Crystal-state studies on *p*-toluenesulfonates of *N*-oxyimides—a possible structural basis of serine proteases inhibition†

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A series of *p*-toluenesulfonates of *N*-oxyimides has been synthesized and their X-ray structures show a flattened pyramidal geometry of the hydroxyimide ring nitrogen. This structural feature is considered to be responsible for a specific chemical reactivity towards nucleophiles and inhibitory properties against proteases of these compounds.

Introduction

N-Hydroxyimides form stable and crystalline ester derivatives with many aryl-, alkylsulfonic, and carboxylic acids.[1,2] In contrast to *N*-hydroxyimidyl esters of carboxylic acids, which are widely used in peptide synthesis and biochemistry as selective acylating reagents,[3] *N*-hydroxyimidyl derivatives of sulfonic acids react with amines through carbonyl groups of the succinimidic ring to form ureido derivatives (Fig. 1). The mechanism of these reactions is closely related to the Lossen rearrangement.[4,5] Many derivatives of these compounds are known as inhibitors of serine proteases, mainly α-chymotrypsin and human leucocyte elastase.[6–10] Enzyme induced ring opening results in instantaneous Lossen rearrangement *via* the *O*-sulfonyl derivative releasing the isocyanate. Reactive isocyanate formed in the active centre reacts with the histidine's imidazoyl ring,[7] irreversibly deactivating the enzyme. Surprisingly, there are only few references concerning the crystal structures of *N*-hydroxyimide sulfonic acid esters.[1,11]

The chemical reactivity of arylsulfonic esters of *N*-hydroxyimides towards amines and a significant biological importance of this class of compounds are the reasons of X-ray diffraction experiments on the esters of *p*-toluenesulfonic and *N*-hydroxysuccinimidic derivatives. Non planar nitrogen geometry in the pentaatomic ring which does not appear in carboxylic esters of *N*-hydroxyimides is a structural feature present in every described arylsulfonic ester of *N*-hydroxyimides. It can be considered as a reason for the observed characteristic chemical reactivity and biological properties of this class of compounds.

We describe here the synthesis, characterization, and results of the crystallographic analysis of esters of *N*-hydroxysuccinimides and (4-methylphenyl)sulfonyl acid (Scheme 1).

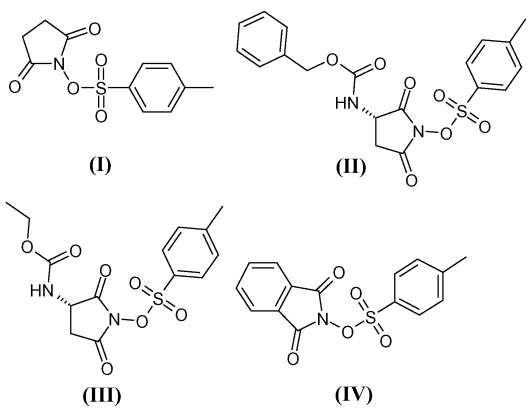
Results and discussion

The *p*-toluenesulfonates of *N*-oxyimides **I–IV** (Scheme 1) were prepared by direct reaction of *N*-hydroxyimides with *p*-toluenesulfonyl chloride in the presence of triethylamine. Tetrahydrofuran was used as a solvent. This procedure is based on Bauer's approach,[4,12] but our modification gave a higher yield.

Two *N*-hydroxyimides, *N*-hydroxysuccinimide and *N*-hydroxyphthalimide, are commercially available while *N*-hydroxyimides used as substrates for compounds **II** and **III** were obtained by direct reaction of corresponding, cyclic anhydrides with hydroxylamine in water–dioxane solution (Fig. 2). This reaction was based on the synthesis of *N*-hydroxyimide described by Anderson *et al.*[13]

The molecular structures of compounds **I–IV** with the atomic numbering schemes are shown in Figs. 3–6, respectively.

The S atoms lie in the same plane as the tosyl aromatic ring in compounds **I**, **II**, and **IV**. Only in **III** the sulfur atom is displaced from the plane of the adjacent aromatic moiety by 0.169(3) Å which can result from the steric hindrance. The configuration of sulfur is a distorted tetrahedron with the S–O1 and S–O2 bonds shorter than the S–O3 bond that is in good agreement with the numerous crystallographic data for



Scheme 1 (**I**) 1-{[(4-methylphenyl)sulfonyl]oxy}pyrrolidine-2,5-dione; (**II**) benzyl (3*S*)-1-[(methylsulfonyl)oxy]-2,5-dioxopyrrolidin-3-ylcarbamate; (**III**) ethyl (3*S*)-1-{[(4-methylphenyl)sulfonyl]oxy}-2,5-dioxopyrrolidin-3-ylcarbamate; (**IV**) 2-{[(4-methylphenyl)sulfonyl]oxy}-1*H*-isoindole-1,3(2*H*)-dione.

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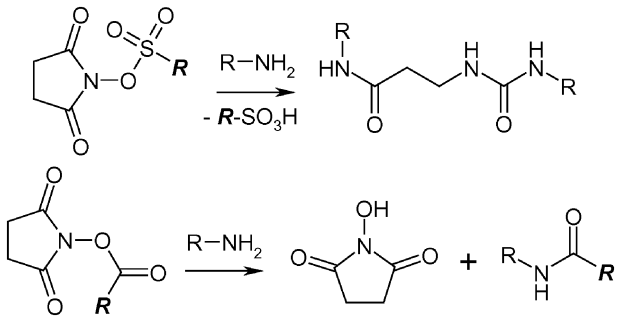

Fig. 1 Comparison of the reactions of aryl/alkylsulfonic and carboxylic acids esters of *N*-oxysuccinimide with amines. ***R***, R = aryl or alkyl moiety.

