The Preparation of Derivatives containing the Imidazo[2,1-*b*]thiazine and 1,2,4-Triazolo[3,2-*b*][1,3]thiazine Systems

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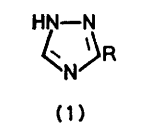
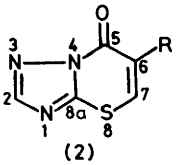
The cyclisation of 3-mercapto-1,2,4-triazole (1a) and 2-mercaptoimidazole (7) with diethyl ethoxymethylenemalonate is shown to produce 6-ethoxycarbonyl[1,2,4]triazolo[3,2-*b*][1,3]thiazin-5-one (2a) and 6-ethoxycarbonylimidazolo[2,1-*b*][1,3]thiazin-5-one (8a) respectively. A minor product associated with the formation of compound (2a) was identified as [1,2,4]triazolo[3,2-*b*][1,3]thiazin-5-one (2b) by *X*-ray analysis. The ^{13}C n.m.r. data for these compounds were useful in correlating their structures.

In the preceding paper we described the preparation of certain pyrazolo[1,5-*a*]pyrimidine- and [1,2,4]triazolo-[1,5-*a*]pyrimidine-carboxylic acids which were required for the preparation of semi-synthetic penicillins.[1] In continuation of this work we describe in the present paper the preparation of derivatives of the imidazo-[2,1-*b*][1,3]thiazine and triazolo[3,2-*b*][1,3]thiazine fused ring systems.

When 3-mercapto-1,2,4-triazole (1a) was refluxed



(1)
a; R = SH
b; R = NH_2



(2)
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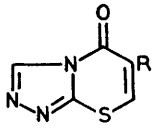
b; R = H
c; R = CO_2H



(3)
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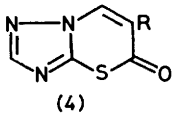
b; R = H



(4)
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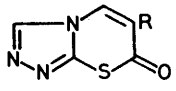

(5)
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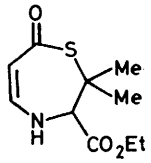
b; R = H



(6)

with diethyl ethoxymethylenemalonate in trichlorobenzene the major product, m.p. 186 °C, was isolated in 58% yield. The analytical and spectroscopic properties of this product suggested it should be formulated as one of the isomeric structures (2a), (3a), (4a), or (5a). Structures (2a) and (3a) would be expected to be derived from initial attack of sulphur on the ethoxymethylene carbon, whereas structures (4a) and (5a) would result from attack of nitrogen at this position. By analogy with the reaction of 3-amino-1,2,4-triazole (1b) with diethyl ethoxymethylenemalonate the correct structure would be expected to be (2a) and this indeed was found to be the case as is shown below.

The i.r. spectrum of the product, m.p. 186 °C, showed two maxima in the carbonyl region, the ester band at 1 740 cm^{-1} and a second band at 1 700 cm^{-1}. The latter must be associated with the amide carbonyl group present in structures (2a) and (3a) since the alternative thiolactones (4a) and (5a) would be expected to absorb at *ca.* 1 625 cm^{-1} as in the case of the thiolactone (6).[2] The thiolactones (4a) and (5a) were also ruled out by the ^{13}C n.m.r. chemical-shift data. The ^{13}C n.m.r. characteristic of a carbonyl group adjacent to sulphur is highly distinctive in that a downfield shift of 190—200 p.p.m. occurs.[3] The lowest resonance observed for the cyclisation product was in fact at 161.2 p.p.m., and this was attributed to the ester carbonyl group (see Table 2).

Also informative was a study of the shifts in the ^1H n.m.r. induced by the lanthanide shift reagent $Eu(fod)_3$ and these are shown in Table 1.

TABLE 1

$Eu(fod)_3$ induced ^1H n.m.r. shifts [a]

Compound [b]		H(7)	H(6)	H(3)	H(2)
(2a)	δ	8.83			8.36
	Δδ [c]	1.31			1.82
(2b)	δ	7.77	6.83		8.26
	Δδ [c]	2.09	4.71		3.93
(8a)	δ	8.75		8.01	7.35
	Δδ [c]	1.37		1.36	0.87

[a] Chemical shifts in p.p.m. from $SiMe_4$, solvent $CDCl_3$. [b] See structure (2) for numbering system. [c] Δδ is the shift in p.p.m. induced by the addition of 0.5 mol equiv. of $Eu(fod)_3$ to the substrate.

