Photoisomerization of Sultams Derived from Saccharin; Part 3: 1,2-Dihydro[1]benzothieno[3,2-b]pyrrole 4,4-Dioxides from Dihydropyrrolo[1,2-b][1,2]benzisothiazole 5,5-Dioxides

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Dedicated to Prof. Howard E. Zimmerman on the occasion of his 75th birthday

Abstract: 1-Substituted 2,3-dihydropyrrolo[1,2-b][1,2]benzisothiazole 5,5-dioxides 7a–c,e undergo a smooth and efficient transformation into the 2,3-dihydro[1]benzothieno[3,2-b]pyrrole 4,4-dioxides 8a–c,e upon irradiation at 254 nm in acetonitrile. The structures of the products have been elucidated by spectroscopic methods and a single crystal X-ray structure determination for 8b.

Key words: photoisomerization, sultams, dihydro[1]benzothieno[3,2-b]pyrrole 4,4-dioxides

The photoreactivity of sulfonamides and sultams is dominated by S–N bond homolysis. 3,4 Among five-membered sultams, saccharin derivatives have been irradiated in solution. 1,2,5,6 For example, upon irradiation, 2,3-dihydro-3-oxo-2-propyl-[1,2]benzisothiazole 1,1-dioxide (1) in ethanol or propanol undergoes extrusion of sulfur dioxide to form N-propylbenzamide (2) by hydrogen uptake, while in benzene as solvent N-propylbiphenyl-2-carboxamide (3) is formed (Scheme 1). 5,6

Scheme 1

When the 3-oxo group is replaced by either two alkyl (or phenyl) groups or one hydrogen atom and an alkyl (or phenyl) group as in 4, a net migration of one oxygen atom from sulfur to nitrogen is observed upon irradiation at 254 nm, whereby the electrophilic substituent on the nitrogen atom (H, alkoxyethyl) is attached to this oxygen atom (Scheme 2). 1,2 Product 5 is in fact a sulfine hydroxamic acid derivative, a functional group not accessible in free form by treating hydroxylamines with sulfinyl halides or esters. 7,8

We wanted to clarify whether a similar oxygen shift as in the case 4 → 5 would also be possible with [b]fused [1,2]benzoisothiazole 5,5-dioxides 7. Compounds 7a–c have been obtained by intramolecular condensation of the oxo group with the activated methylene group adjacent to R in the side chain (Scheme 3). It soon became apparent, however, that a similar oxygen shift as outlined above did not take place. We report here the outcome of this photoreaction, which appears to be another type of reaction, being in fact a skeletal rearrangement of 7.

The amide 7e was obtained from the carboxylic acid derivative 7d (R = CO₂H), which was prepared by hydrolyzing the methyl ester 7b or the ethyl ester 7c in acetone with added 10% aqueous sodium hydroxide solution at room temperature. Upon neutralization with dilute hydrochloric acid the carboxylic acid 7d was obtained in good yield and converted into the acid chloride by boiling with excess thionyl chloride. The acid chloride in turn was refluxed with p-toluidine in anhydrous benzene to give the amide 7e. All the new synthesized compounds were unambiguously characterized by both elemental analyses and spectroscopic techniques.

The UV spectrum of the ethyl ester 7c shall be discussed briefly. In acetonitrile, two distinct structureless bands are observed: A broad band with an onset of absorption at
\[ \lambda_{\text{max}} = 400 \text{ nm} \text{ and } \lambda_{\text{max}} = 324 \text{ nm (log } \varepsilon = 4.00) \text{, and a second band (} \lambda_{\text{max}} = 250 \text{ nm, log } \varepsilon = 3.91) \text{. In benzene, the long wavelength band appears at the same wavelength and shows the same intensity as in acetonitrile. Whereas irradiation at the long wavelength absorption using Duran-filtered (} \lambda \geq 280 \text{ nm) UV light slowly gave a complex mixture of products in low yield, it had been found that selective irradiation into the short wavelength absorption band (254 nm) gave an efficient transformation (see below), which probably involves an higher excited singlet state.}

