Unexpected Rearrangement Products from Aminations of 5-Bromo-2-nitrothiazole

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While reaction of 2-bromo-5-nitrothiazole (**2**) with weakly basic secondary aliphatic amines gives the expected 2-amino products from nucleophilic displacement of the bromine, reaction of the isomeric 5-bromo-2-nitrothiazole (**3**) with such amines gives mixtures of the expected 5-amino products together with 2-aminated 5-nitrothiazole rearrangement products. The identity of the latter were detemined by alternative synthesis, and by X-ray crystallographic determination of a derivative. The mechanism proposed is a slow thermal isomerization of 5-bromo-2-nitrothiazole (**3**) to the much more reactive 2-bromo-5-nitro isomer **2** which competes, in the case of relatively weak amine nucleophiles, with the direct (but slow) nucleophilic displacement of the 5-bromo group to form the normal displacement products.

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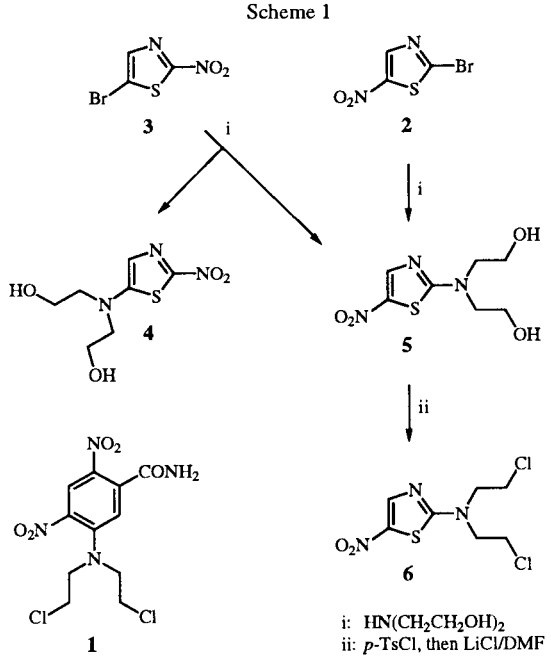
In studies aimed at the development of heterocyclic analogues of the hypoxia-selective cytotoxin (**1**) [1], we required the isomeric nitrothiazole diols **4** and **5** as necessary precursors of the corresponding nitrogen mustards. While reaction of 2-bromo-5-nitrothiazole (**2**) with diethanolamine gave a high yield (87%) of the corresponding 5-nitrodiol **5**, similar reaction of the isomeric 5-bromo-2-nitrothiazole (**3**) with diethanolamine in DMSO at 60° for 1 hour gave two products in low yield (Scheme 1). The major product (yellow, mp 108-110°, 22% yield) was identified as the 5-nitrodiol **5** by comparison with the authentic sample prepared above, while the desired 2-nitrodiol **4** (orange, mp 128-130°) was only a minor product (11% yield). Confirmation of the structure of the major product as **5** was obtained by its conversion into the corresponding (highly crystalline) mustard **6**, and determination of the structure of this by X-ray crystallography (Figure 1).

Scheme 1



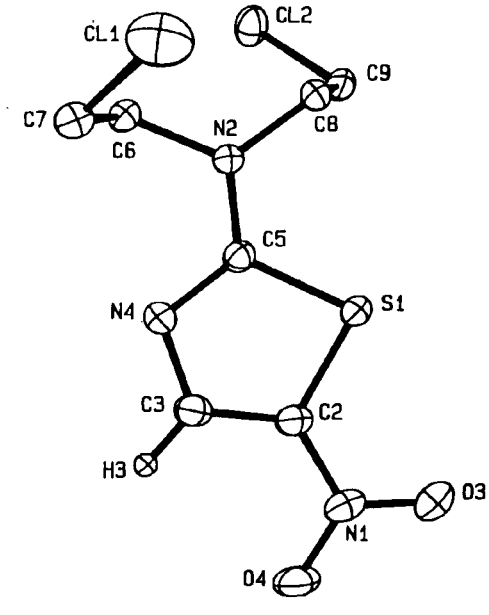


Figure 1. ORTEP diagram of **6**.