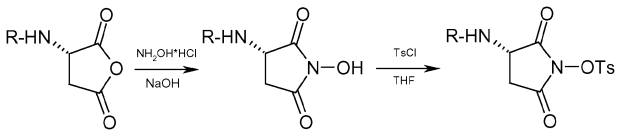

Fig. 2 The scheme of synthesis of compounds **II–III**.

this residue.[1,14] The increased angle O2–S–O3 and the resulting angle C1–S–O2, smaller than typical tetrahedral values for sulfonic groups, are attributed to the Thorpe–Ingold effect.[15]

The O1–N1–C1, O1–N1–C4, and C1–N1–C4 angles (Table 1) are very similar to those observed for (−)-*N*-hydroxyimide of (10-pinene-2-yl) succinimic acid[16] and *N*-hydroxy-1*H*-isoindole-1,3(2*H*)-dione[17] where the nitrogen atom is planar, and for 2-[(phenylsulfonyl)oxy]-1*H*-benzo[*de*]isoquinoline-

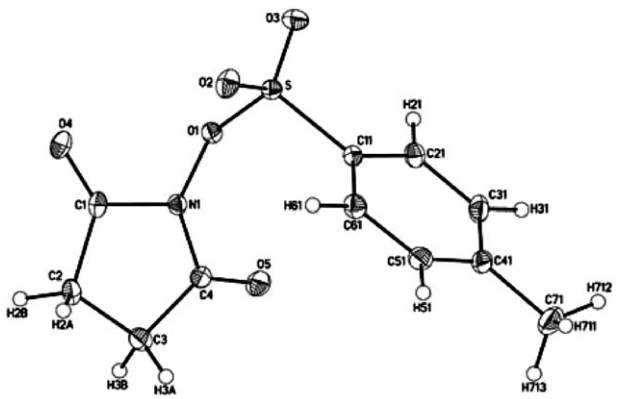

Fig. 3 Molecular geometry and atom-numbering scheme of **I**. Displacement ellipsoids are drawn at the 30% probability level.

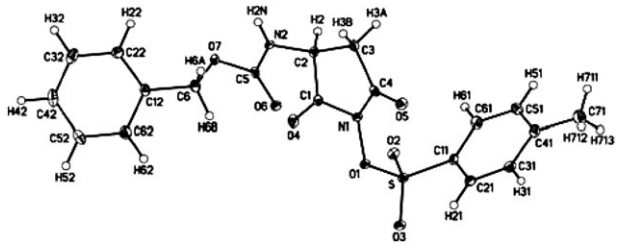

Fig. 4 Molecular geometry and atom-numbering scheme of **II**. Displacement ellipsoids are drawn at the 30% probability level.

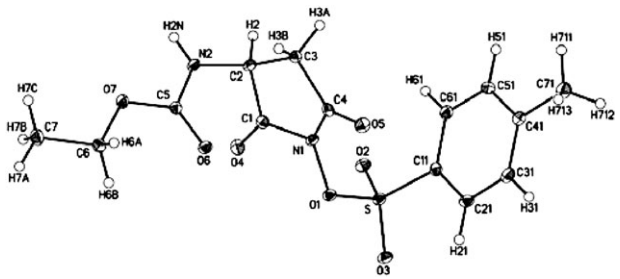

Fig. 5 Molecular geometry and atom-numbering scheme of **III**. Displacement ellipsoids are drawn at the 30% probability level.

1,3(2*H*)-dione and 1-[(2-naphthylsulfonyl)oxy]pyrrolidine-2,5-dione, where nitrogen atoms were also found to be flattened pyramids with deviation from the plane of the surrounding atoms equal to 0.150(1) Å.[1,11] Deviations of the succinimide nitrogen atom from the C1–O1–C4 plane for the described compounds equal 0.214(1), 0.180(1), 0.200(2), and 0.243(2) Å for **I**, **II**, **III**, and **IV**, respectively.

The N1–C4 and N1–C1 bond lengths of **I**, **II**, **III** [average 1.402 Å], and **IV** [average 1.417 Å] are longer than typical N–C peptide bonds [*ca.* 1.32 Å][18] and longer than typical N–C bonds in the succinimide ring [*ca.* 1.384 Å].[2,19]

This change of bonds length and also displacement of the nitrogen atom from the plane defined by C1, O1, and C4 atoms can be considered as an evidence that the charge distribution in molecules of *N*-oxyimido sulfonates is different from that of cyclic imides. The shift of the electron pair from nitrogen to the carbon atom is significantly reduced. Consequently the charge density on carbon is decreased and the carbonyl group is more susceptible to the nucleophile attack.[20] These features of the succinimidic ring can explain the biological activity of some similar structures of aryl- and alkylsulfonic esters of succinimides.

