Sultam and Sultim Structures, Part 3 [1].
Strong and Weak Hydrogen Bonds in 3-Oxosultams,
3-Oxosultims and 3-Alkoxysultams

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Dedicated to Professor Dr. Klaus Schulze on the occasion of his 70th birthday

In order to study hydrogen bonding networks in cyclic sulfin- and sulfonamides, X-ray structures
were determined for 3-oxosultams 3a,c–e, 3-alkoxysultams 5b,f and 3-oxosultim 2f, all of which
show predominantly weak intermolecular hydrogen bonds. The 3-oxosultam 3a forms tetrameric
units by combining two symmetry-independent molecules through weak aromatic C-H···O-S-O hy-
drogen bonds without participation of the carbonyl groups. The 3-oxosultam 3c, with two chloro
substituents in the N-aryl ring show a polymer arrangement of the molecules through intermolecular
association of the SO2 and CO groups also with the aromatic H-atoms of the aryl rings. Sultam 3d
shows the first polymer chain in the 3-oxosultam series by the strong O-H···O=C hydrogen bonds
without participation of the SO2 group. Two new ‘head-to-head’ dimers with a 10-membered ring are
found for 3-alkoxysultams 5b,5f through weak C-H···O-S-O hydrogen bonds. In the 3-oxosultim 2f
weak intermolecular hydrogen bonds are observed to form a two-dimensional network with the two
methylene groups, the carbonyl function and the chloro atom but, surprisingly, without the strong
S-oxide acceptor group.

Key words: Sultims, Sultams, Intermolecular Hydrogen Bonds

Introduction

Isothiazol-3(2H)-ones and their metal salt com-
plexes are effective industrial microbiocides because
of their antibacterial and antifungal activities, particu-
larly the 2-octyl- and mixtures of 2-methylisothiazol-
3(2H)-one with 5-chloro analogue [2a]. Furthermore
they are reactive intermediates in the synthesis of vari-
ous organic substances [2b, c], including pharmaceuti-
cal chemicals [2d, e].

The 3-oxosultams are prepared by oxidation of
isothiazolones with CPBA or by oxidation of 3-un-
substituted isothiazoles [3 – 5]. A series of monocyclic
2-phenyl-isothiazol-3(2H)-one 1,1-dioxides were syn-
thesized by oxidation of isothiazolium perchlorates [6]
and the inhibition of the serine proteases cathepsin G,
chymotrypsin and human leukocyte elastase (HLE)
was verified [7].

We have recently described the X-ray diffraction
analysis of 3-hydroxy- and 3-hydroperoxysultims and
-sultams, which are precursors of 3-oxosultams 3 [1].

We have found a variety of intermolecular contacts
leading to ‘head-to-tail’ cyclodimers, tetramers, and
polymers with strong intermolecular S-O···H-O hy-
drogen bonds and weak C-H···O=C interactions.

In this paper, we wish to report on the synthesis
and X-ray diffraction analysis of compounds 2,3 with
sulfonyl, sulfoxide and carbonyl group which are ef-
ficient hydrogen-bonding acceptors. 3-Alkoxysultams
5 were also included in the series. Although described
in the literature [8, 9], these compounds have not been
thoroughly characterized yet.

We will show here how the three-dimensional struc-
ture of highly oxy-functionalized sultim 2 and sul-
tams 3, 5 results from noncovalent interactions be-
tween molecules with predominantly weak hydrogen
bonds.

Results and Discussion

The 2-aryl-3-oxosultams 3a [6d] and 3c–e are con-
nveniently synthesized by the oxidation of isothe-
azolium salts 1 with H₂O₂ in glacial acetic acid (80 °C, 8 h). S-oxide 2f is obtained from the rac-cis-3-hydroperoxysultim by elimination of water [2c] (Scheme 1).

The oxidation of salts 1 with magnesium monoper-oxyphthalate (MMPP-6H₂O) in alcohol (ultrasound, 50 °C) gives the 3-alkoxysultams 5b, f [8,9].

