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STRUCTURE OF 2,6-DINITROPHENYLSULFANYLETHANENITRILE AND 2,4,6-TRINITROPHENYLSULFANYLETHANENITRILE AND THEIR RING CLOSURE GIVING 2-CYANO BENZO[*d*]THIAZOLE-3-OXIDES

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Abstract – The base-catalysed ring closure of 2,6-dinitrophenylsulfanylethanenitrile and 2,4,6-trinitrophenylsulfanylethanenitrile gives 2-cyano-7-nitrobenzo[*d*]thiazole-3-oxide and 2-cyano-5,7-dinitrobenzo[*d*]thiazole-3-oxide, respectively. Structure of the starting phenylsulfanyl-ethanenitriles has been studied both in crystal and in solution.

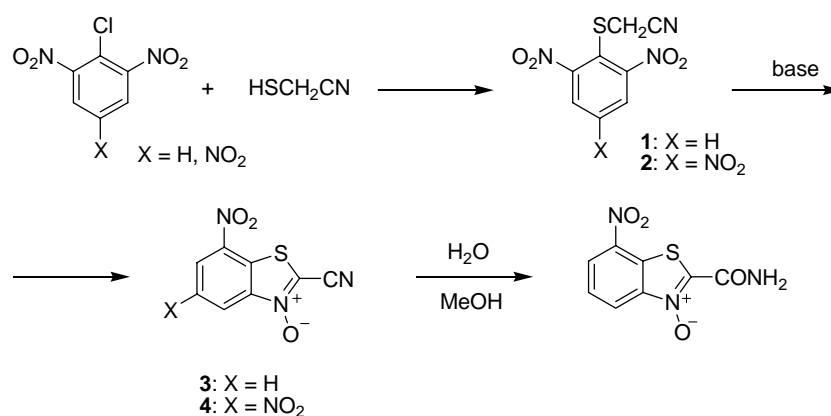
INTRODUCTION

The structure of substituted methyl 2-nitrophenylsulfanylethanoates was studied by us earlier^{1,2} in the context of their ring closure giving substituted 2-methoxycarbonylbenzo[*d*]thiazole-3-oxides.³⁻⁵ Whereas methyl 2,6-dinitrophenylsulfanylethanoate readily undergoes ring closure by action of bases, giving 2-methoxycarbonyl-7-nitrobenzo[*d*]thiazole-3-oxide, the isomeric 2,4-dinitro derivative does not,^{3,4} although the electronic effect of nitro groups at *o*- and *p*-positions upon the acidity of –SCH₂COOCH₃ group must be very similar. The different behaviour of the two compounds mentioned was explained^{4,5} by entropic effects: Nitro groups at 2- and 6-positions enforce the side chain conformation in which the methylene group gets very close to the *o*-nitro group attacked. This hypothesis was confirmed on the basis of X-ray diffraction analysis of methyl dinitrophenylsulfanylethanoates and structurally similar compounds; in addition, it was found out that the *ortho*-standing nitro group is deviated from the plane of ring so much that it enables an intramolecular attack of nucleophile (carbanion) at a direction virtually perpendicular to the plane of the nitro group.

What has been said above is also experimentally confirmed by the fact that the ring closure also takes place with the 2-nitro derivatives carrying 6-substituents of only slightly electron-acceptor nature (Cl, Br) or even mildly electron-donor substituents (CH₃, CH(CH₃)₂). The aim of this work is to study the structure of nitrophenylsulfanylethanenitriles and products of their base-catalysed ring closure.

RESULTS AND DISCUSSION

Purity of all the substances prepared (Scheme 1) was confirmed by elemental analyses and by ¹H and ¹³C NMR spectra. In the case of the starting compounds (**1** and **2**) their crystal structure was also studied by means of X-ray.



Scheme 1

The crystal data and refinement parameters are summarized in Table 1.