Non-planar nitrogen atom exists also in β-lactam antibiotics and is believed to be responsible for their biochemical properties. In Woodward's opinion a pronounced pyramidal character of the nitrogen atom in the β-lactam ring results in a decreased charge density on the carbon atom in the carbonyl group, which is a cause of the increased reactivity of the lactam

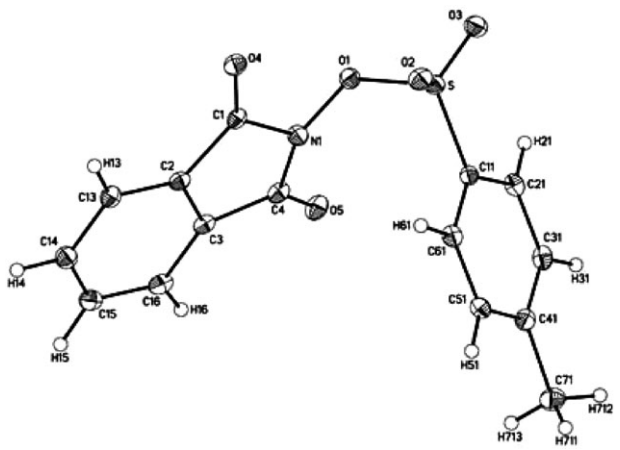

Fig. 6 Molecular geometry and atom-numbering scheme of **IV**. Displacement ellipsoids are drawn at the 30% probability level.

Table 1 Selected bond distances (Å), bond angles (°), and torsion angles (°) for compounds **I–IV**

	I	II	III	IV
Distance/Å				
O1–N1	1.391 (2)	1.397 (2)	1.396 (2)	1.398 (2)
N1–C1	1.406 (2)	1.399 (2)	1.404 (2)	1.414 (3)
N1–C4	1.403 (2)	1.401 (2)	1.399 (2)	1.421 (2)
C1–O4	1.203 (2)	1.202 (2)	1.193 (2)	1.202 (2)
C4–O5	1.200 (2)	1.204 (3)	1.204 (2)	1.199 (2)
C2–C3	1.529 (2)	1.545 (2)	1.534 (3)	1.397 (3)
C1–C2	1.503 (2)	1.533 (2)	1.536 (3)	1.495 (3)
C4–C3	1.505 (2)	1.509 (3)	1.502 (3)	1.484 (3)
C2–N2	—	1.452 (2)	1.440 (2)	—
N2–C5	—	1.355 (2)	1.351 (2)	—
C5–O7	—	1.346 (2)	1.339 (2)	—
C5–O6	—	1.213 (2)	1.220 (2)	—
Bond angle/°				
C1–N1–O1	120.0(1)	118.6(2)	118.9(2)	120.9(2)
O1–N1–C4	118.5(1)	120.4(2)	120.9(2)	117.4(2)
C1–N1–C4	114.4(2)	115.0(2)	115.3(2)	113.5(2)
C1–C2–C3	106.0(1)	104.9(2)	105.2(2)	109.2(2)
C4–C3–C2	106.1(2)	105.9(2)	106.5(2)	109.0(2)
N1–C1–C2	105.8(1)	105.7(2)	105.1(2)	103.4(2)
N1–C4–C3	105.3(2)	105.4(2)	105.4(2)	103.8(2)
Torsion angle/°				
C61–C11–S–O2	14.2(2)	4.7(2)	20.1(2)	23.9(2)
C21–C11–S–O3	−26.4(2)	−39.0(2)	−26.5(2)	−17.3(2)
C1–N1–O1–S	98.1(2)	103.3(2)	100.9(2)	102.5(2)
C4–N1–O1–S	−112.8(1)	−105.3(2)	−105.0(2)	−111.1(2)
N1–C1–C2–N2	—	−127.4(2)	−127.7(2)	—
Cremer and Pople parameters[26] (N1–C1–C2–C3–C4)				
q_2	0.140(2) Å	0.160(2) Å	0.144(2) Å	0.098(3) Å
ψ_2	163(1)°	154(1)°	154(1)°	182(2)°
Closest description	Twisted on C4–N1	Twisted on C4–N1	Twisted on C4–N1	Envelope on N1

ring toward nucleophiles. In this case biological activity is a result of irreversible reaction of the β-lactam ring with a serine residue in the transpeptidase active center.[21] Other authors,[22] however, claim that the pyramidal atom is not the only source of biological activity because of the lack of simple correlation between the pyramidal character of nitrogen and antibacterial activities of investigated β-lactams.

The N1–O1 bond lengths for sulfonic esters of *N*-oxyimides are in the range of 1.384(2)[11]–1.398(2) Å (for **IV**). These values are slightly longer than values observed for non-tosylated *N*-hydroxyimides, like *N*-hydroxyphthalimide [1.375(5) Å][17] and *N*-hydroxysuccinimide [1.377(2) Å][19] and noticeably longer than the N–O bond lengths existing in *N*-oxyimides anions [1.360(2) Å],[23] but similar to those reported for carboxylic esters of *N*-oxyimides[2] and *N*-oxyimides carbonates.[24] The torsion angles of the carbamate moiety of **II** and **III** (C1–C2–N2–C5), 53.3(2)° and 48.9(2)°, respectively, are also similar in magnitude to those found for succinimide peptides.[25] The plane of the N2–C5–O6 atoms in **II** and **III** is approximately perpendicular (89° and 83°) to the succinimide ring, which has also been found in the structures of hydroxysuccinimide-based

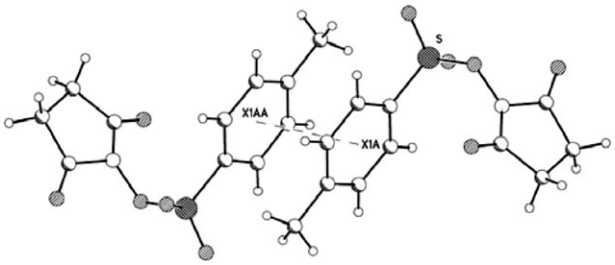

Fig. 7 The scheme showing the stacking of adjacent molecules of **I** [code of symmetry: $-x+1, -y+1, -z+1$]. To indicate a molecule with the x, y, z code of symmetry the S atom has been labelled. Dashed line is the distance between the midpoints X1A and X1AA of adjacent aromatic rings which equals 3.717(2) Å. The distance between the planes of parallel rings is 3.58(2) Å.

peptidomimetics.[3] The angle between the succinimide ring and the benzyl and toluyl groups of **II** is equal to 33(1)° and 58(1)°, respectively.