Physical properties and spectroscopic data of the novel 3-oxosultams 3c–e are described in the experimental part. The solid-state structure of the sulfonamides 3a, c–e is revealed with the aid of X-ray crystallography. The crystallographic data are presented in Table 1, selected bond distances and angles in Table 2. We compare the solid-state structure of these compounds with each other and with those of 2f [2c], 5b [8] and 5f [9].

The structure of 3-oxosultam 3a is presented in Fig. 1. The behavior of the two symmetry-independent molecules of 3a towards the hydrogen bonds varies.
One of the independent molecules forms a dimer with centrosymmetrically related molecule through intermolecular hydrogen bonds C(10)-H(10)...O(1A)-S(1A) and C(10A)-H(10A)...O(1)-S(1) (Fig. 2). The other molecule is connected to this dimeric unit by the hydrogen bond C(9)-H(9)···O(3B) and the isothiazole ring is 68.2° in 3a and 65.7° in 3a*. The 3-oxosultam 3c, with two chloro substituents at the N-aryl ring, is arranged as a polymer and indicates the intermolecular association between the O-atom of the SO2 and CO groups and the H-atoms of the aryl rings (Fig. 3). The o-chloro substituted N-aryl (79.5°) and also the 4-aryl ring (99.6°) are almost perpendicular to the isothiazole plane. Compound 3c builds up a complex three-dimensional network structure with weak hydrogen bonds. Each molecule contributes three hydrogen bonds (Fig. 3, molecule with atom S(1B)). The hydrogen bonds over the C(15)-H(15)...O(3B) form a helix along the monoclinic b-axis, caused by the

### Table 1. Crystal data and structure refinement for 3-oxosultams 3a–e.

<table>
<thead>
<tr>
<th></th>
<th>3a</th>
<th>3c</th>
<th>3d</th>
<th>3e</th>
</tr>
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<tr>
<td>Empirical formula</td>
<td>C11H10ClNO3SC16H11Cl2NO3SC16H13NO4SC17H12F3NO3S</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Formula weight</td>
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<td>368.22</td>
<td>315.33</td>
<td>367.34</td>
</tr>
<tr>
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<td>218(2)</td>
<td>213(2)</td>
<td>243(2)</td>
<td>223(2)</td>
</tr>
<tr>
<td>Crystal system</td>
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<td>orthorhombic</td>
<td>monoclinic</td>
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<tr>
<td>Space group</td>
<td>P21/c</td>
<td>P21/c</td>
<td>Pna21(1)</td>
<td>P21/n</td>
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<tr>
<td>α [°]</td>
<td>11.6206(4)</td>
<td>8.075(3)</td>
<td>7.3309(13)</td>
<td>5.2956(4)</td>
</tr>
<tr>
<td>β [°]</td>
<td>93.963(1)</td>
<td>98.314(6)</td>
<td>90.0</td>
<td>93.460(2)</td>
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<tr>
<td>γ [°]</td>
<td>90</td>
<td>90</td>
<td>90</td>
<td>90</td>
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<tr>
<td>Volume [Å³]</td>
<td>2392.72(15)</td>
<td>1600.6(10)</td>
<td>1405.8(4)</td>
<td>1602.9(2)</td>
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<tr>
<td>Absorption coeff. [mm⁻¹]</td>
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<td>0.549</td>
<td>0.249</td>
<td>0.251</td>
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<td>θ Range for data collect. [°]</td>
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<td>2.09 – 27.00</td>
<td>2.12 – 25.98</td>
<td>1.75 – 28.27</td>
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<td>Index ranges</td>
<td>h ≤ 15, k ≤ 34, l ≤ 25</td>
<td>h ≤ 9, k ≤ 12, l ≤ 14</td>
<td>h ≤ 6, k ≤ 8, l ≤ 11</td>
<td>h ≤ 6, k ≤ 8, l ≤ 11</td>
</tr>
<tr>
<td>Volume [Å³]</td>
<td>2392.72(15)</td>
<td>1600.6(10)</td>
<td>1405.8(4)</td>
<td>1602.9(2)</td>
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<tr>
<td>Density [Mg/m³]</td>
<td>1.509</td>
<td>1.528</td>
<td>1.490</td>
<td>1.522</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>SADABS</td>
<td>SADABS</td>
<td>SADABS</td>
<td>SADABS</td>
</tr>
<tr>
<td>Max./min. transmission</td>
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<td>0.30 × 0.20 × 0.20</td>
<td>0.30 × 0.20 × 0.20</td>
<td>0.80 × 0.20 × 0.10</td>
</tr>
<tr>
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<td>9229</td>
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<td>10182</td>
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<td>Independent reflections</td>
<td>5697</td>
<td>3489</td>
<td>2652</td>
<td>3864</td>
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<tr>
<td>Goodness-of-Fit on F²</td>
<td>0.916</td>
<td>1.048</td>
<td>1.139</td>
<td>1.084</td>
</tr>
<tr>
<td>Final R indices [I &gt; 2σ(I)]</td>
<td>R₁ = 0.0368</td>
<td>R₁ = 0.0307</td>
<td>R₁ = 0.0385</td>
<td>R₁ = 0.0497</td>
</tr>
<tr>
<td>wR₂ = 0.0988</td>
<td>wR₂ = 0.0823</td>
<td>wR₂ = 0.0768</td>
<td>wR₂ = 0.1166</td>
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</tr>
<tr>
<td>R Indices (all data)</td>
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<td>R₁ = 0.0379</td>
<td>R₁ = 0.0486</td>
<td>R₁ = 0.0696</td>
</tr>
<tr>
<td>wR₂ = 0.1082</td>
<td>wR₂ = 0.0865</td>
<td>wR₂ = 0.0804</td>
<td>wR₂ = 0.1244</td>
<td></td>
</tr>
<tr>
<td>Lest diff peak/hole [e Å⁻³]</td>
<td>0.32/−0.330</td>
<td>0.302/−0.256</td>
<td>0.235/−0.270</td>
<td>0.380/−0.278</td>
</tr>
</tbody>
</table>