The generation of the isomeric 5-nitrodiol **5** in the latter reaction is surprising. Such isomerisations of substituted thiazoles have been observed previously [2,3], but only under photochemical conditions, and have been proposed to proceed *via* diradical intermediates. Both of the nitrodiols **4** and **5** were stable to prolonged exposure to the reaction conditions (diethanolamine in DMSO) indicating that **5** is not formed from **4** *via* base-catalysed rearrangement. Similarly, when 5-bromo-2-nitrothiazole (**3**) was stirred in DMSO in either the presence or absence of the non-nucleophilic base triethylamine for up to 68 hours, the only change was a slow accumulation of decomposition products, and no isomeric 2-bromo-5-nitrothiazole (**2**) could be detected. However, **2** is much more reactive, with a pure sample decomposing completely to baseline

products in 1 hour under similar conditions. It therefore seems likely that the production of **5** results from slow thermal isomerization of 5-bromo-2-nitrothiazole (**3**) to the much more reactive 2-bromo-5-nitro isomer **2**. In the absence of a nucleophile (as above), the reactive **2** rapidly decomposes, but in the presence of the weakly nucleophilic diethanolamine it reacts as soon as it is formed to produce **5**. With weak nucleophiles, this rearrangement is able to compete with direct (but slow) nucleophilic displacement of the 5-bromo group to form **4**.

Scheme 2

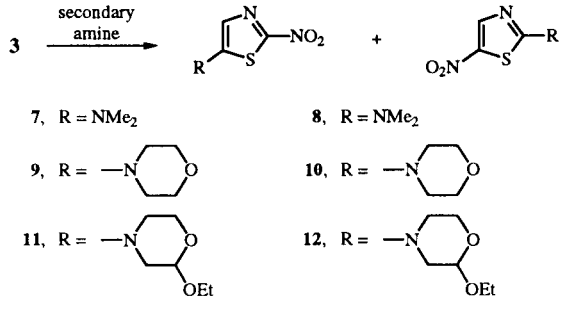


Table 1

Products (and percentage isolated yields) from the Reaction of 5-Bromo-2-nitrothiazole (**3**) with Secondary Amines of Varying Nucleophilicity

Amine	5-Amino (normal)	2-Amino (rearrangement)
dimethylamine	**7** (91)	**8** (0)
morpholine	**9** (87)	**10** (<5[a])
2-ethoxymorpholine	**11** (79)	**12** (16)
diethanolamine	**4** (11)	**5** (22)

[a] Estimated from tlc.

Table 2

Chemical Shifts (δ) of H-4 and C-4 Nuclei in Isomeric Nitroaminothiazole Derivatives (in deuteriochloroform unless stated otherwise)

	5-Amino-2-nitro (A)			2-Amino-5-nitro (B)		
R	No.	H-4	C-4	No.	H-4	C-4
NMe_2	**7**	6.83	118.7	**8**	8.16	146.1
N-morpholyl	**9**	6.99	119.8	**10**	8.14	145.0
N-(2-ethoxymorpholyl)	**11**	6.98	119.9	**12**	8.13	145.5
$N(CH_2CH_2OH)_2$	**4**	7.12[a]	121.1[a]	**5**	8.18[b]	147.2[b]
$N(CH_2CH_2Cl)_2$				**6**	8.13	144.9

[a] Determined in DMSO-d_6. [b] Determined in perdeuterioacetone.

Consistent with this hypothesis, reaction of **3** with more nucleophilic amines gave higher proportions of "normal" 2-nitro-5-amino products analogous to **4**, at the expense of the "rearrangement" 5-nitro-2-amino products analogous to **5**. Thus reaction of **3** with dimethylamine was complete within 5 minutes, giving only the "normal" product **7** (Table 1). Reaction with morpholine was complete within 10 minutes, producing an 87% yield of the "normal" 2-nitro product **9** and only a trace of the

Table 3

Crystal and Structure Refinement Data for 2-[*N*,*N*-Bis-(2-chloroethyl)amino]-5-nitrothiazole (**6**)

Empirical formula	$C_7H_9Cl_2N_3O_2S$
Formula weight	270.14
Temperature	293(2) °K
Wavelength	0.71069 Å
Crystal system	monoclinic
Space group	P21/c
a	13.744(2) Å
b	12.381(1) Å
c	6511(3) Å
β	97.22(2)°
Volume	1099.1(4) Å^3
Z	4
Density (calc)	1.645 g/cm^3
μ	0.764 mm^{-1}
F(000)	560
Crystal size	0.22 x 0.18 x 0.15 mm
θ (max)	26.01°
Unique data	2027
Unique data, $F_o>2.5\sigma$ (F_o)	1757 [R(int) = 0.0295]
Parameters refined	172
Goodness-of-fit on F^2	1.052
Weight modifier, K	0.001925
R	0.0335
R_w	0.0370
Largest diff. peak and hole	0.398 and -0.370 e.Å^{-3}