ORTEP⁶ views of the five independent molecules of compound **1** and of the molecule of compound **2** are shown in Figures 1-3. Compound **1** displays an uncommon crystal structure where the asymmetric unit is built up by five independent molecules with different conformations of -S-CH₂-C≡N side chain and different rotations of *ortho*-nitro groups (Figures 1, 2). In spite of these various conformations all five molecules show short interactions between sulfur S1 and oxygens of nitro groups at distance of about 3 Å, shorter than sum of van der Waals radii of 3.25 Å. These short S···O contact distances can be ascribed to a hypervalent interaction between a pair of electrons in a filled *p*-orbital from a nitro oxygen with an empty *d* sulfur orbital.^{7,8} The molecule of compound **2** (Figure 3) shows a side chain conformation similar to those observed in conformers **1b** and **1c**, and intramolecular S···O distances of 3.062(3) and 3.219(3) Å. In all molecules both the *ortho*-nitro groups are essential to maintain short S···O contacts which are responsible for an approaching of methylenic C7H₂ group to O1 oxygen of nitro group. Accordingly, all these conformations represent an incipient transition state toward the formation of the benzothiazole ring.²

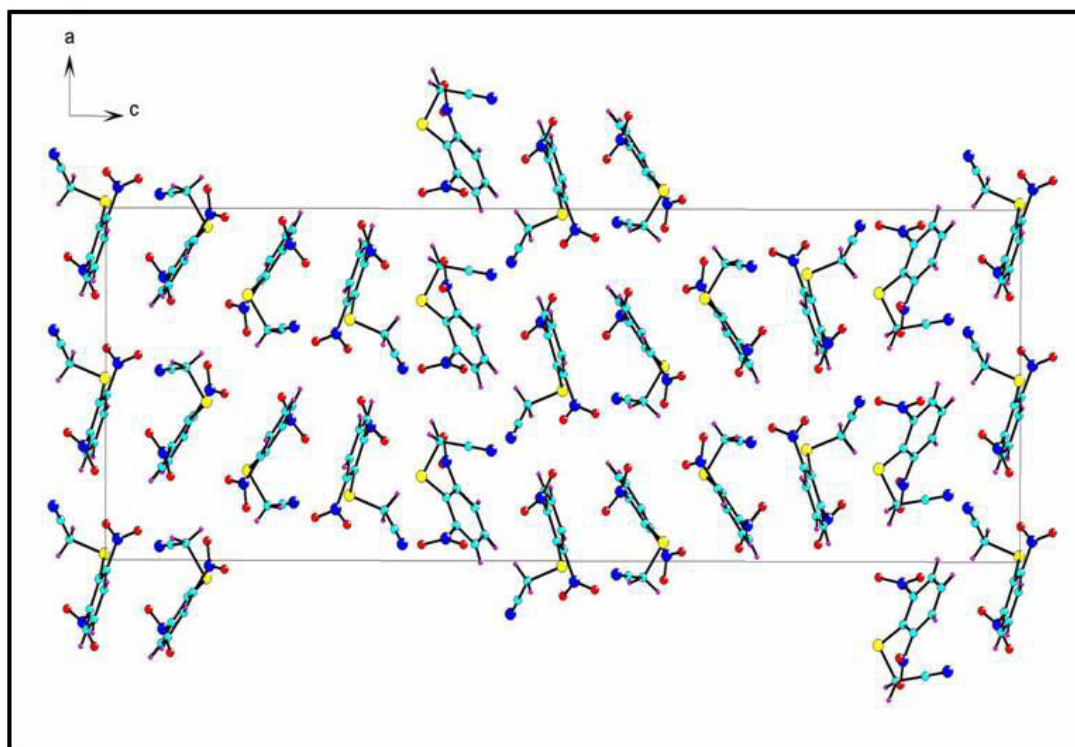


Figure 1. The unit cell of compound **1** viewed down the crystallographic *b* axis.