Fig. 3. Polymer arrangement of the molecules 3c by hydrogen bonds C(15)-H(15)...O(3B) and C(3B)-H(3B)...O(2D)-S(1D).
3e

S(1)-O(1) 1.428(7) 117.4(4)
S(1)-O(2) 1.426(8) 114.7(4)
S(1)-N(1) 1.426(8) 116.1(4)
S(1)-C(3) 1.426(8) 117.4(4)
O(3)-C(3) 1.426(8) 117.4(4)
N(1)-C(1) 1.426(8) 117.4(4)
S(1)-C(8) 1.426(8) 117.4(4)
C(1)-C(16) 1.426(8) 117.4(4)
C(1)-C(2) 1.426(8) 117.4(4)

Table 2. Selected bond lengths [Å] and angles [°] for 3a-e with estimated standard deviations in parentheses.

<table>
<thead>
<tr>
<th>Bond lengths [Å]</th>
<th>Angles[°]</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(1)-O(1)</td>
<td></td>
</tr>
<tr>
<td>S(1)-O(2)</td>
<td></td>
</tr>
<tr>
<td>S(1)-N(1)</td>
<td></td>
</tr>
<tr>
<td>S(1)-C(3)</td>
<td></td>
</tr>
<tr>
<td>O(3)-C(3)</td>
<td></td>
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<tr>
<td>N(1)-C(1)</td>
<td></td>
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<tr>
<td>S(1)-C(8)</td>
<td></td>
</tr>
<tr>
<td>C(1)-C(16)</td>
<td></td>
</tr>
<tr>
<td>C(1)-C(2)</td>
<td></td>
</tr>
</tbody>
</table>