Table 4

Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for 2-[*N*,*N*-Bis(2-chloroethyl)amino]-5-nitrothiazole (**6**). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor

	x	y	z	U(eq)
S(1)	4114(1)	4726(1)	2599(1)	24(1)
Cl(1)	11186(1)	4254(1)	6653(1)	44(1)
Cl(2)	8892(1)	3361(1)	222(1)	32(1)
O(3)	6101(1)	4012(1)	2254(3)	34(1)
O(4)	5753(1)	2369(1)	1205(3)	36(1)
N(1)	5511(1)	3273(2)	1778(3)	27(1)
N(2)	2148(1)	4760(1)	2636(3)	21(1)
N(3)	2862(1)	3148(1)	1704(3)	23(1)
C(2)	2928(1)	4181(2)	2275(3)	20(1)
C(4)	3760(2)	2760(2)	1488(3)	25(1)
C(5)	4513(2)	3475(2)	1880(3)	24(1)
C(6)	1188(2)	4234(2)	2474(3)	23(1)
C(7)	11071(2)	1495(2)	-726(4)	28(1)
C(8)	2243(2)	5898(2)	3216(3)	22(1)
C(9)	2266(2)	6646(2)	1388(4)	24(1)

"rearrangement" compound **10** (synthesised unequivocally from **2**). Similarly, 2-ethoxymorpholine [4] gave a 79% yield of the 2-nitro-5-amino isomer **11** and 16% of the 5-nitro isomer **12**.

The isomeric products could be distinguished by their chromatographic behaviour, with the yellow 2-amino derivatives consistently eluting from silica gel before the orange 5-amino isomers. Their nmr spectra was also diagnostic. In the 5-amino compounds, the H-4 proton resonances occur at δ 6.8-7.1 ppm, and in the 2-amino compounds at δ 8.1-8.2 ppm (Table 2). The C-4 carbon resonances are also diagnostic, occurring at *ca.* δ 120 ppm in the 5-amino derivatives and at *ca.* δ 146 ppm in the 2-amino compounds (Table 2).

Table 5
Bond Lengths [Å] and Angles [°] for 2-[*N,N*-Bis(2-chloroethyl)amino]-5-nitrothiazole (**6**)

S(1)-C(5)	1.727(2)	Cl(1)-C(7)	1.795(3)
S(1)-C(2)	1.752(2)	Cl(2)-C(9)	1.792(2)
N(3)-C(2)	1.332(3)	N(1)-C(5)	1.404(3)
N(3)-C(4)	1.349(3)	O(3)-N(1)	1.236(3)
C(5)-C(4)	1.361(3)	O(4)-N(1)	1.239(3)
N(2)-C(2)	1.335(3)	C(6)-C(7)	1.503(3)
N(2)-C(8)	1.461(3)	C(8)-C(9)	1.511(3)
N(2)-C(6)	1.463(3)		
C(5)-S(1)-C(2)	86.80(10)	O(3)-N(1)-C(5)	118.1(2)
C(2)-N(3)-C(4)	109.8(2)	O(4)-N(1)-C(5)	118.4(2)
N(3)-C(2)-S(1)	115.7(2)	C(2)-N(2)-C(8)	121.0(2)
N(3)-C(2)-N(2)	122.4(2)	C(2)-N(2)-C(6)	119.1(2)
N(2)-C(2)-S(1)	121.9(2)	C(8)-N(2)-C(6)	120.0(2)
N(3)-C(4)-C(5)	115.6(2)	N(2)-C(6)-C(7)	113.2(2)
C(4)-C(5)-N(1)	126.8(2)	C(6)-C (7)-Cl(1)	110.9(2)
C(4)-C(5)-S(1)	112.0(2)	N(2)-C(8)-C(9)	113.4(2)
N(1)-C(5)-S(1)	121.2(2)	C(8)-C (9)-Cl(2)	110.69(14)
O(3)-N(1)-O(4)	123.5(2)		

EXPERIMENTAL

Analyses were performed by the Microchemical Laboratory, University of Otago, Dunedin, NZ. Melting points were determined using an Electrothermal Model 9200 digital melting point apparatus, and are as read. The nmr spectra were measured on Bruker AC-200 or AM-400 spectrometers, and referenced to TMS. Chemical shifts are reported in ppm (δ). Mass spectra were recorded either on a Varian VG 7070 spectrometer at nominal 5000 resolution or a Finnigan MAT 900Q spectrometer. Analytical thin-layer chromatography was conducted with aluminium-backed silica gel plates, using ultraviolet visualisation. Reagents were purchased from the Aldrich Chemical Company (Milwaukee, WI).