When 1-substituted 2,3-dihydropyrrolo[1,2-b][1,2]benzisothiazole 5,5-dioxides \(7a-c,e\) are irradiated with the 254 nm emission of the low-pressure mercury lamp in argon-purged acetonitrile (through a quartz jacket retaining the 185 nm emission), a smooth and efficient isomerization into the 2,3-dihydro[1]benzothieno[3,2-b]pyrrole 4,4-di-oxide derivatives \(8a-c,e\) is observed (Scheme 4). The same result was obtained using methanol as the solvent. This photochemical isomerization of \(7a-c,e\) to \(8a-c,e\) could be rationalized through the biradical \(A\) which is formed via homolytical S–N rupture. This biradical is resonance stabilized and, following rotation around the C–C bond, ring-closure occurs from conformer \(B\) producing \(8a-c,e\) (Scheme 4). No attempts have been made to trap the biradical, since intramolecular combination forming a five-membered ring seemed highly favourable. Practically it has been noticed that the more electron-withdrawing the character of the substituent \(R\), the faster the transformation of \(7\) into \(8\). This observation is in complete agreement with the proposed mechanistic pathway. By monitoring the reaction with thin layer chromatography it was found that for \(R = \text{CN (}7a\) the shortest time was needed for the appearance of the irradiation product in the reaction medium, and the rate of conversion and the percent yield of the product (based on the consumed starting material) was higher than that of the esters \(7c,b\), followed by the amide derivative \(7e\), which was photolyzed very slowly. The low yield (22% with 63% recovery of \(7e\) and the long time of irradiation required for the amide \(7e\) may be rationalized not only by the low electron-withdrawing effect of the amide group (especially, if the \(N\)-substituent was aromatic) but also, by the steric influence of the phenyl group which might have hindered the final ring-closure. Moreover, the presence of the \(N\)-phenyl group may cause a retardation due to absorption of some of the incident UV light.

The structures of \(8a-c,e\) may be delineated primarily from the mass spectral and NMR data but are firmly supported by a single crystal X-ray structure determination for compound \(8b^{10}\) (Figures 1 and 2, Table 1).
Due to the formation of a new stereogenic centre (C-3a) in 8, the A₃X₂ pattern of the CH₂–CH₂ fragment in the nearly planar 7 is changed into a complicated pattern in 8 giving rise to the occurrence of several multiplets, one of which overlaps with the resonances of the diastereotopic ester methylene protons (in 8b). An attempt to resolve all multiplets has not been made. Thus, the ¹H NMR spectrum of 7b shows two triplets at δ = 3.33 and 3.81 for 2 H at C-2 and 2 H at C-3, respectively. These four protons in the product 8b are all under different environments, thus a pattern of four multiplets at δ = 2.62, 2.93, 4.33 and 4.65 is obtained. Also, the ¹³C NMR of 8b reveals a new sp³ carbon signal at δ = 82.0 attributable to the new quaternary stereogenic centre (C-3a). The analogous products 8a,c,e likewise show a quaternary carbon at δ = 70.1, 82.2, and 83.5, respectively. In the infrared spectra, the carbonyl absorption band in 7b (being an α,β-unsaturated ester) at 1706 cm⁻¹ was shifted by 19.0 cm⁻¹ towards higher wavenumber and appeared at 1725 cm⁻¹ in 8b as a typical value for normal esters.

In summary, we have found a remarkably clean light-induced transformation of pyrrolo[1,2-b][1,2]benzothiazole 5,5-dioxides into [1]benzothieno[3,2-b]pyrrole 4,4-oxides. The formally related case of formation of 3,4-benzo-2-thia-6-azabicyclo[3,2,0]hepta-3,6-dienes initiated by [2+2] photocycloaddition of electron-rich alkynes to 1,2-benzothiazoles,¹¹ has been interpreted in a different way, however.

