* **1974**, *39*, 2458–2459.

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IR (KBr) 1200 (S=O?), 1730 (CO_2H), and 3450 (br, NH, OH) cm^{-1}; Anal. Calcd for $C_{18}H_{22}NO_3ClS$: C, 58.77; H, 6.03; N, 3.81. Found: C, 59.28; H, 6.08; N, 3.73.

The same procedure applied to L-4 gave a 56% yield of (2*R*,4*R*)-2-benzyl-3-((2-phenylethyl)sulfonimidoyl)propionic acid (L-6) as the hydrochloride: mp 148.5–150.5 °C; $[\alpha]_D = +4°$ (*c* = 7.5, MeOH); 400-MHz ^1H NMR (CD_3OD) δ 7.3 (m, 10 H), 4.1 (dd, *J* = 10.1, 15.2 Hz, 1 H), 4.05 (m, 2 H), 3.75 (dd, *J* = 2.5, 15.2 Hz, 1 H), 3.4 (m, 1 H), 3.3 (m, 1 H), 3.08 (m, 3 H); 100-MHz ^{13}C NMR (CD_3OD) δ 29.77, 40.04, 47.03, 56.55, 56.97, 127.54, 127.75, 129.54, 129.59, 129.72, 130.36, 139.42, 140.38, and 180.39; IR (KBr) 1200 (S=O?), 1730 (CO_2H), and 3450 (br, NH, OH) cm^{-1}. Anal. Calcd for $C_{18}H_{22}NO_3ClS$: C, 58.77; H, 6.03; N, 3.81. Found: C, 59.10; H, 6.05; N, 3.75.

Similarly obtained were D-5 (mp 145.5–147.5 °C) and D-6 (mp 147–148 °C). Spontaneous recyclization to **3** and **4** occurs in weakly acidic solution (pH ~3).[4] An analytical separation of **5** and **6** by HPLC could not be obtained.

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Supplementary Material Available: X-ray crystallographic data for compounds **3** and **4** (14 pages). Ordering information is given on any current masthead page.

Vilsmeier–Haack Reaction with Glutarimides. Synthesis of 2,6-Dichloro-1,4-dihydropyridine-3,5-dicarboxaldehydes[1]

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4-Aryl-1,4-dihydropyridines are an important class of drugs which are used in the treatment of various cardiovascular disease states.[3-5] It is surprising that for a group of compounds which has been so intensively studied, relatively few useful syntheses thereof are known,[6,7] especially for those which bear substituents other than hydrogen atoms or methyl groups at C-2 and C-6. This publication shows that 4-arylglutarimides, upon reaction with the Vismeier–Haack reagent, are converted into 1,4-dihydro-2,6-dichloro-4-arylpyridine-3,5-dicarboxaldehydes, which may show promise as precursors of still other novel dihydropyridine derivatives.

Kvitko and Panfilova have reported[8] that N-substituted succinimides were converted into 2,5-dichloropyrrole-3,4-dicarboxaldehyde derivatives upon reaction with an excess of the Vilsmeier–Haack reagent. If an analogous reaction were to occur with 4-arylglutarimides, the corresponding 1,4-dihydro-2,6-dichloro-4-arylpyridine-3,5-dicarboxaldehydes would be the expected products. Indeed, Weissenfels and Kubisch[9] have shown that *N*-arylglutarimides, and even glutarimide itself, are converted into the expected dihydropyridine derivatives in the presence of an excess of the Vilsmeier–Haack reagent at 100 °C. Furthermore, Aubert et al.[10] have recently shown that 1-substituted 7-chloro-2,3,4,5-tetrahydroazepin-2-ones are converted into 2,7-dichloro-4,5-dihydroazepine-3,6-dicarboxaldehydes under similar conditions.

Table I. Synthesis of Some Pyridine and Dihydropyridine Derivatives

R	% yield 3	4[a]	5
C_6H_5	72	87	
3-ClC_6H_4	80	98	
3-$NO_2C_6H_4$	61	87	
3-$CF_3C_6H_4$	75	88	94
H	65	56[b]	91

[a] Yield based on **3** unless otherwise specified. [b] Yield based on **1e**.

A study of the reaction of 4-phenylglutarimide (**1a**, Scheme I) with the Vilsmeier–Haack reagent ($POCl_3$–DMF)[11] showed that this imide was consumed under conditions which were much milder than those reported by Weissenfels and Kubisch.[9] For example, after 15 h at room temperature, in the presence of 4 molar equiv of the reagent and subsequent hydrolysis of the reaction mixture with excess aqueous sodium acetate, an orange-colored solid was obtained in over 70% yield. This substance, analyzed for $C_{15}H_{14}Cl_2N_2O$, had no NH stretching absorptions in the infrared spectrum, and the NMR spectrum (90 MHz) showed five singlet absorptions at δ 3.20 (6 H), 5.40 (1 H), 7.28 (5 H), 7.89 (1 H), and 9.95 (1 H). These properties are not consistent with those anticipated for **4a**, but they are compatible with the 3-((dimethylamino)-methylene)-3,4-dihydropyridine structure **3a**, provided that rapid rotation is assumed about the formal $CHNMe_2$ single bond on the NMR time scale (see below). This is a reasonable assumption, in view of the observation by Katritzky et al.,[12] that the dimethylamino moiety of 2,4-dichloro-3-((dimethylamino)methylene)-1,4-cyclohexadiene-1,5-dicarboxaldehyde has a coalescence temperature of −25 °C. Compound **3a** was very sensitive to acidic hydrolysis being rapidly converted into the desired dicarboxaldehyde **4a** with 1 equiv of 0.5 N HCl in THF solution at room temperature.

Under conditions identical to those described above, the meta-substituted 4-arylglutarimides **1b–d** were also converted into the 3,4-dihydro- and the 1,4-dihydropyridine derivatives **3b–d** and **4b–d**, respectively (Table I). In addition, the (*m*-(trifluoromethyl)phenyl-1,4-dihydropyridine derivative **4d** was oxidized to 2,6-dichloro-4-(3-(trifluoromethyl)phenyl)pyridine-3,5-dicarboxaldehyde (**5d**) in over 90% yield, with ceric ammonium nitrate in aqueous acetone.[13]

At this stage it was of interest to reexamine the reaction of glutarimide itself with the Vilsmeier–Haack reagent in the light of the above observations. Repetition of the

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(2) Research completed in partial fulfillment for the degree of "Maestria en Ciencias" at the Departamento de Quimica, Division de Estudios Superiores, Universidad Nacional Autonoma de Mexico, Mexico, D.F.
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