A noticeable difference in the C2–C3 bond length between investigated sulfonic esters of *N*-hydroxysuccinic acid and ester of *N*-hydroxyphthalimide can be explained by the aromatic character of the phthalimic six-membered ring. Other C–C bond lengths differences can be considered as a result of different packing of molecules in a unit cell. C1–C2–C3 and C4–C3–C2 angles are significantly larger for compound **IV** than for other investigated compounds because of the shorter C2–C3 bond length. The differences in the bonds and angles values mentioned above for **I**, **II**, and **III** result in the puckered and twisted succinic ring. This twist is characterized by a pseudo twofold axis bisecting the middle of the C4–N1 bond and C2 atom, and the pentaatomic ring in **IV** is in the envelope conformation. The Cremer and Pople parameters[26] are listed in Table 1.

The analysis of the aromatic rings arrangement showed classical stacking interactions in the crystals of **I** (Fig. 7). The distance between the aromatic rings centers in adjacent molecules is equal to 3.717(2) Å, straight distance between the rings planes is 3.58(2) Å. The angle between the normal and line linking middle points (X1A and X1AA) of the aromatic rings involved in stacking and the plane of the aromatic ring equals 20(1)° (Fig. 7). Stacking interactions involving aromatic rings of tosyl groups can be also recognized for compound **IV** (Fig. 8) The distance between the middle points of stacked rings is 3.796(2) Å, and the distance between the rings planes is 3.56(2) Å. Fitting of structures **I** and **IV** confirms a significant structural agreement between the pentaatomic rings of mentioned compounds (Fig. 9a). This noticeable compatibility is caused by significant similarities of the C1–N1–O1–S and C4–N1–O1-S torsion angles.

Noticeable differences in the values of the C61–C11–S–O2 and C21–C11–S–O3 torsion angles can explain the lack of fitting of the tosyl group rings in compounds **II** and **III**. Fitting of the pentaatomic rings and the protected amino moiety for compounds **II** and **III** is almost complete (Fig. 9b).

A short contact between the C1 and O4 atoms of adjacent carbonyl groups indicates short antiparallel carbonyl interactions in the crystal structure of compound **I**. The distance between carbon of one carbonyl group and the oxygen atom of

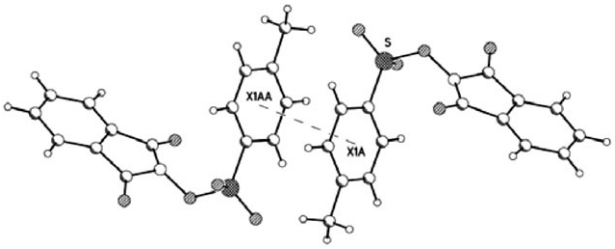

Fig. 8 The scheme showing the stacking of adjacent molecules of **IV** [code of symmetry: $2 - x$, $2 - y$, $-z$]. To indicate a molecule with the x, y, z code of symmetry the S atom has been labelled. Dashed line is the distance between the midpoints X1A and X1AA of adjacent aromatic rings which equals 3.796(2) Å. The distance between the planes of parallel rings is 3.56(2) Å.

another (symmetry operation: $-x$, $2 - y$, $1 - z$) is 2.918(3) Å. The carbonyl group involved in the imide bond in compound **II** interacts with the oxygen atom of sulfonyl group of the adjacent molecule. The distance of this weak interaction is equal to 2.943(2) Å ($1 + x$,y,z). Three C–H···O short interactions were recognized for compound **I**. They are suspected with other weak interactions to increase structure's packing and the stacking interaction mentioned above. Packing of **I** is presented in Fig. 10. In compound **II**, four intermolecular interactions were recognized, including one typical hydrogen bond N2–H2N···O5 and three C–H···O type short contacts. In compound **III**, the C2 carbon atom as an H2 atom donor creates two short interactions of the C–H···O type with the O3 ($2 - x$, $-1/2 + y$, $3/2 - z$) and O5 atoms ($3 - x$, $-1/2 + y$, $3/2 - z$) of surrounding molecules. Compound **III** is characterized by one typical N2–H2N···O5 and four C–H···O type short interactions. There are no typical hydrogen bonds in compound **IV**, in which only three C–H···O type short contacts were recognized. All hydrogen bond parameters are shown in Table 2. The hydrogen bond donor atom in presented compounds **II** and **III** is nitrogen of the carbamate bond. Carbonyl groups in the succinimic ring are hydrogen bond acceptors. The adjacent molecules of **II** and **III** are linked together by N–H···O hydrogen and C–H···O bonding interactions, forming a three-dimensional network. Packings of **II**, **III** and **IV** within the unit cell are shown in Figs. 11–13, respectively.