Reaction of 2-Bromo-5-nitrothiazole (**2**) with Diethanolamine.

A solution of 2-bromo-5-nitrothiazole (**2**) (0.29 g, 1.39 mmoles) and diethanolamine (0.31 g, 2.91 mmoles) in *p*-dioxane (5 ml) was warmed at 50° for 30 minutes, and the reaction mixture was adsorbed directly onto silica gel by removal of the solvent under reduced pressure and chromatographed. Elution with ethyl acetate gave foreruns, while methanol/ethyl acetate (1:99) eluted 2-[*N,N*-bis(2-hydroxyethyl)amino]-5-nitrothiazole (**5**) (0.28 g, 87%), mp (ethyl acetate/light petroleum) 108-110°; R_f 0.40 (silica gel, 2 x developments with ethyl acetate) as a characteristic yellow spot; ^{1}H nmr (perdeuterioacetone): δ 8.18 (s, 1 H, H-4), 3.89 (t, J = 5.4 Hz, 4 H, NCH_2), 3.81 (br s, 4 H, CH_2OH), 2.90 (br s, 2 H, exchangeable with deuterium oxide, OH); ^{13}C nmr δ 172.8, 147.2 (C-4), 135.3, 57.9, 57.7.

Anal. Calcd. for $C_7H_{11}N_3SO_4$: C, 36.04; H, 4.75; N, 18.02. Found: C, 36.05; H, 4.77; N, 17.66.

Reaction of 5-Bromo-2-nitrothiazole (**3**) with Diethanolamine.

A solution of 5-bromo-2-nitrothiazole (**3**) [5] (2.13 g, 10.2 mmoles) in DMSO (15 ml) was treated with diethanolamine (2.25 g, 21.4 mmoles) at 60° (bath) for 1 hour. The cooled mixture was poured into brine and extracted into ethyl acetate to give a red-brown oil, which was chromatographed on silica gel. Elution with ethyl acetate/methanol (10:1) gave firstly 2-[*N,N*-bis(2-hydroxyethyl)amino]-5-nitrothiazole (**5**) (0.50 g, 22%), identical with the sample prepared above. Later eluates gave 5-[*N,N*-bis(2-hydroxyethyl)amino]-2-nitrothiazole (**4**) (0.25 g, 11%), mp (ethyl acetate/methanol) 128-130°; R_f 0.20 (silica gel, 2 x developments with ethyl acetate) as a characteristic orange spot; ^{1}H nmr (DMSO-d_6): δ 7.12 (s, 1 H, H-4), 4.35 (br s, 2 H, exchangeable with deuterium oxide, OH), 3.90 (t, J = 5.4 Hz, 4 H, NCH_2OH), 3.74 (t, J = 5.4 Hz, 4 H, NCH_2); ^{13}C nmr: δ 164.3, 144.9, 121.1 (C-4), 57.7 (*C*H_2OH), 56.9 (*C*H_2N).

Anal. Calcd. for $C_7H_{11}N_3O_4S$: 36.05; H, 4.75; N, 18.02. Found: C, 36.33; H, 4.77; N, 17.70.

Reaction of 5-Bromo-2-nitrothiazole (**3**) with Dimethylamine.

Reaction of **3** (125 mg, 0.6 mmole) with dimethylamine hydrochloride (103 mg, 1.26 mmoles) and triethylamine (0.18 ml, 1.32 mmoles) in DMSO (2 ml) at 50-60° for 5 minutes gave 5-(dimethylamino)-2-nitrothiazole (**7**) (95 mg, 91%), mp (ethyl acetate/methanol) 184-185°; ^{1}H nmr (deuteriochloroform): δ 6.83 (s, 1 H, H-4), 3.16 (s, 6 H, N(CH_3)$_2$); ^{13}C nmr: δ 162.9, 140.8, 118.7 (C-4), 42.8 (CH_3).