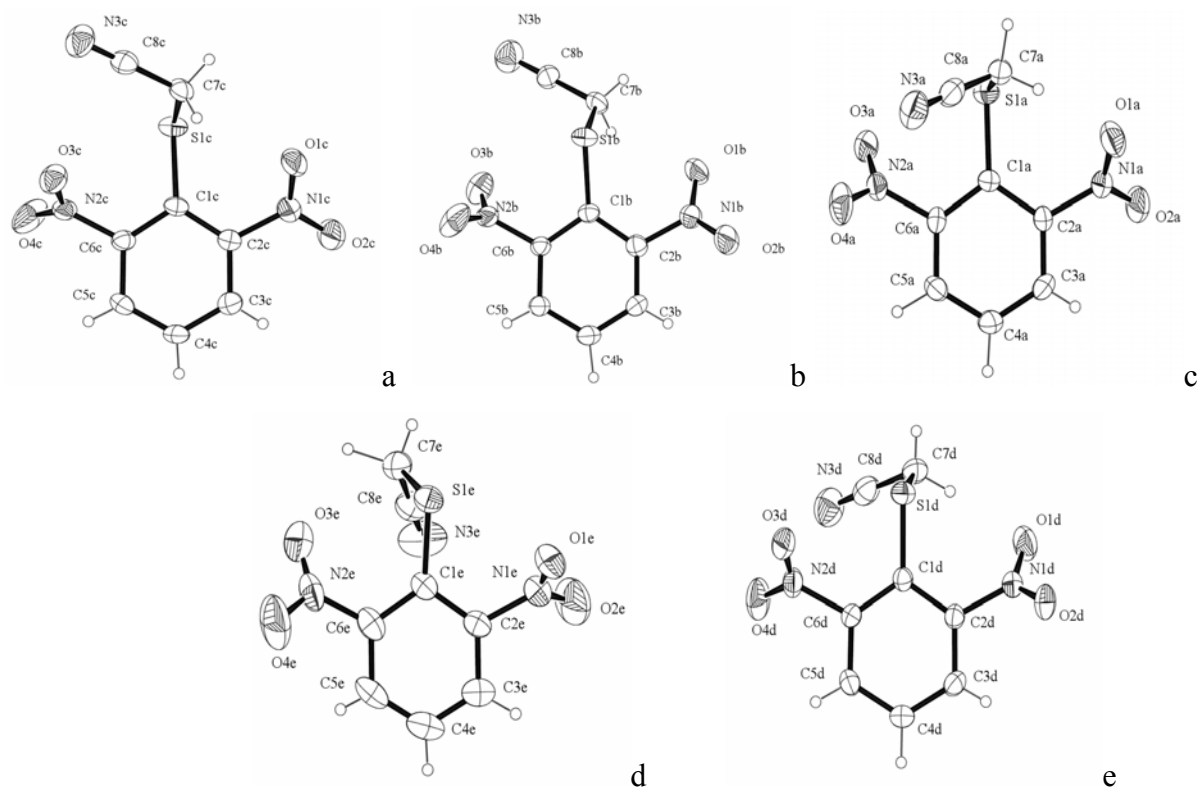


Figure 2. ORTEP views of the five independent conformers **a-e** of molecule **1** in the asymmetric crystal unit. Thermal ellipsoids are drawn at 30% probability level.

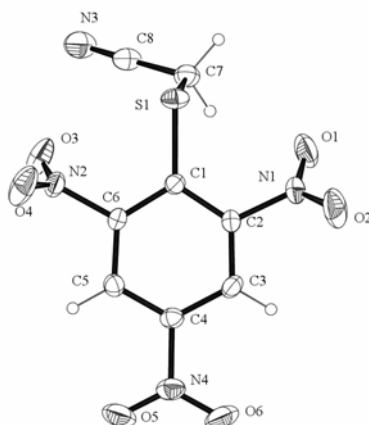


Figure 3. ORTEP view of compound **2**. Thermal ellipsoids are drawn at 30% probability level.

In some molecules the $-C7H_2 \cdots O1$ approach is determined by intramolecular $C-H \cdots O$ hydrogen bonds, as in **1a**, **1d** and **2**, and by simple $C7 \cdots O$ electrostatic interactions in the others. The methylenic $-C7H_2$ hydrogens, not implied in intramolecular hydrogen bonds, are sufficiently acidic to form an extended network of intermolecular $C-H \cdots O$ hydrogen bonds.

Table 1. Crystal data.

Compound	1	2
Formula	$C_8H_5N_3O_4S$	$C_8H_4N_4O_6S$
M	239.21	284.21
System	Orthorhombic	Orthorhombic
Space Group	$Pna2_1$	$Pna2_1$
a/Å	15.1600(1)	12.4631(3)
b/Å	7.5840(1)	13.9687(4)
c/Å	44.3217(5)	6.6276(1)
U/Å ³	5095.8(1)	1153.8(1)
Z	20	4
$D_c/g\text{ cm}^{-3}$	1.559	1.636
T/K	295	295
μ/cm^{-1}	3.20	3.12
$\theta_{\min}-\theta_{\max}/^\circ$	3.7-27.0	4.4-30.0
Unique Refl.ns	10490	3181
R_{int}	0.054	0.032
Observed Refl.ns [$I > 2\sigma(I)$]	6199	2981
R (Obs. Refl.ns)	0.0464	0.0489
wR (All Refl.ns)	0.1110	0.1299
S	0.99	1.08
$\Delta\rho_{\max}; \Delta\rho_{\min}/e\text{ \AA}^{-3}$	0.21;-0.20	0.47;-0.19

The base-catalysed ring closure of nitrophenylsulfanylethanenitriles **1** and **2** gives quantitative yields of substituted 2-cyanobenzo[*d*]thiazole-3-oxides **3** and **4** (Scheme 1). In the case of compound **2**, subsequent solvolysis of nitrile group to amide **5** was observed in the most basic buffers used (*N*-methylpiperidine buffers) during prolonged reaction times (Figure 4) even if the methanol adopted had been dried with magnesium.