The down-field proton singlet in compound (2a) at δ 8.83 was assigned to the proton in the six-membered ring and the singlet at δ 8.36 p.p.m. to the triazole ring proton. The shift reagent would be expected to bind predominantly to the ring carbonyl in compounds (2a) and (3a) but to both carbonyls, in a bidentate manner, in the thiolactones (4a) and (5a). Since the observed shift difference (Δδ, 1.82) for the triazole ring proton was

greater than that for the six-membered-ring proton ($\Delta\delta$, 1.31) it was concluded that the shift reagent was bound to a single carbonyl, indicative of structure (2a) or (3a). Moreover since the proton in the five-membered ring in structure (3a) was adjacent to the site of co-ordination it would be expected to experience a large shift in comparison to the six-membered-ring proton. Since, as we have seen, the respective shifts were 1.82 and 1.31 p.p.m. it was concluded that (2a) was the likely structure. Thus, in summary, the i.r., the ^{13}C n.m.r. and the induced proton-shift data eliminated structures (4a) and (5a) for the cyclisation product, m.p. 186 °C, and the induced shift data also favoured structure (2a) rather than (3a).

Further evidence came from the isolation of a second, minor product, m.p. 235 °C, from the cyclisation reaction of 3-mercapto-1,2,4-triazole (1a) with diethyl ethoxymethylenemalonate. This product was identified as [1,2,4]triazolo[3,2-*b*]thiazin-5-one (2b) by *X*-ray analysis. Compound (2b) may be considered to be formally derived from (2a) by ester hydrolysis and decarboxylation. A comparison of the ^1H n.m.r. and ^{13}C n.m.r. data for compound (2b) with those of the major product of cyclisation, enabled us firmly to establish (2a) as the structure of the latter. The ^1H n.m.r. spectrum of (2b) (see Table 1) indicated a singlet proton at δ 8.26 attributed to the triazole proton H(2). Since the corresponding proton in compound (2a) was observed at δ 8.36 this was good evidence for compounds (2a) and (2b) having the same isomeric form of the triazole ring. Indeed the trazole ring proton in the alternative structure (3a) would be expected to resonate around δ 9.00 in view of the reported values for this proton in related compounds.[4]

Table 1 also shows the effect of the addition of Eu(fod)$_3$ on the proton resonances in compound (2b). It is of interest to note that while the shift data cannot be reconciled with the isomeric structures (4b) and (5b), which would be expected to show larger shifts for the two six-membered-ring protons compared with the shift of the proton in the five-membered ring, the data do not distinguish between alternative structures (2b) and (3b).

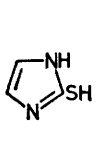
TABLE 2

^{13}C N.m.r. Chemical-shift data and carbon–hydrogen coupling constants for compounds (2a), (2b), (8a), and (8b) [a]

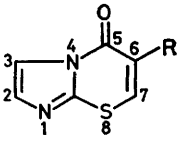
Carbon atom [b]	(2a)	(2b)	(8a)	(8b)
7	145.6 (d, *J* 183 Hz)	137.8 (d, *J* 183 Hz)	147.0	138.6
6	119.9	117.4 (d, *J* 174 Hz)	117.2	114.8 or 114.4
5	152.2	155.7 (d, *J* 13 Hz)	154.4	157.7
3			116.0	114.4 or 114.8
2	152.8 (d, *J* 213 Hz)	152.5 (d, *J* 213 Hz)	131.6	131.0
8a	150.7	152.5 (t, *J* 10 Hz)	138.8	140.2
Ester CO	161.2		161.8	

[a] P.p.m. to down-field from $SiMe_4$; solvent $(CD_3)_2SO$. Multiplicity and carbon–hydrogen coupling constants are indicated in brackets where appropriate. [b] See structure (2) for numbering system.