The NMR spectra were recorded on Bruker WM 300 and DRX 500 spectrometers (300 MHz and 500 MHz, respectively for ¹H, 75 and 125 MHz, respectively, for ¹³C) using TMS as internal standard and the deuterated solvent as lock. IR spectra were obtained by using a Perkin-Elmer 983 spectrophotometer (m: medium intense, s: strong). Electron impact ionisation mass spectrometry (EIMS) was performed on a Varian AMD 604 instrument using 70 eV ionization energy. Melting points (mp) are uncorrected. All the chromatographic separations were performed on 48 × 20 cm glass plates covered with an air-dry layer (1 mm thick) of silica gel (Merck Kieselgel PF₂₅₄). Reactions were monitored by TLC.

![Figure 1](image1.png)

**Figure 1** ORTEP-plot of molecular structure of 8b in the crystal (the crystallographic numbering does not reflect the systematic numbering)

![Figure 2](image2.png)

**Figure 2** Stereo-view of crystal packing of 8b

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Selected Bond Lengths and Angles of Compound 8b in the Crystal (The Crystallographic Numbering does not Reflect Systematic Numbering)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bond Lengths (pm)</td>
<td>Bond Angles (°)</td>
</tr>
<tr>
<td>C8–S</td>
<td>181.93 (16)</td>
</tr>
<tr>
<td>C8–C7</td>
<td>152.8 (2)</td>
</tr>
<tr>
<td>C8–C9</td>
<td>152.8 (2)</td>
</tr>
<tr>
<td>C8–C11</td>
<td>153.24 (2)</td>
</tr>
<tr>
<td>C7–N</td>
<td>126.83 (2)</td>
</tr>
<tr>
<td>C1–S</td>
<td>176.46 (16)</td>
</tr>
<tr>
<td>C10–N</td>
<td>148.22 (21)</td>
</tr>
<tr>
<td>C9–C8–S</td>
<td>119.27 (0.119)</td>
</tr>
<tr>
<td>C7–C8–C11</td>
<td>110.72 (0.12)</td>
</tr>
<tr>
<td>C7–C8–C7</td>
<td>102.19 (0.10)</td>
</tr>
<tr>
<td>C9–C8–C7</td>
<td>100.10 (0.12)</td>
</tr>
<tr>
<td>C6–C7–C8</td>
<td>113.67 (0.13)</td>
</tr>
<tr>
<td>C8–C7–N</td>
<td>115.07 (0.14)</td>
</tr>
<tr>
<td>C9–C10–N</td>
<td>105.69 (012)</td>
</tr>
<tr>
<td>C7–N–C10</td>
<td>107.47 (013)</td>
</tr>
</tbody>
</table>
N-Substituted 1,2-benzoisothiazol-3(2H)-one 1,1-dioxides 6a–c were prepared following the literature procedure. 3

2.3-Dihydro[1,2-b]benzoisothiazole 5,5-Dioxides 7a–c; General Procedure
To a solution of NaOH (0.07 mol) in tert-butyl alcohol (100 mL) at 110 °C was added powdered 6a–c (0.035 mol) in one lot. The reaction mixture was kept at 110 °C for 20–25 min, then poured into concd HCl–ice mixture. The resulting solid was filtered, washed with H2O, and air-dried.

2.3-Dihydro[1,2-b][1,2]benzoisothiazole-1-carbonitrile 5,5-Dioxide (7a)
Colorless solid (2.1 g, 23%); mp 227 °C (EtOH). UV (MeCN): λmax (log ε) = 3337 (s), 1648 (s) cm⁻¹.
IR (KBr): ν = 2242 (m), 1653 (m), 1337 (s). MS: m/z (%) = 340 (M⁺, 100), 234 (100), 164 (8), 75 (9). Anal. Calcd for C16H12N2O2S: C, 63.20; H, 4.64; N, 8.12; S, 9.23.