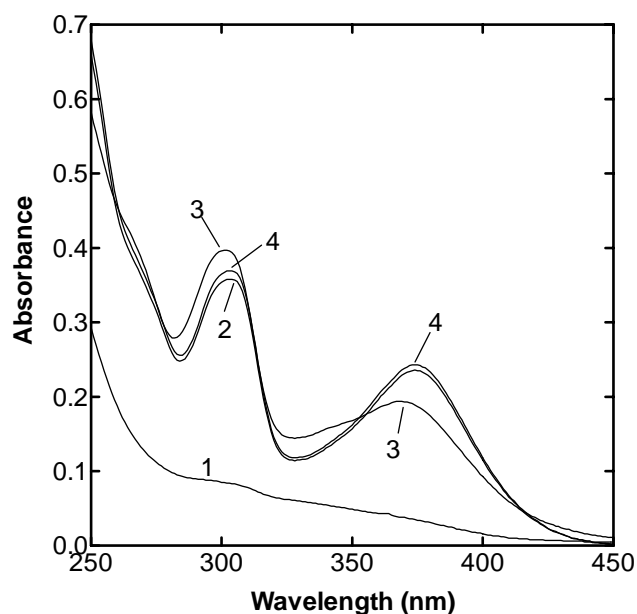


Figure 4. UV-VIS spectra: 1 – compound **1**, 2 – reaction mixture after 9-min reaction period, 3 – reaction mixture after another 40-min reaction period, 4 – product of ring closure, compound **3**; in all the cases: basic methanolic buffer *N*-methylpiperidine – *N*-methylpiperidinium chloride 4:1, concentration of base 0.4 M, concentrations of the substances measured $4.2 \cdot 10^{-5}$ M, temperature 25 °C.

The spectrum 2 of the reaction mixture recorded after a 9-min reaction period in the buffer mentioned shows that almost all the compound **1** has been transformed to product **3**. After another 40-min period the nitrile group is hydrolysed to a considerable extent (Figure 4, spectrum 3). Spectral recording of the ring closure course of compound **1** in a more acidic *N*-methylpiperidine buffer is shown in Figure 5, wherefrom it is obvious, that in the more acidic *N*-methylpiperidine buffer (ratio of the buffer components is 1:1) the ring closure is not complicated by subsequent hydrolysis of the nitrile, and similar situation is also observed in the buffers *N*-methylmorpholine – *N*-methylmorpholinium chloride (the pK_a values of *N*-methylpiperidinium chloride and *N*-methylmorpholinium chloride in methanol at 25 °C are 11.05 and 9.12, respectively). The only products of the base-catalyzed reactions under these conditions are substituted 2-cyanobenzo[*d*]thiazole-3-oxides.

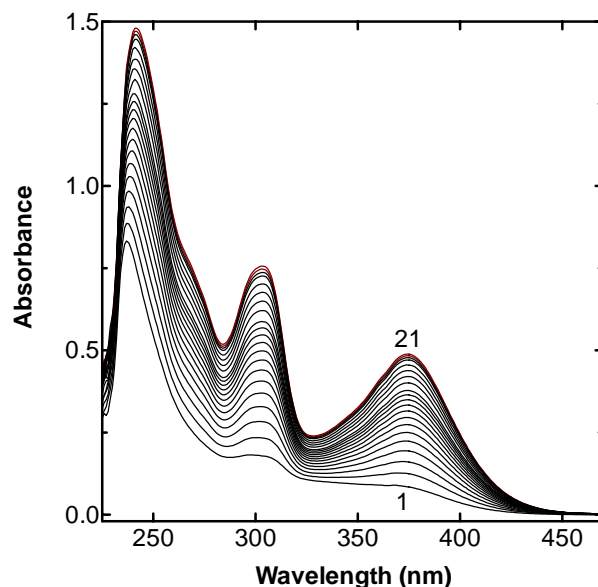


Figure 5. Spectral recording of ring closure kinetics of compound **1** in *N*-methylpiperidine buffer 1:1 at 25 °C. Concentration of *N*-methylpiperidine 0.08 M. Spectrum 1 was measured 5 s after injecting solution of compound **1** into the buffer, spectra 2-13 were measured in the intervals of 20 s, spectra 14-17 in the intervals of 50 s, and spectra 18-21 in the intervals of 100 s.