Anal. Calcd. for $C_5H_7N_3O_2S$: C, 34.68; H, 4.07; N, 24.26. Found: C, 34.79; H, 3.80; N, 24.57.

Careful tlc analysis of the reaction against authentic 2-(dimethylamino)-5-nitrothiazole (**8**) revealed no trace of the latter. Authentic **8** was obtained by reaction of **2** with dimethylamine (1 minute at 20°, 80% yield), mp (ethyl acetate) 157-159°; ^{1}H nmr (deuteriochloroform): δ 8.16 (s, 1 H, H-4), 3.23 (s, 6 H, N(CH_3)$_2$); ^{13}C nmr: δ 172.9, 146.1 (C-4), 137.2, 40.1 (CH_3).

Anal. Calcd. for for $C_5H_7N_3O_2S$: C, 34.68; H, 4.07; N, 24.26. Found: C, 34.68; H, 3.80; N, 24.24.

Reaction of **3** with Morpholine.

Reaction of **3** (0.21 g, 1.02 mmoles) and morpholine (0.19 g, 2.14 mmoles) in DMSO (2 ml) at 50-60° (bath) for 10 minutes gave 5–[4-morpholino]-2-nitrothiazole (**9**) (0.19 g, 87%), mp (methanol/chloroform) 162-164°; ^{1}H nmr (deuteriochloroform): δ 6.99 (s, 1 H, H-4), 3.89 (m, 4 H, CH_2O), 3.35 (m, 4 H, CH_2N); ^{13}C nmr (deuteriochloroform): δ 162.5, 150.3, 119.8 (C-4), 65.5 (CH_2O), 50.2 (CH_2N).

Anal. Calcd. for $C_7H_9N_3O_3S$: C, 39.06; H, 4.21; N, 19.52. Found: C, 39.06; H, 4.15; N, 19.41.

Analysis of the reaction mixture by tlc against standards detected traces (<5%) of the isomeric 2-[4-morpholino]-5-

nitrothiazole (**10**). An authentic sample of **10** was obtained by reaction of **2** with morpholine (2 minutes at 20°, 82% yield), mp (ethyl acetate) 144-146°; ^{1}H nmr (deuteriochloroform): δ 8.14 (s, 1 H, H-4), 3.84 (t, J = 5.0 Hz, 4 H, CH_2O), 3.63 (t, J = 5.0 Hz, 4 H, CH_2N); ^{13}C nmr: δ 173.1, 152.3, 145.0 (C-4), 66.4 (CH_2O), 48.1 (CH_2N).

Anal. Calcd. for $C_7H_9N_3O_3S$: C, 39.06; H, 4.21; N, 19.52. Found: C, 39.22; H, 4.18; N, 19.52.

Reaction of **3** with 2-Ethoxymorpholine.

2-Ethoxymorpholine [4] (4.90 g, 37.4 mmoles; generated from 4-benzyl-2-ethoxymorpholine by reduction with hydrogen/Pd/C in methanol immediately before use) was added to a stirred solution of 5-bromo-2-nitrothiazole (**3**) (3.91 g, 18.7 mmoles) in DMSO (10 ml) at 20°. The reaction was then stirred at 50-60° (bath) while triethylamine (2.60 ml, 18.7 mmoles) was added slowly, then for a further 40 minutes. The cooled mixture was poured into brine and extracted into ethyl acetate. Workup of the organic layer gave a residue which was chromatographed on silica gel. Elution with ethyl acetate/light petroleum (1:5) gave, firstly, 2-[4-(2-ethoxymorpholino]-5-nitrothiazole (**12**) (0.79 g, 16%) mp (ethyl acetate) 93-95° as yellow rods; ^{1}H nmr (deuteriochloroform): δ 8.13 (s, 1 H, H-4) 4.81 (t, J = 3.1 Hz, 1 H, H-2'), 4.20-3.50 (m, 8 H, morpholino H and CH_2CH_3), 1.23 (t, J = 7.0 Hz, 3 H, CH_3); ^{13}C nmr (deuteriochloroform): δ 173.0, 145.5 (C-4), 137.5, 95.0 (OCHO), 63.7 (CH_2), 59.2 (CH_2), 51.5 (CH_2), 47.2 (CH_2), 15.0 (CH_3).

Anal. Calcd. for $C_9H_{13}N_3O_4S$: C, 41.69; H, 5.05; N, 16.21; S, 12.37. Found: C, 41.99; H, 5.17; N, 16.07; S, 12.32.