The ^{13}C n.m.r. chemical-shift data were particularly informative and are summarised in Table 2. In compound (2b), of known structure, the doublet at 152.5 p.p.m. with a coupling constant to hydrogen of 213 Hz was assigned to C(2) in view of the fact that in 3-mercapto-1,2,4-triazole (1a) the C(5)-carbon, a doublet at 140.3 p.p.m, showed a similar coupling constant of 216 Hz. The doublet at 137.8 p.p.m. (*J* 183 Hz) was

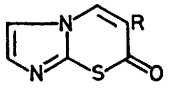


(7)



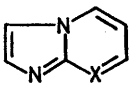
(8)

a; R = CO_2Et
b; R = H
c; R = CO_2H



(9)

a; R = CO_2Et
b; R = H



(10)

a; X = CH
b; X = N

then assigned to C(7). The carbon resonance at 155.7 p.p.m. was a doublet with a 13-Hz coupling constant, whereas the resonance at 152.5 p.p.m. appeared as a triplet (double doublet) with *J* 10 Hz. The former resonance must be due to C(5) with coupling to H(6) and the latter to C(8a) with coupling to H(7) and H(2). From these assignments for compound (2b), those for (2a) were readily derived. The shift value, 152.8 p.p.m. of the triazole ring carbon in compound (2a) clearly indicated (2a) to have the same isomeric form of the triazole ring as (2b).

The minor product (2b), m.p. 235 °C, was isolated with some difficulty from the cyclisation reaction and was invariably contaminated with compound (2a). It was found that compound (2b) could be readily prepared in 65% yield by heating the thiol (1a) with ethyl propiolate in acetic acid.

Similar reactions were carried out with 2-mercaptoimidazole (7). After considerable investigation, the thiol (7) was found to react with diethyl ethoxymethylenemalonate using propionic acid in 1,2-dichlorobenzene and xylene as co-solvent. The product, m.p. 134 °C, was isolated in 29% yield and identified as compound (8a) rather than (9a) on the basis of its i.r., $\nu_{max.}$ 1 718 (ester), 1 680 cm^{-1} (amide carbonyl), and ^1H n.m.r. (δ 8.75, 7-*H*) spectra. The effects of the lanthanide shift reagent on the proton n.m.r. of (8a) are recorded in Table 1. The actual shift differences could not be

reconciled with the alternative structure (9a), but on the other hand, on the basis of the values for compound (2a), one would have predicted a larger induced shift for H(3) compared with H(7) than was observed. Presumably this is a consequence of increased co-ordination, in the case of (8a), of the shift reagent to the ester carbonyl group. A minor product with loss of the ethoxycarbonyl group was also isolated in this reaction and this was assigned structure (8b). A convenient alternative *pre*paration of compound (8b) involved reaction of the thiol (7) with ethyl propiolate.

The ^{13}C chemical-shift data for compounds (8a) and (8b) are shown in Table 2. In the case of compound (8a) assignments of carbon atoms C(7), C(6), and C(5) were readily made on the basis of their multiplicities and by reference to compounds (2a) and (2b). Of the remaining three ring-carbon atoms C(8a) was distinguished on the basis of its multiplicity and low signal intensity as was observed for the corresponding carbons in (2a) and (2b). The resonance at 131.6 p.p.m. was assigned to C(2) and that at 116.0 p.p.m. to C(3) on the basis of the reported values for the related compounds (10a) and (10b).[5]

Finally, the free acids (2c) and (8c) were prepared in good yield by hydrolysis in sodium hydroxide of the corresponding esters (2a and (8a).

EXPERIMENTAL

M.p.s were determined on a Büchi apparatus and are uncorrected. I.r. measurements were made on a Perkin-Elmer 457 grating spectrophotometer. U.v. data were obtained on a Pye–Unicam SP 1800 spectrometer. ^1H N.m.r. data were recorded at 90 MHz on a Perkin-Elmer R32 instrument and ^{13}C measurements using a Varian CFT-20 spectrometer. Both ^1H and ^{13}C n.m.r. spectra were recorded at ambient temperatures with $SiMe_4$ as internal standard. Mass spectra were obtained at 70eV using an AEI MS9 instrument operating at 8 kV. Analytical t.l.c. was performed on pre-coated Merck Kieselgel 60 F 254.