3c

S(1)-O(1) 1.429(16) 117.4(10)
S(1)-O(2) 1.428(16) 117.4(10)
S(1)-N(1) 1.428(16) 117.4(10)
S(1)-C(3) 1.428(16) 117.4(10)
O(3)-C(3) 1.428(16) 117.4(10)
N(1)-C(1) 1.428(16) 117.4(10)
S(1)-C(8) 1.428(16) 117.4(10)
C(1)-C(16) 1.428(16) 117.4(10)
C(1)-C(2) 1.428(16) 117.4(10)

Table 3. Geometric dataa for the hydrogen bonds, in the solid-state of 3-oxo-sultim 2f, 3-oxo-sultams 3a-e and 3-alkoxy-sultams 5b and 5f.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C(4E)-H(4E)···Cl(1B)</td>
<td>1.08</td>
<td>2.77</td>
<td>3.848</td>
<td>175.5</td>
</tr>
<tr>
<td>C(7F)-H(7F)···O(1E)</td>
<td>0.99</td>
<td>2.43</td>
<td>3.140</td>
<td>128.2</td>
</tr>
<tr>
<td>C(9)-H(9)···O(1B)</td>
<td>1.00</td>
<td>2.42</td>
<td>3.233</td>
<td>139.0</td>
</tr>
<tr>
<td>C(10)-H(10)···O(1A)</td>
<td>0.98</td>
<td>2.55</td>
<td>3.476</td>
<td>157.0</td>
</tr>
<tr>
<td>C(3B)-H(3B)···O(2D)</td>
<td>0.89</td>
<td>2.49</td>
<td>3.279</td>
<td>147.3</td>
</tr>
<tr>
<td>C(15)-H(15)···O(3B)</td>
<td>0.91</td>
<td>2.59</td>
<td>3.466</td>
<td>161.5</td>
</tr>
<tr>
<td>O(4)-H(4)···O(3)</td>
<td>1.15</td>
<td>1.80</td>
<td>2.829</td>
<td>145.5</td>
</tr>
<tr>
<td>C(13)-H(13)···F(2)</td>
<td>0.89</td>
<td>2.44</td>
<td>2.746</td>
<td>100.3</td>
</tr>
<tr>
<td>Cl(1H)···Cl(1O)</td>
<td>0.10</td>
<td>2.51</td>
<td>3.400</td>
<td>147.1</td>
</tr>
<tr>
<td>C(7)-H(7B)···O(3)</td>
<td>0.95</td>
<td>2.60</td>
<td>3.472</td>
<td>153.5</td>
</tr>
</tbody>
</table>

a Data calculated by using the program SHELXL [10]; b D: donor atom; A: acceptor atom.

Fig. 4. Molecular structure of 3d with labelling and displacement ellipsoids at the 50% probability level.

Fig. 5. Polymer structure of 3d with strong O-H···O=C bonds. The chains are formed by a glide plane in the space group P21/c.

21-screw axis. The symmetry connections between the atoms S(1B) and S(1), respectively S(1C) and S(1B) are -x, 0.5+y, 0.5-z. The S(1C)-atom and the S(1)-atom are transferred into each other by the translation x, 1+y, z. The third hydrogen bond is built up between the atoms C(3B)-H(3B)···O(2D)-S(1D). These hydrogen bonds are formed by the c-glide plane. The symmetry relation among S(1B) and S(1D) is x, 0.5-y, 0.5+z. By combination of the screw axis and the glide plane, the molecules with the atoms S(1) and S(1A) are situated centrosymmetrically to each other.

Interestingly, the 3-oxosultam 3d (Fig. 4 and 5), with a 2-hydroxy substituent in the N-aryl ring, forms polymer chains through strong intermolecular C=O···H-O bridges (2.829 Å) in which the 2-OH sub-
Fig. 6. Molecular structure of 3e with labelling and displacement ellipsoids at the 50% probability level.

Substituted N-aryl ring (96.1°) is perpendicular to the sultam ring (Fig. 5). The chains are formed by a glide plane in the space group \( P2_1/c \) and proceed in direction of the \( a \)-axis. The \( \text{SO}_2 \) group is not involved.