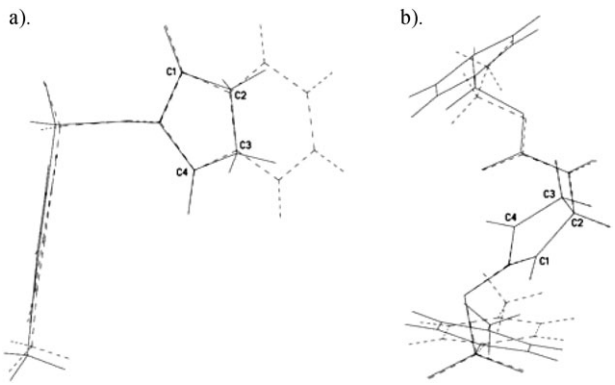

Fig. 9 The comparisons of structures: (a). **I** and **IV**; (b). **II** and **III**; The common reference points are C1, C2, C3, and C4 atoms.

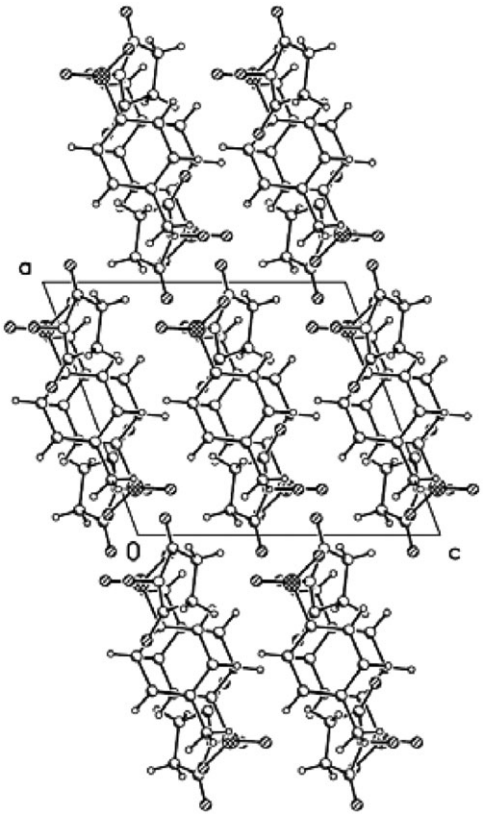

Fig. 10 The packing arrangement of **I** along the *b* axis.

Presented analysis of molecular packing shows that the nitrogen atom geometry is not dependent on the molecular arrangement in the described crystals. The structures of four compounds presented in this work can be divided into two types distinguished according to the structural motifs that are presented in Fig. 9. Previously described 1-[(2-naphthylsulfonyl)oxy]pyrrolidine-2,5-dione was characterized also by the non planar nitrogen atom.[11]

Conclusions

Present study has shown the structural features which might be responsible for specific chemical reactivity towards nucleophiles and biological activity of arylsulfonic esters of *N*-hydroxyimides. All four structures are characterized by non-planar nitrogen of the pentaatomic ring and relatively long C1–N1 and C4–N1 bonds that imply reduction of the amide resonance in comparison to carboxylic esters of succinimides. In arylsulfonic esters the nucleophilic attack of amines on succinimide carbonyls results in Lossen type rearrangements of these compounds and opening of the succinimidic ring[4,5] (Fig. 1). This effect may also play a role in inhibitory properties shown by *p*-toluenesulfonates of *N*-oxyimides in respect to proteolytic enzymes. According to literature data, interaction of *N*-hydroxyimidyl sulfonates with proteolytic enzymes is initiated by nucleophilic opening of the imide ring. A similar effect is also observed for β-lactam antibiotics where nitrogen aplanarity is also considered to play a key role in activity of those systems.[21]

Table 2 Hydrogen bond geometry details of **I**, **II**, **III**, and **IV**

Compound		D–H/Å	H···A/Å	D···A/Å	D–H···A/°	Symmetry operations on A
I	C2–H2A···O3	0.92(2)	2.46(2)	3.076(2)	125(2)	$x, 3/2 - y, -1/2 + z$
	C3–H3A···O5	0.95(2)	2.54(2)	3.191(2)	126(2)	$1 - x, 2 - y, 1 - z$
	C31–H31···O4	0.98(2)	2.44(2)	3.383(2)	162(2)	$1 + x, 3/2 - y, 1/2 + z$
II	N2–H2N···O5	0.77(2)	2.54(2)	3.073(2)	128(2)	$1 - x, 1/2 + y, 1/2 - z$
	C2–H2···O5	0.98(2)	2.58(2)	3.116(2)	115(2)	$1 - x, 1/2 + y, 1/2 - z$
	C3–H3A···O6	0.96(2)	2.63(2)	3.555(2)	163(2)	$1 - x, 1/2 + y, 1/2 - z$
	C6–H6A···O4	0.98(2)	2.59(2)	3.389(2)	140(2)	$x - 1, y, z$
III	N2–H2N···O5	0.79(2)	2.35(2)	2.963(2)	134(2)	$3 - x, y - 1/2, 3/2 - z$
	C2–H2···O3	0.96(2)	2.52(2)	3.107(2)	118(2)	$2 - x, y - 1/2, 3/2 - z$
	C2–H2···O5	0.96(2)	2.54(2)	3.133(2)	121(2)	$3 - x, y - 1/2, 3/2 - z$
	C3–H3A···O6	0.93(2)	2.58(2)	3.475(2)	159(2)	$3 - x, y - 1/2, 3/2 - z$
	C71–H712···O6	0.98	2.48	3.346(3)	165	$5/2 - x, 1 - y, 1/2 + z$
IV	C16–H16···O2	0.89(2)	2.50(3)	3.369(2)	161(2)	$1/2 + x, 3/2 - y, 1/2 + z$
	C21–H21···O3	0.96(2)	2.50(3)	3.334(2)	146(2)	$2 - x, 1 - y, -z$
	C61–H61···O4	0.98(2)	2.43(3)	3.392(2)	167(2)	$3/2 - x, 1/2 + y, 1/2 - z$