Photoconversion of 2,3-Dihydro[1,2-b]benzoisothiazole 5,5-Dioxides 7a–c into Dihydro[1]benzothieno[3,2-b]pyrrole 4,4-Dioxides 8a–c; General Procedure
Samples of 7a–c (1.1 mmol each) in MeCN (80 mL) were irradiated for the time listed using a quartz immersion well in connection with a Hanau TNN 15 low pressure mercury lamp (15W input) with continuous argon purging. After concentration the residue was chromatographed on two silica gel plates with EtOAc–hexane (1:1). The Rf values of the appropriate zones are given below.

7b
Methyl 2,3-Dihydro[1,2-b][1,2]benzoisothiazole-1-carboxylate 5,5-Dioxide (7b)
Colorless crystals (0.95 g, 21%); mp 181 °C (MeOH). UV (MeCN): λmax (log ε) = 250 (3.67), 324 nm (3.65).

7c
Methyl 2,3-Dihydro[1,2-b][1,2]benzoisothiazole-1-carboxylate 5,5-Dioxide (7c)
Colorless crystals (2.92 g, 54%); mp 153 °C (EtOH). UV (MeOH): λmax (log ε) = 250 (3.91), 324 nm (4.03).

2.3-Dihydro[1,2-b][1,2]benzoisothiazole-1-carboxylic Acid 5,5-Dioxide (7d)
A 10% aq NaOH solution (0.5 mL) was added to a solution of 1.00 g (3.80 mmol) of the methyl ester 7b (or the ethyl ester 7e) in acetonitrile (5 mL) at 0 °C. Then the mixture was stirred at r.t. for 4 h (TLC-monitoring) and H2O (50 mL) was added. The resulting clear solution was neutralized with dil. HCl and the precipitate was collected by filtration and washed with H2O.

Colorless crystals (0.89 g, 89%); mp 227 °C (EtOH).

IR (KBr): ν = 3200s–2800s (br, OH), 1676s (C=O) 1318s, 1177s (SO2) cm⁻¹.

7e
Ethyl 2,3-Dihydro[1,2-b][1,2]benzoisothiazole-1-carboxylate 5,5-Dioxide (7e)
Colorless crystals (2.92 g, 58%); mp 153 °C (EtOH). UV (MeOH): λmax (log ε) = 250 (3.91), 324 nm (4.03).

2.3-Dihydro[1,2-b][1,2]benzoisothiazole-1-carboxylate 5,5-Dioxide (7f)
A mixture of 7e (1.00 g, 91%) and excess SOCl2 (5 mL) was refluxed for 4 h at 85–90 °C. Then the unreacted SOCl2 was evaporated in vacuo to give the crude acid chloride as a pale yellow solid which was used directly in the next step. A mixture of the acid chloride (0.86 g, 3.2 mmol) and p-toluidine (0.34 g, 3.18 mmol) was refluxed for 4 h (TLC-monitoring) in anhyd benzene (50 mL). The solvent was evaporated completely in vacuo and the residue was washed several times with 10% aq NaHCO3 solution, then with H2O, and air-dried.

Pale yellow crystals (0.81 g, 74%); mp 219–220 °C (EtOH). UV (MeCN): λmax (log ε) = 250 (4.21) 340 nm (4.29).

IR (KBr): ν = 3337s (NH), 1648s (C=O), 1337s (SO2) cm⁻¹.

1H NMR (CDCl3): δ = 3.81 (s, 3 H, OCH3), 2.93 (m, 1 H, 3-H), 2.62 (m, 2 H, 3-H), 2.21 (s,3 H, CH3).

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IR (KBr): ν = 1725 s (C=O), 1648 m (C= N), 1515 s, 1153 s (SO2) cm⁻¹.