6-*Ethoxycarbonyl*[1,2,4]*triazolo*[3,2-b][1,3]*thiazin-5-one* (2a).—3-Mercapto-1,2,4-triazole (1a) (1.01 g) and diethyl ethoxymethylenemalonate (2.16 g) were refluxed in 1,2,4-trichlorobenzene (30 ml) and xylene (15 ml). The xylene was distilled off during 2 h and the resulting solution refluxed for a further 22 h. After cooling the reaction mixture was diluted with light petroleum (b.p. 60—80 °C) and chilled. The dark brown solid was filtered off and crystallised from ethyl acetate (charcoal) to yield the *product* as colourless plates, m.p. 186—188 °C (1.3 g, 58%), $\nu_{max.}$ (KBr) 3 430br, 1 740, 1 700, 1 536, and 1 496 cm^{-1}; $\lambda_{max.}$ (EtOH) 211 (ε 14 200), 255 (6 350), and 300 nm (8 570); δ_H [$(CD_3)_2SO$] 1.29 (3 H, t, CH_3), 4.30 (2 H, q, CH_2), 8.58 (1 H, s, 2-H), 9.18 (1 H, s, 7-H); *m/e* (relative intensity) 225 ($M^{+\cdot}$, 37), 152 (73), 125 (100), 53 (49), and 43 (90) (Found: C, 42.6; H, 3.1; N, 18.9; S, 14.6. $C_8H_7N_3O_3S$ requires C, 42.7; H, 3.1; N, 18.7; S, 14.2%). A minor component isolated from the mother liquors was found to be [1,2,4]*triazolo*-[3,2-b][1,3]*thiazin-5-one* (2b), m.p. 235—236 °C, $\nu_{max.}$ (KBr) 3 450br, 1 695, and 1 492 cm^{-1}; $\lambda_{max.}$ (EtOH) 214 (ε 11 100), 248 (3 870), and 288 nm (7 100); δ_H [$(CD_3)_2SO$] 6.91 (1 H, d, *J* 10 Hz, 6-*H*), 8.33 (1 H, d, *J* 10 Hz, 7-*H*), and 8.50 (1 H, s, 2-*H*); *m/e* (relative intensity) 153 ($M^{+\cdot}$, 100), 125 (8), and 98 (24) (Found: C, 39.4; H, 2.0; N, 27.6; S, 21.1. $C_5H_3N_3OS$ requires C, 39.2; H, 2.0; N, 27.4; S, 20.9%).

6-*Ethoxycarbonylimidazo*[2,1-b][1,3]*thiazin-5-one* (8a).—2-Mercaptoimidazole (7) (2.0 g) and diethyl ethoxymethylenemalonate (4.32 g) in 1,2-dichlorobenzene (40 ml), xylene (20 ml), and propionic acid (4 ml) were refluxed in a Dean–Stark apparatus. The xylene and propionic acid were distilled off during 6 h, and the solution cooled, filtered, and evaporated to dryness. The residue was crystallised from ethyl acetate (charcoal) to give the *product*, m.p. 134—136 °C (1.3 g, 29%), $\nu_{max.}$ (KBr) 1 718, 1 680, and 1 533 cm^{-1}; $\lambda_{max.}$ (EtOH) 223 (ε 14 400), 238 (14 200), and 333 (6 050) nm; δ_H [$(CD_3)_2SO$] 1.31 (3 H, t, CH_3), 4.31 (2 H, q, CH_2), 7.50 (1 H, d, *J* 1 Hz, 2-*H*), 8.15 (1 H, d, *J* 1 Hz, 3-*H*), and 9.22 (1 H, s, 7-*H*); *m/e* (relative intensity) 224 ($M^{+\cdot}$, 100), 196 (17), 179 (98), 152 (90), and 124 (30) (Found: C, 47.9; H, 3.6; N, 12.3; S, 14.3. $C_9H_8N_2O_3S$ requires C, 48.2; H, 3.6; N, 12.5; S, 14.3%). A minor component isolated from the mother liquors was found to be *imidazo*[2,1-b]-[1,3]*thiazin-5-one* (8b), m.p. 119—120 °C, $\nu_{max.}$ (KBr) 1 675, 1 552, and 1 514 cm^{-1}; $\lambda_{max.}$ (EtOH) 227 (ε 16 600), 256 (3 600), and 320 nm (4 460); δ_H [$(CD_3)_2SO$] 6.73 (1 H, d, *J* 10 Hz, 6-*H*), 7.40 (1 H, d, *J* 1 Hz, 2-*H*), 8.00 (1 H, d, *J* 1 Hz, 3-*H*), and 8.35 (1 H, d, *J* 10 Hz, 7-*H*); *m/e* (relative intensity) 152 ($M^{+\cdot}$, 100), 124 (24), and 97 (17) (Found: C, 47.6; H, 2.7; N, 18.2; S, 21.1. $C_6H_4N_2OS$ requires C, 47.4; H, 2.7; N, 18.4; S, 21.1%).