This study shows the structural features of investigated compounds in the solid state which might help in understanding the chemical reactivity and biological activity of alkyl- and arylsulfonic esters of *N*-hydroxyimides and which play a pivotal role in the design of new potentially active serine protease "suicide" inhibitors.

Experimental

Investigated compounds were synthesized according to the procedures described below. Melting points (uncorrected) were measured with a Boethius PHMK (VEB Analytik, Dresden, Deutschland) apparatus. The optical rotation was measured with a Jasco DIP 1000 polarimeter (Tokyo, Japan) at 546 nm. ^{1}H NMR spectra were recorded on a Bruker spectrometer at 500 MHz using TMS as the internal standard. Mass spectra were obtained on a Finnigan TSQ-700 instrument equipped with an electrospray ion source. MeOH containing 10^{-4} M NaCl was used as a solvent for ESI-MS measurements.

Syntheses

1-{[(4-Methylphenyl)sulfonyl]oxy}pyrrolidine-2,5-dione (I). 1-Hydroxypyrrolidine-2,5-dione (10.7 g, 93 mmol) and tosyl chloride (19.65 g, 100 mmol) were dissolved in tetrahydrofuran (100 ml) and then triethylamine (14.70 ml) was added dropwise for 20 minutes. After 40 minutes the solvent was removed *in vacuo* and 100 ml of distilled water with 3 drops of concentrated hydrochloric acid were added. The product was filtered off, washed twice with water and crystallized from ethyl acetate to give **I** (23.10 g, 92% yield). For crystallographic studies the product was recrystallized from dichloromethane by slow evaporation. mp = 143–144 °C, ESI-MS *m*/*z* 292 ([MNa]$^+$), ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.44 (s, 3H), 2.76 (s, 4H), 7.35 (d, 2H, J = 8.4 Hz), 7.87 (d, 2H, J = 8.4 Hz).

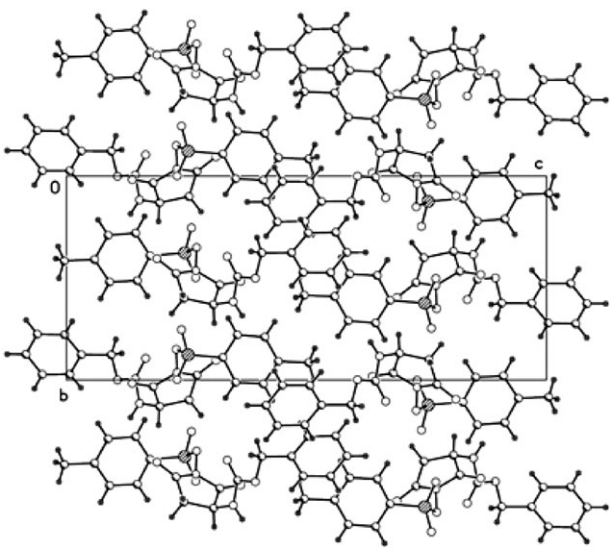

Fig. 11 The packing arrangement of **II** along the *a* axis.

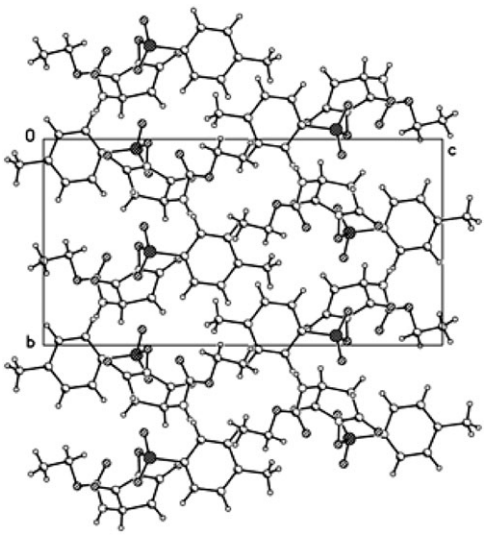

Fig. 12 The packing arrangement of **III** along the *a* axis.

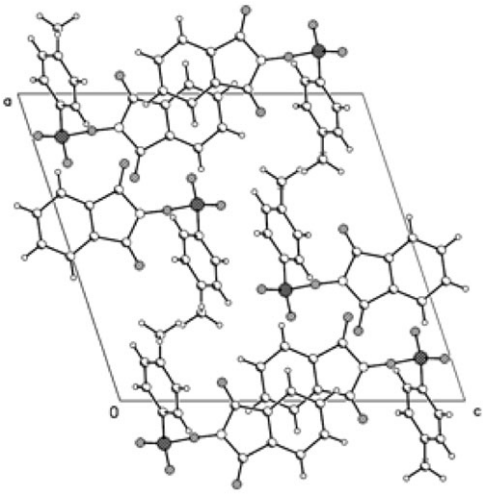

Fig. 13 The packing arrangement of **IV** along the *b* axis.