In the structure 3e (Fig. 6), only the intramolecular hydrogen bonds \( C(13)-H(13)\cdots F(2) \) and \( C(1)-H(1)\cdots O(3)-C(10) \) exist in the solid state. The N-aryl and 4-aryl ring maintain angles of 140.2° and 113.9° with the isothiazole plane.

The bicyclic 1-oxide 2f (Fig. 7) shows intermolecularly stabilized associations with participation of the allylic methylene groups, the carbonyl group, and the chloro atoms (3.139 Å and 3.848 Å) in the three further molecules. Therefore the structure exists in the two-dimensional network with hydrogen bonds. The N-aryl group is 51.0° out of the plane of the isothiazole ring. The connections of the molecules in the direction of the \( a \)-axis is built up by the atoms \( C(7F)-H(7F)\cdots O(1E)-C(1E) \) by translation, and in the \( b \)-direction with the atoms \( C(4E)-H(4E)\cdots Cl(1B) \) also by translation; the S-O bonds are not involved in the hydrogen bond system.

For a comparative study, we also investigated sultams 5b and 5f with 3-alkoxy substituents. Compound 5b forms, surprisingly, new ‘head-to-head’ dimers in the solid-state with a 10 membered ring stabilized through two interactions \( C(1)-H(1)\cdots O(2A)-S(1A) \) and \( C(1A)-H(1A)\cdots O(2)-S(1) \) related by the centre of symmetry inversion (Fig. 8).

The sultam 5f forms also centrosymmetric ‘head-to-head’ dimers. These dimers are then translated along the \( a \)-axis by the slipping-mirror-plane \( a \). For the sake of clearness, the \( p \)-chloro phenyl ring is not shown in Fig. 8. The torsion angle between the isothiazole ring and the N-aryl substituent is 9.5° in 5b and 12.7° in 5f, respectively.

Fig. 7. Two dimensional network of 2f.

In conclusion, the discussed sultams and the sultim were found to exist as centrosymmetric dimers, polymer structures and a two-dimensional network through predominantly weak intermolecular hydrogen bonds with participation of CO, \( \text{SO}_2 \), aromatic CH, CH\(_2\) groups, and also a chloro substituent.

The 3-oxosultams 3a and 3c form weak hydrogen bonds between the O-acceptor of the \( \text{SO}_2 \) group and the aromatic CH donor function of a aryl ring. If there is only one chloro substituent in the N-aryl ring, a tetrameric structure 3a is created by a second C-H\cdots O-S-O hydrogen bond, the strong O-acceptor of the CO group does not participate. In the case of two chloro substituents in the N-aryl ring and another 4-aryl substituent in 3c, the CO group forms additional hydrogen bonds with the aromatic CH function of the N-aryl ring. In 3-alkoxy sultams 5b, f, 1,1-dioxides without a CO function, intermolecular O-S-O\cdots H-C hydrogen bonds to centrosymmetric dimers are also found.

Surprisingly, a two dimensional network with one weak C=O\cdots H-CH and another Cl\cdots H-CH hydrogen bond was found in the 1-oxide 2f. The participation of the SO group, a strong hydrogen bond acceptor, could not be observed.

The 3-oxosultam 3d shows the typical polymer structure through the strong O-H\cdots O=O=C hydrogen bonds.
Experimental Section

General. M. p.: Boetius micro-melting-point apparatus; corrected. IR spectra: Genisis FTIR Unicam Analytical System (ATI Mattson); KBr pellets; values in cm$^{-1}$. $^1$H NMR: Varian Gemini-200 and Varian Unity-400; $\delta$ in ppm rel. to TMS as internal standard, $J$ in Hz. $^{13}$C NMR spectra: 50 or 100 MHz, recorded on the above-mentioned spectrometers. $^{19}$F NMR spectrum has also been measured at 188 MHz on the named spectrometer with CFCl$_3$ as standard. MS: Quadrupol-MS VG 12-250; 70 eV. Elemental analysis: Heraeus CHNO Rapid Analyzer.