[1,2,4]*Triazolo*[3,2-b][1,3]*thiazin-5-one* (2b).—3-Mercapto-1,2,4-triazole (1a) (1.01 g) and ethyl propiolate (0.98 g) in acetic acid (20 ml) were refluxed for 20 h. On cooling the product (2b) crystallised, and was filtered off and dried (1.0 g, 65%); it was found to be spectroscopically and chromatographically identical to a sample of (2b) obtained as above.

Imidazo[2,1-b][1,3]*thiazin-5-one* (8b).—2-Mercaptoimidazole (7) (0.5 g) and ethyl propiolate (0.5 g) in acetic acid (10 ml) were refluxed overnight. The solution was cooled and the crystalline product (8b) filtered off (0.35 g, 46%) and found to be spectroscopically and chromatographically identical to a sample of (8b) obtained as above.

6-*Carboxy*[1,2,4]*triazolo*[3,2-b][1,3]*thiazin-5-one* (2c).—The ethyl ester (2a) (0.75 g) was heated in 5M-sodium hydroxide (4.5 ml) and water (20 ml) at 90 °C for 1 h. After cooling the solution was acidified at 0 °C to pH 2 (5M-HCl) and the *product* filtered off and dried, m.p. 188—190 °C (0.55 g, 83%), $\nu_{max.}$ (KBr) 3 100—3 600br, 1 730, 1 719, 1 615, and 1 540 cm^{-1}; $\lambda_{max.}$ (0.3% $NaHCO_3$) 274 nm (ε 9 230); δ_H [$(CD_3)_2SO$] 8.74 (1 H, s, 2-*H*), 9.20 (1 H, s, 7-*H*), and 12.67 (4 H, broad, exchangeable in D_2O) (Found: C, 32.2; H, 2.6; N, 18.7. $C_6H_3N_3O_3S{\cdot}1.5H_2O$ requires C, 32.1; H, 2.7; N, 18.7%).

6-*Carboxyimidazo*[2,1-b][1,3]*thiazin-5-one* (8c).—The ethyl ester (8a) (200 mg) was heated in 2.5M-sodium hydroxide (2 ml) and water (8 ml) at 90 °C for 1 h. After cooling the aqueous solution was acidified at 0 °C to pH 1.5 (5M-HCl) and filtered. The *product* was washed with water and acetone and then dried, m.p. 220 °C (decomp.) (100 mg, 57%), $\nu_{max.}$ (KBr) 3 200—3 700br, and 1 300—1 700br; $\lambda_{max.}$ (0.3% $NaHCO_3$) 211 (ε 14 914) and 271 nm (14 322); δ_H (NaOD–D_2O) 7.12 (2 H, s, 3-*H* and 2-*H*) and 7.36 (1 H, s, 7-*H*) (Found: C, 36.5; H, 3.0; N, 12.4. $C_7H_4N_2O_3S{\cdot}2H_2O$ requires C, 36.2; H, 3.5; N, 12.1%).

Crystal Structure Determination of [1,2,4]*Triazolo*[3,2-b]*thiazin-5-one*(2b).—*Crystal data*. $C_5H_5N_3OS$, $M = 153.1$.

Monoclinic $a = 12.356$ (3), $b = 6.842$ (2), $c = 7.150$ (2) Å, $\beta = 95.3$ (1)°, $U = 601.9$ Å^3, $D_c = 1.69$, $Z = 4$, $D_m = 1.67$ g cm^{-3}, $F(000) = 312$. Space group $P2_1/c$ (from systematic absences), Mo-K_α radiation (graphite monochromator) $\lambda = 0.710\ 69$ Å, $\mu = 4.46$ cm^{-1}.