Benzyl (3*S*)-1-[(4-methylphenyl)sulfonyl]-oxy-2,5-dioxopyrrolidin-3-ylcarbamate (II). The synthesis of benzyl (3*S*)-1-hydroxy-2,5-dioxopyrrolidin-3-ylcarbamate was carried out by condensation of Cbz-L-aspartic acid anhydride (Cbz = carbobenzoxy), obtained according to the standard procedure,[27] with hydroxylamine. Cbz-L-aspartic acid anhydride (5 g, 20 mmol) was added to a solution of hydroxylamine hydrochloride $NH_3(OH)Cl$ (1.54 g, 22 mmol) and NaOH (0.83 g, 21 mmol) dissolved in 12 ml of the water–dioxane mixture (1 : 1). The solution was stirred for 15 minutes at room temperature and then for 2 h at 60 °C. Then water and dioxane were evaporated under reduced pressure and the residue was heated at 145 °C for 5 minutes *in vacuo*. The product was extracted with ethyl acetate. The extracts were evaporated and benzyl (3*S*)-1-hydroxy-2,5-dioxopyrrolidin-3-ylcarbamate (**2**) was washed with diethyl ether and dried over P_2O_5 (4 g, 75% yield, mp = 139–142 °C $[\alpha]_D^{24} = -39.8$ (*c* = 1.4, MeOH), ESI-MS *m*/*z* 287 ($[MNa]^+$). *p*-Toluenesulfonic chloride (0.87 g, 4.5 mmol) and **2** (1.12 g, 4.2 mmol) were dissolved in tetrahydrofuran (10 ml) and then triethylamine (0.67 ml) was added dropwise for 5 minutes. After 60 minutes the solvent was removed *in vacuo* and the obtained oil was dissolved in the mixture of water and ethyl acetate. The organic phase was dried with anhydrous $MgSO_4$. Product **II** crystallized after addition of pentane and was purified by crystallization from benzene–octane (1 : 1) (1.54 g, 87% of theoretical yield). Single crystals of **II** were obtained from dichloromethane. mp = 128–129 °C, $[\alpha]_D^{24} = +8.56$ (*c* = 1, MeOH), ESI-MS *m*/*z* 441 ($[MNa]^+$), ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.44 (s, 3H), 2.86 (m, 1H), 3.11 (m, 1H), 4.379 (broad s, 1H), 5.08 (s, 2H), 5.69, (broad s, 1H), 7.31 (m, 7H), 7.90 (d, 2H, *J* = 7.7 Hz).

Ethyl (3*S*)-1-[(4-methylphenyl)sulfonyl]-oxy-2,5-dioxopyrrolidin-3-ylcarbamate (III). L-Aspartic acid (40 g, 300 mmol) was dissolved in 75 ml of 4 M NaOH and 31.4 ml of ethyl chloroformate and 90 ml of 4 M NaOH were added alternately for 30 minutes. After bringing pH to 1 with conc. HCl the product was extracted with ethyl acetate. The organic phase was evaporated giving 38 g of CEt-L-aspartic acid (61.7% yield), mp = 141–142 °C, $[\alpha]_D^{24} = -3.78$ (*c* = 2.2, MeOH), ESI-MS *m*/*z* 228 ($[MNa]^+$). Next CEt-L-aspartic acid (CEt = carboethoxy) (36.30 g, 0.177 mmol) and *N*,*N*′-dicyclohexylcarbodiimide (36.52 g, 0.177 mmol) were dissolved in 30 ml of THF and incubated for 12 h at 0 °C. After filtering off the *N*,*N*′-dicyclohexylurea precipitate THF was evaporated under reduced pressure. The obtained crude anhydride (18.5 g, 99 mmol) was added to the solution of hydroxylamine hydrochloride (7.56 g, 108 mmol) in 29.6 ml of dioxane and 27.2 ml of 4 M NaOH. Reaction was carried out for one hour at 60 °C. Then water and dioxane were evaporated under reduced pressure and the residue was heated at 145 °C for 5 minutes *in vacuo*. Ethyl (3*S*)-1-hydroxy-2,5-dioxopyrrolidin-3-ylcarbamate was extracted with acetone and the solution was evaporated to dryness (ESI-MS *m*/*z* 225 ($[MNa]^+$). Attempts at crystallization of the product failed. Obtained product (9.8 g, 48.5 mmol) and *p*-toluenesulfonic chloride (10 g, 52.4 mmol) were dissolved in 150 ml of tetrahydrofuran and then 7.70 ml of triethylamine were added for 15 minutes and the solution was stirred for one hour. Then the solution was evaporated and the solid residue was washed with water. Finally 10.60 g of pure and crystalline compound **III** were obtained *via* recrystallization from ethyl acetate. mp = 137–139 °C, $[\alpha]_D^{24} = +3.89$ (*c* = 1.7 , MeOH), ESI-MS *m*/*z* 379 ($[MNa]^+$), ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.23 (t, 3H, *J* = 7.06), 2.45 (s, 3H), 2.88 (m, 1H), 3.15 (m, 1H), 4.12 (q, 2H *J* = 7.03) 4.38 (broad s, 1H), 5.30, (broad s, 1H), 7.36 (d, 2H, *J* = 8.05), 7.92 (d, 2H, *J* = 8.20 Hz).