Later eluates gave 5-[4-(2-ethoxymorpholino]-2-nitrothiazole (**11**) (3.79 g, 78%), mp (ethyl acetate/light petroleum) 53-55° as an orange solid; ^{1}H nmr (deuteriochloroform): δ 6.98 (s, 1 H, H-4) 4.84 (t, J = 3.3 Hz, 1 H, H-2'), 4.20-3.30 (m, 8 H, morpholino H and CH_2CH_3), 1.25 (t, J = 7.0 Hz, 3 H, CH_3); ^{13}C nmr (deuteriochloroform): δ 162.5, 150.0, 119.9 (C-4), 95.0 (OCHO), 63.9 (CH_2), 59.1 (CH_2), 53.5 (CH_2), 49.6 (CH_2), 15.0 (CH_3).

Anal. Calcd. for $C_9H_{13}N_3O_4S$: C, 41.69; H, 5.05; N, 16.21; S, 12.37. Found: C, 42.18; H, 5.27; N, 16.34; S, 12.49.

Preparation and X-ray Crystal Structure Determination of 2-[*N,N*-Bis(2-chloroethyl)amino]-5-nitrothiazole (**6**).

The diol **5** (2.11 g, 9.06 mmoles) was treated with *p*-toluenesulfonyl chloride (6.92 g, 36.2 mmoles), 4-(dimethylamino)pyridine (1.33 g, 10.9 mmoles) and triethylamine (5.04 ml, 36.2 mmoles) in dichloromethane (90 ml) at 20° for 3 hours. Volatiles were removed under reduced pressure, and the residue was dissolved in ethyl acetate and washed successively with water, 1 *N* hydrochloric acid and water, and worked up to give the crude ditosylate. This was treated directly with lithium choride (10 g) in DMF (40 ml) at 100° for 1 hour, then cooled and partitioned between ethyl acetate and water. The ethyl acetate layer was worked up and the resulting product was chromatographed on silica gel. Elution with ethyl acetate/petroleum ether (1:5) gave 2-[*N,N*-bis(2-chloroethyl)amino]-5-nitrothiazole (**6**) (0.20 g, 8%), mp (ethyl acetate/petroleum ether) 89-90°; ^{1}H nmr (deuteriochloroform): δ 8.13 (s, 1 H, H-4), 3.96 (t, J = 6.3 Hz, 4 H, CH_2Cl), 3.83 (t, J = 6.3 Hz, 4 H, CH_2N); ^{13}C nmr (deuteriochloroform): δ 171.5, 144.9 (C-4), 138.5, 54.6 (CH_2N) 40.2, (CH_2Cl).

Anal. Calcd. for $C_7H_9Cl_2N_3O_2S$: C, 31.12; H, 3.36; N, 15.56; S, 11.87. Found: C, 31.30; H, 3.37; N, 15.69; S, 11.84.

A crystal of **6** (from ethyl acetate/methanol; dimensions 0.22 x 0.18 x 0.15 mm) was mounted on a Nonius CAD-4 diffractometer. Cell dimensions were determined from a least-squares refinement of 25 widely dispersed reflections. Intensity data of 2364 reflections (indices h -16 to 16, k 0 to 15, l 0 to 8) were collected using Mo Kα radiation to a maximum θ = 26° with variable $\varpi/2\theta$ scan. The data were corrected for Lorentz and polarizations effects, but not absorption. Measured intensities were merged to give 2027 unique reflections (R_{int} = 0.02) of which 1757 were considered observed ($I>2.56\sigma(I)$) (see Table 3). The non-hydrogen atoms were located by direct methods using SHELX-S [6], and subsequent refinement carried out using SHELX-76 [7]. Anisotropic thermal parameters were used for all non-H atoms and isotropic for H atoms, found from successive difference Fourier maps. Final R and R_w values were 0.0335 and 0.0370 respectively with $w=1.0000/[\sigma^2(F) + 0.001925\ F^2]$. Refinement was terminated when the shift/e.s.d. was less than 0.06, and the maximum and minimum residual electron densities in the final difference Fourier map were 0.390 and -0.367 e/Å^3 respectively. Figure 1 shows that the thiazole ring of **6** is, as expected, planar. The nitro group makes an angle of 2.05° with it, and the aminoethyl portion of the mustard makes an angle of 3.33° with the ring. There are no marked distortions from typical bond lengths and angles [8], which are given in Tables 4 and 5.

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