The crystal parameters were initially found from oscill-

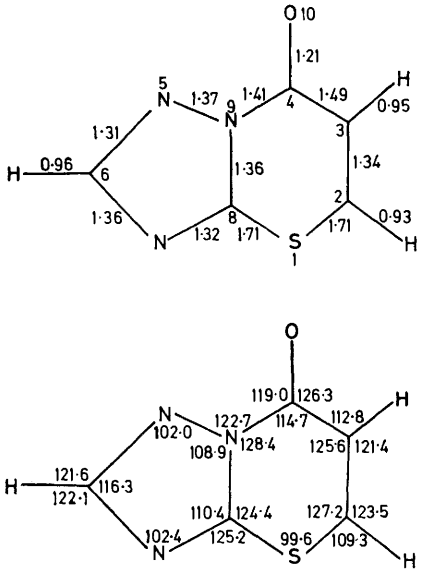


FIGURE 1 Bond lengths (Å) and angles (°) of compound (2b)

ation and Weissenberg photographs and were then refined from the setting angles of 23 reflections measured on a Hilger-Watt four-circle diffractometer. Reflections were measured for $\theta \leqslant 30°$ ($\omega - 2\theta$ scan mode) and were deemed observed if $I \geqslant 3\sigma(I)$; 1 314 of the 1 541 observable reflections satisfied this criterion. Lorentz and polarisation, but not absorption, corrections were made.

The solution of the structure was unexpectedly difficult.

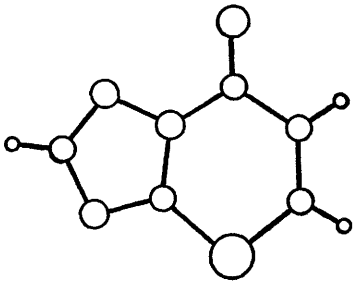


FIGURE 2 Perspective drawing of compound (2b)

The heavy-atom method failed and several attempts at a direct-methods solution using MULTAN [6] only yielded a six-atom fragment containing one atom (assumed to be sulphur) attached to a five-membered ring. Using this fragment, Fourier methods then rapidly led to a complete solution. Refinement proceeded normally; the nitrogen and carbon atoms in the five-membered ring were clearly differentiated by their isotropic temperature factors and the assignment was confirmed when a difference-map showed the hydrogen atoms. In the final cycles of refinement the heavier atoms were treated anisotropically and the hydrogen atoms were refined isotropically, the weighting scheme used was of the form $w = 1/[1 + [(F_o - A)/B]^2]$ with $A = 14.0$ and $B = 16.0$. At convergence the maximum shift/standard deviation for non-hydrogen atoms was 0.02 and R was 4.0%. The standard deviations of lengths and angles for parameters not involving hydrogen were in the range 0.002—0.003 Å and 0.09—0.18°, and involving hydrogen 0.017 Å and 1.5—1.9°.

Figure 1 shows the bond lengths and angles and indicates the crystallographic numbering. Figure 2 is a perspective drawing of the molecule which was shown by calculation to have a planar fused-ring system. Table 3 gives the

TABLE 3

Fractional atomic co-ordinates for compound (2b) ($\times 10^4$) with standard deviations in parentheses

Atom *	x/a	y/b	z/c
S(1)	6 870(1)	6 527(1)	4 497(1)
C(2)	8 164(2)	6 561(3)	5 594(3)
C(3)	8 773(1)	5 022(3)	6 163(3)
C(4)	8 458(1)	2 992(3)	5 927(3)
N(5)	6 992(1)	862(2)	4 610(2)
C(6)	6 033(1)	1 272(3)	3 769(3)
N(7)	5 787(1)	3 205(2)	3 554(2)
C(8)	6 670(1)	4 058(2)	4 333(2)
N(9)	7 415(1)	2 692(2)	4 991(2)
O(10)	8 995(1)	1 584(3)	6 463(3)
H(2)	8 394(24)	7 853(28)	5 756(38)
H(3)	9 456(16)	5 179(41)	6 857(35)
H(6)	5 533(17)	265(30)	3 335(33)

* The crystallographic numbering of atoms is given in Figure 1.

fractional co-ordinates. The thermal parameters of the atoms and a listing of the observed and calculated structure factors are available in Supplementary Publication No. SUP 22671 (13 pp.).*

Apart from MULTAN, crystallographic computations were done using the Oxford 'CRYSTALS' package,[7] and the drawing was prepared using PLUTO.[8]

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* For details of the Supplementary publication scheme, see Notice to Authors No. 7, *J.C.S. Perkin I*, 1979, Index issue.

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