2-{[(4-Methylphenyl)sulfonyl]oxy}-1*H*-isoindole-1,3(2*H*)-dione (IV). 2-Hydroxy-1*H*-isoindole-1,3(2*H*)-dione (5.00 g, 30.7 mmol) and *p*-toluenesulfonic chloride (5.84 g, 30.7 mmol) were dissolved in tetrahydrofuran (100 ml) and then triethylamine (5 ml) was added dropwise for 15 minutes. After 40 minutes the solvent was removed *in vacuo* and 30 ml of distilled water with 1 drop of concentrated hydrochloric acid were added. Pure product **IV** was filtered off and washed twice with water (8.85 g, 91% yield). The product **IV** was recrystallized from ethyl acetate. mp = 155–157 °C, ESI-MS *m*/*z* 340 ($[MNa]^+$), ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.48 (s, 3H), 7.39 (d, 2H, *J* = 8.2 Hz), 7.78 (m, 2H), 7. 85 (m, 2H) 7.93 (d, 2H, *J* = 8.3 Hz).

Crystallography

X-ray data were collected using an 'Xcalibur PX κ geometry diffractometer' (ω and ϕ-scans) with a graphite-monochromatized MoK_α radiation. All structures were solved by direct methods using the SHELXS97 program[28] and refined using SHELXL97.[29] The absolute configurations of **II** and **III** were defined from the Flack parameters and are equal to the stereochemistry of L-aspartic acid.

All positions of the H atoms, except hydrogens of methyl moieties of all compounds, were found from difference Fourier maps and refined isotropically with $U_{iso}(H) = 1.2U_{eq}$ (C) for aromatic, CH, and CH_2 moieties and $1.5U_{eq}$ (C) for methyl H atoms. The hydrogens from methyl groups were positioned geometrically using AFIX 137 instructions.

All figures were generated using XP[30] and Ortep for Windows.[31] The details of structure refinements and crystal data are given in Table 3. The comparison of selected angles and

Table 3 Experimental data

	I	II	III	IV
Crystal data				
Empirical formula	$C_{11}H_{11}NO_5S$	$C_{19}H_{18}N_2O_7S$	$C_{14}H_{16}N_2O_7S$	$C_{15}H_{11}NO_5S$
Molecular weight/g mol^{-1}	269.27	418.41	356.35	317.31
Crystal system	Monoclinic	Orthorhombic	Orthorhombic	Monoclinic
Space group	$P2_1/c$	$P2_12_12_1$	$P2_12_12_1$	$P2_1/n$
a/Å	9.847(3)	7.900(2)	7.764(2)	14.343(4)
b/Å	11.791(3)	10.140(3)	10.265(3)	6.654(2)
c/Å	11.014(3)	23.717(4)	19.787(4)	15.080(4)
β/°	110.58(3)			108.16(3)
V/Å^3	1197.2(6)	1899.8(8)	1577.0(7)	1367.5(7)
Z	4	4	4	4
D_{calc}/g cm^{-3}	1.494	1.463	1.501	1.541
μ/mm^{-1}	0.283	0.217	0.246	0.261
$F(000)$	560	872	744	656
Crystal size/mm	0.40 × 0.30 × 0.15	0.20 × 0.20 × 0.03	0.25 × 0.20 × 0.05	0.30 × 0.15 × 0.10
Crystal form	Block	Plate	Plate	Needle
Crystal colour	Colourless	Colourless	Colourless	Colourless
Data collection				
Monochromator	Graphite	Graphite	Graphite	Graphite
Radiation type	MoK_α	MoK_α	MoK_α	MoK_α
T/K	120(2)	100(2)	100(2)	100(2)
$2\theta_{max}$ /°	60.00	56.78	60.00	60.00
Indexes range	$-12 \le h \le 13$ $-16 \le k \le 16$ $-15 \le l \le 15$	$-10 \le h \le 10$ $-10 \le k \le 13$ $-27 \le l \le 31$	$-10 \le h \le 10$ $-14 \le k \le 14$ $-27 \le l \le 27$	$-19 \le h \le 20$ $-9 \le h \le 8$ $-20 \le h \le 21$
Absorption correction	None	None	None	None
No. of measured reflections	17 300	12 930	29 265	23 525
No. of independent reflections	3488	4431	4579	3986
No. of observed reflections ($I > 2\sigma(I)$)	3105	3822	4096	3100
R_{int}	0.0535	0.0375	0.0785	0.0714
Refinement				
Refinement on	F^2	F^2	F^2	F^2
Number of parameters	188	308	250	224
R ($F_o > 2\sigma(F_o)$)	R = 0.0423	R = 0.0333	R = 0.0422	R = 0.0563
R (all data)	R = 0.0469 w$R2$ = 0.1193	R = 0.0431 w$R2$ = 0.0657	R = 0.0525 w$R2$ = 0.0852	R = 0.0795 w$R2$ = 0.1437
GooF = S	1.059	1.023	1.055	1.157
Weighting parameter a	0.080	0.0350	0.040	0.0832
Weighting parameter b	0.357	0	0	0
	$w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, where $P = (F_o^2 + 2F_c^2)/3$			
$(\Delta/\sigma)_{max}$	0.005	0	0	0
$\Delta\rho_{max}$/eÅ^{-3}	0.44	0.21	0.33	0.62
$\Delta\rho_{min}$/eÅ^{-3}	−0.43	−0.33	−0.39	−0.44

bond distances of four investigated compounds is listed in Table 1. The geometry of hydrogen bonds and C–H···O short contacts is given in Table 2.

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