EXPERIMENTAL

The NMR spectra were measured using Bruker Avance 500 (500.13 MHz for ^1H , and 125.77 MHz for ^{13}C). Hexamethyldisiloxane was used as the internal standard for ^1H (δ 0.05). The ^{13}C NMR spectra were standardised by means of the middle signal of the solvent multiplet (δ 77.0 in CDCl_3). The ^{13}C NMR spectra were measured in standard way and by means of the APT pulse sequence.

Melting points were determined with a Kofler hot-stage microscope and were not corrected. The microanalyses were carried out with a FISON EA 1108 automatic analyser.

The crystal data for compounds **1** and **2** were collected at room temperature using a Nonius Kappa CCD diffractometer with graphite monochromated Mo-K α radiation and corrected for Lorentz and polarization effects. The structures were solved by direct methods (SIR97⁹) and refined using full-matrix least-squares. All non-hydrogen atoms were refined anisotropically and hydrogens isotropically. All the calculations were performed using SHELXL-97¹⁰ and PARST¹¹ implemented in WINGX¹² system of programs. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC-669330 and 669331. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Compounds:

2,6-Dinitrochlorobenzene and 2,4,6-trinitrochlorobenzene were prepared according to Refs.^{13,14} *S*-Acetylsulfanylethanenitrile and sulfanylethanenitrile were prepared by the procedures described in Ref.¹⁵

2,6-Dinitrophenylsulfanylethanenitrile (1) was prepared by reaction of 2,6-dinitrochlorobenzene (2.50 g, 14.8 mmol) with sulfanylethanenitrile (1.50 g, 14.8 mmol) in 1,2-dimethoxyethane (50 mL) and triethylamine (1.75 mL, 14.8 mmol in 5 mL 1,2-dimethoxyethane) for a period of 3.5 h. The mixture was stirred at rt for another 1h, poured into 100 mL diluted HCl (ca 10 %), and the product was extracted with Et₂O. The solvent was distilled off, and the residue (2.00 g) was separated by column chromatography (silica gel, CHCl₃ – EtOAc 7:1 v/v). 2,6-Dinitrophenylsulfanylethanenitrile (**1**) (R_F 0.5) was recrystallized from a mixture of benzene and cyclohexane, yield 0.77 g (26 %), mp 58-59 °C. ¹H NMR (δ/ppm, CDCl₃): 8.01 (A₂ part), 7.81 (B part) A₂B system (3H, ³J=8.0 Hz (Ar)), 3.84 (s, 2H, (CH₂)). ¹³C NMR (δ/ppm, CDCl₃): 155.6 (C-2,6), 132.7 (C-4), 127.1 (C-3,5), 118.4 (C-1), 114.2, (CN), 22.1 (CH₂). *Anal.* Calcd for C₈H₅N₃O₄S: C, 40.17; H, 2.11; N, 17.57; S, 13.41. Found C, 40.25; H, 2.10; N, 17.50; S, 13.63.

2,4,6-Trinitrophenylsulfanylethanenitrile (2) was prepared from 2,4,6-trinitrochlorobenzene (2 g, 8.08 mmol in 25 mL 1,2-dimethoxyethane) and sulfanylethanenitrile (0.59 g, 8.08 mmol in 25 mL 1,2-dimethoxyethane) and pyridine (0.74 mL, 9 mmol in 15 ml 1,2-dimethoxyethane) under argon atmosphere for a period of 5.5 h. After another 15 min, the mixture was acidified (25 mL 2% aqueous HCl) and extracted with CH₂Cl₂. The crude product was recrystallized from a mixture of EtOAc and heptane (1:3 v/v). Yield 1.10 g (48 %), mp 104.5 – 106 °C. ¹H NMR (δ/ppm, CDCl₃): 8.85 (s, 2H (H-3,5)), 3.87 (s, 2H (CH₂)). ¹³C NMR (δ/ppm, CDCl₃): 154.5 (C-2,6), 148.8 (C-4), 126.0 (C-1), 122.5 (C-3,5), 116.4 (CN), 22.0 (CH₂). *Anal.* Calcd for C₈H₄N₄O₆S: C, 33.81; H, 1.42; N, 19.71; S, 11.28. Found: C, 33.75; H, 1.60; N, 19.52; S, 11.42.