Syntheses. The salts 1c–e were prepared according to the literature procedure [6d]. 1c: yield 91%, m. p. 147–148°C; 1d: yield 78%, m. p. 115–116°C; 1e: yield 73%, m. p. 101–104°C. The 1-oxide 2f is described in [2c], the 3-oxosultam 3a in [6d], and the 3-alkoxysultams 5b, f in [8, 9].
2-Aryl-5-methyl-4-phenyl-2,3-dihydro-isothiazol-3-one 1,1-dioxide (3)

H₂O₂ (0.7 ml, 30%) was added to a stirred suspension of 1 (0.26 mmol) in AcOH (0.7 ml) at 80 °C. After 8 h a colorless precipitate 3 crystallized. The crude product was washed with H₂O, recrystallized from ethanol.

2-(2,5-Dichlorophenyl)-5-methyl-4-phenyl-2,3-dihydro-isothiazol-3-one 1,1-dioxide (3c)

Yield: 56%. M. p. 143 – 145 °C. – IR (KBr): ν = 555 (CH₂), 1132s (SO₂), 1332s (SO₂), 1737s (CO). – UV (ethanol): C₁₆H₁₁Cl₂NO₃S (368.24): calcd. C 52.19, H 3.01, N 3.80, S 10.23. – 1H NMR ([D₆]-DMSO): δ: 2.55 (s, 3H, 5-CH₃), 7.56 – 7.84 (m, 8H, arom. H). – 13C NMR ([D₆]-DMSO): δ = 9.3 (5-CH₃), 127.8, 129.0, 129.5, 130.9, 131.3, 132.8, 133.0, 133.1, 133.9, 134.6, 134.9 (C-4), 145.4 (C-5), 159.3 (C-3). – MS: m/z = 368.0 (M⁺). – C₁₆H₁₃Cl₂NO₃S (368.24): calcd. C 52.19, H 3.01, N 3.80, S 10.23; found C 52.31, H 3.08, N 3.76, S 10.17; found C 52.19, H 3.01, N 3.80, S 10.23.

2-(2,5-Dichlorophenyl)-5-methyl-4-phenyl-2,3-dihydro-isothiazol-3-one 1,1-dioxide (3e)

Yield: 43%. M. p. 124 – 125 °C. – IR (KBr): ν = 1124s (SO₂), 1323s (SO₂), 1737s (CO). – UV (ethanol): λmax (lg ε): 223.0 (4.19) nm. – 1H NMR ([D₆]-DMSO): δ = 2.47 (s, 3H, 5-CH₃), 7.56 – 7.65 (m, 5H, arom. H). – 13C NMR ([D₆]-DMSO): δ = 8.8 (5-CH₃), 124.6, 127.1, 128.3, 128.8, 130.1, 130.3, 130.5, 131.1, 134.1 (C-4), 134.6, 145.3 (C-5), 159.3 (C-3). – MS: m/z = 367.0 (M⁺). – C₁₇H₁₂F₃NO₃S (367.35): calcd. C 55.49, H 3.18, N 3.98, S 8.73; found C 55.58, H 3.27, N 3.94, S 8.75.

Single crystal X-ray diffractometry

The crystals of 3a, 3e – e were obtained from acetone. The intensities were measured on a Siemens SMART CCD diffractometer. The relevant crystallographic data are listed in Table 1. The structures were solved by direct methods with SHELXS-97 [10]. The refinement was done with SHELXL-97 [10]. The details of the structure analyses have been deposited at the Cambridge Crystallographic Data Centre, CCDC-245824 for 3a, -245825 for 3c, -245826 for 3d and -245827 for 3e. The copies of the data can be obtained, free of charge, from CCDC, 12 Union Road, Cambridge, CB2 1EZ UK (fax: +44-1223-336033; e-Mail: deposit@ccdc.cam.ac.uk; internet: //www.ccdc.cam.ac.uk).

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