1H NMR (CDCl₃): δ = 7.95 (m, 1 H, aryl-H), 7.85 (m, 1 H, aryl-H), 7.75 (m, 2 H, aryl-H), 4.65 (m, 1 H, 2-H), 4.25 (m, 3 H, 2-H and OCH3CH3 overlap), 2.91 (m, 1 H, 3-H), 2.82 (m, 1 H, 3-H), 1.15 (t, 3 H, J = 7.0 Hz).

13C NMR (CDCl₃): δ = 168.2, 164.1, 148.0, 134.1, 133.0, 132.0, 124.1, 122.5, 82.2, 67.2, 64.1, 30.2, 14.1.

MS: m/z (%) = 136 (M+ , 25), 135 (100), 133 (44), 130 (21), 129 (100), 128 (21), 124 (1), 122 (16), 115 (86), 101 (73), 89 (22), 77 (14).

Anal. Calcd for C₁₃H₁₃NO₄S (279.23): C, 55.91; H, 4.65; N, 5.01; S, 11.29.

Crystal data and structure refinement: Crystal size 0.55 × 0.24 × 0.18 mm, from MeOH. C₁₂H₁₁NO₄S, formula weight 279.23. Triclinic system, P–1. Unit cell dimensions: a = 6.923(2), b = 7.126(2), c = 12.471(3) Å; α = 82.67(2), β = 78.60(2), γ = 73.52(2)°; Z = 4, cell volume 576.6(3) Å³, $d_v = 1.528$ g cm⁻³, $\mu = 0.1703$ Å⁻¹ (MoKα), $\mu = 0.287$ mm⁻¹. F(000) = 276, $\Theta = 2.99–27.00°$, limiting indices −8 ≤ h ≤ 0, −9 ≤ k ≤ 8, −15 ≤ l ≤ 15. A Siemens P4RA four-circle diffractometer with graphite monochromator and scintillation counter was used to collect 2728 reflections, 2514 of which were unique (R = 0.0204). ψ-Scan, transmission range 0.884–0.794. Refinement method: Full-matrix least-squares on F². 2514 data, 165 parameters. Goodness of fit on F² 1.082, final R indices, all data (I ≥ 2σ(I)), R1 = 0.0361 (0.0323), wR2 = 0.0885 (0.0855). Extinction coefficient: 0.013(3). Residual electron density between −0.367 and 0.445 eÅ⁻³. The programs SHELXS-97 for crystal structure solution and SHELXL-97 for crystal structure refinement by Sheldrick, G. M., University of Göttingen, Germany, 1997 have been used. All crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-152473. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

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References


(10) Crystal data and structure refinement: Crystal size 0.55×0.24×0.18 mm, from MeOH. C₁₂H₁₁NO₄S, formula weight 265.28. Triclinic system, P–1. Unit cell dimensions: a = 6.923(2), b = 7.126(2), c = 12.471(3) Å; α = 82.67(2), β = 78.60(2), γ = 73.52(2)°; Z = 4, cell volume 576.6(3) Å³, $d_v = 1.528$ g cm⁻³, $\mu = 0.1703$ Å⁻¹ (MoKα), $\mu = 0.287$ mm⁻¹. F(000) = 276, $\Theta = 2.99–27.00°$, limiting indices −8 ≤ h ≤ 0, −9 ≤ k ≤ 8, −15 ≤ l ≤ 15. A Siemens P4RA four-circle diffractometer with graphite monochromator and scintillation counter was used to collect 2728 reflections, 2514 of which were unique (R = 0.0204). ψ-Scan, transmission range 0.884–0.794. Refinement method: Full-matrix least-squares on F². 2514 data, 165 parameters. Goodness of fit on F² 1.082, final R indices, all data (I ≥ 2σ(I)), R1 = 0.0361 (0.0323), wR2 = 0.0885 (0.0855). Extinction coefficient: 0.013(3). Residual electron density between −0.367 and 0.445 eÅ⁻³. The programs SHELXS-97 for crystal structure solution and SHELXL-97 for crystal structure refinement by Sheldrick, G. M., University of Göttingen, Germany, 1997 have been used. All crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-152473. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.