2-Cyano-7-nitrobenzo[d]thiazole-3-oxide (3) was prepared from 2,6-dinitrophenylsulfanylethanenitrile (**1**) (110 mg, 0.46 mmol) in MeOH (10 mL) by action of *N*-methylpiperidine buffer (25 mL) in MeOH (1:2 acidic; the concentration of base 0.05 M). After 20 min stirring at rt, the mixture was poured into aqueous HCl (25 mL, 10%) and extracted with Et₂O. The crude product (70 mg, mp 168-178 °C) was purified chromatographically (silica gel, CHCl₃ – EtOAc, 7:1 v/v). Yield, 60 mg (57 %), mp 174-175 °C. ¹H NMR (δ/ppm, CDCl₃): 8.71 (dd, 1H, (H-4, ³J=8.0 Hz, ⁴J=1.0 Hz)), 8.60 (dd, 1H, (H-6), ³J=8.0 Hz, ⁴J=1.0 Hz)), 7.93 (t, 1H, (H-5, ³J=8.0 Hz)). ¹³C NMR (δ/ppm, CDCl₃): 143.8, 142.7, 132.3, 124.7 (4×C_q), 129.2, 127.6, 125.6 (3×CH), 109.1 (CN). *Anal.* Calcd for C₈H₃N₃O₃S: C, 43.44; H, 1.37; N, 19.00; S, 14.50. Found: C, 43.52; H, 1.49; N, 18.73; S, 14.42.

2-Cyano-5,7-dinitrobenzo[d]thiazole-3-oxide (4) was prepared in the same way as compound **3** with application of triethylamine as the base. Yield 56 %, mp 209.5-211 °C. ¹H NMR (δ/ppm, CDCl₃): 9.28 (d, 1H (H-6, ⁴J = 2.0 Hz)), 9.14 (d, 1H (H-4, ⁴J = 2.0 Hz)). ¹³C NMR (δ/ppm, CDCl₃): 147.2, 142.8, 142.4,

130.2, 121.2 (4×C_q), 121.4, 119.1 (2×C_t), 109.7 (CN). *Anal.* Calcd for C₈H₂N₄O₅S: C, 36.10; H, 0.76; N, 21.05; S, 12.04. Found: C, 36.06; H, 0.96; N, 20.86; S, 11.90.

2-Aminocarbonyl-7-nitrobenzo[d]thiazole-3-oxide (5) was prepared at the conditions of kinetic experiments and also by independent synthesis. A solution of **1** (100 mg, 0.42 mmol) and *N*-methylpiperidine (2 mL, 16.5 mmol) in MeOH (20 mL) was stirred at rt for 4 h, whereupon the mixture was acidified with ca 5% aqueous HCl (50 mL) and extracted with CH₂Cl₂. The extract was shaken with water, and then the organic layer was separated, dried, and the solvent was distilled off in vacuum. Yield 21 mg (21 %) 2-aminocarbonyl-7-nitrobenzo[d]thiazole-3-oxide (**5**), Mp >265 °C (decomp.).

A solution of methyl 2,6-dinitrophenylsulfanylethanoate (300 mg, 1.1 mmol) in MeOH (25 mL) was treated with aqueous ammonia (5 mL) added in one portion. The reaction mixture was stirred at rt for 10 min, whereupon the separated product was collected by suction; yield 200 mg (76 %). The crude product was recrystallized from glacial acetic acid; decomposition above 250 °C. ¹H NMR (δ/ppm, CDCl₃): 9.51 and 8.86 (bs, 2H (CONH₂)), 8.80 (dd, 1H, (H-6, ³J=7.2 Hz, ⁴J=0.7 Hz)), 8.66 (dd, 1H, (H-4, ³J=7.2 Hz, ⁴J=0.7 Hz)), 8.07 (t, 1H, (H-5, ³J=7.2 Hz)). ¹³C NMR (δ/ppm, CDCl₃): 158.1 (CO), 145.6, 143.4, 142.4, 122.9 (4×C_q), 129.2, 126.7, 125.1 (3×CH). *Anal.* Calcd for C₈H₅N₃O₄S: C, 40.17; H, 2.11; N, 17.57; S, 13.41. Found: C, 40.23; H, 2.28; N, 17.52; S, 13.64.

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