Chemistry of the Phenoxathiins and Isosterically Related Heterocycles. XXIX [1]. The Crystal and Molecular Structure of 5-(3'-Hydroxypyridyl-2'-thio)-4-nitro-1-methylimidazole

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Reaction of the dianion of 3-hydroxypyridine-2(1H)-thione with 5-chloro-4-nitro-1-methylimidazole in N,N-dimethylformamide led to the formation of 5-(3'-hydroxypyridyl-2'-thio)-4-nitro-1-methylimidazole, which failed to cyclize to the desired pyrid[1,4]oxathiinoimidazole derivative. In an effort to determine why the intermediate phenolate sulfide had failed to cyclize, the crystal structure of the isolated product was determined. The structure refined to R = 0.036.

Nucleophilic displacement of nitro-group activated halogens from imidazole substrates have been reported for various alkoxide [3-5] and thiolate species [6-8]. Displacement of both the 4- and 5-substituents from 5-bromo-4-sulfonamidoimidazole in ethanolic ammonia has also been reported [9,10]. To the best of our knowledge, there has been only one report of the nucleophilic displacement of both halo- and nitro-substituents from 4,5-disubstituted imidazoles, this by secondary amine [4]. We were thus interested in examining this type of reaction further as a possible means of preparing benzo[1,4]oxathiinoimidazoles and pyrid[1,4]oxathiinoimidazoles.

To minimize potential problems associated with the exchangeable proton of the imidazole ring, we elected to utilize 1-methylimidazole derivatives. Thus, 5-chloro-1-methylimidazole (**1**) was subjected to nitration according to the procedure of Sarasin and Wegmann [11] to afford the corresponding 5-chloro-4-nitro-1-methylimidazole (**2**) (Scheme I). A solution of **2** in dry, distilled N,N-dimethylformamide (DMF) was then added to a stirred DMF solution of the disodium salt of 3-hydroxypyridine-2(1H)-thi-
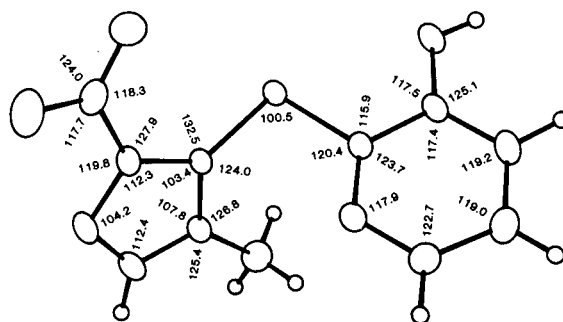

Figure 2. Bond angles in **6**. Esds are in the range 0.1-0.2°.
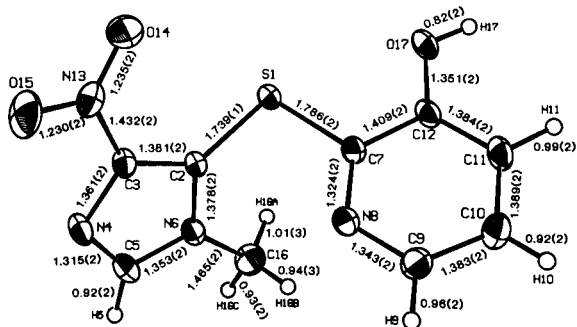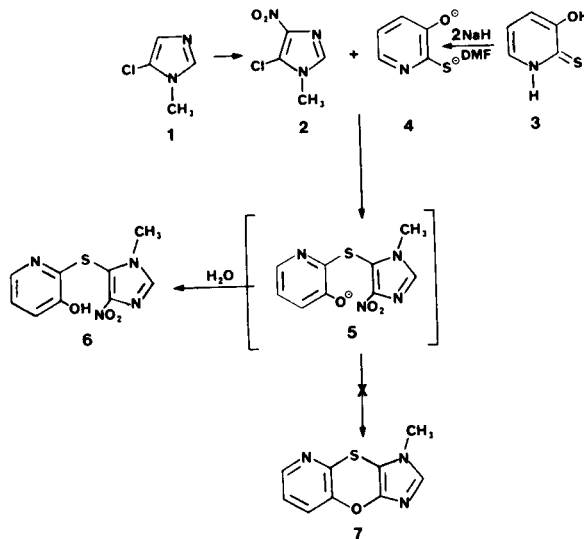

Scheme I

Figure 1. View of **6** illustrating atom labeling, thermal ellipsoids and bond lengths with esds in parentheses.

Table I

Positions in Fractional Coordinates and U (for H) or
U_{eq} [a] for Atoms in $C_9H_8N_4O_3S$

Atom	X	Y	Z	U
S1	.07365(5)	.08363(2)	.21748(5)	.02355(13)
C2	.0096(2)	.17235(7)	.1628(2)	.0182(4)
C3	.0943(2)	.23601(7)	.2393(2)	.0202(4)
N4	−.0017(2)	.29370(6)	.1444(2)	.0254(4)
C5	−.1454(2)	.26598(7)	.0088(2)	.0257(5)
N6	−.1447(2)	.19375(6)	.0128(2)	.0206(4)
C7	−.1316(2)	.05237(7)	.2522(2)	.0190(4)
N8	−.2667(2)	.09764(6)	.2505(2)	.0226(4)
C9	−.4180(2)	.07130(8)	.2772(2)	.0268(5)
C10	−.4361(2)	−.00034(8)	.3085(2)	.0270(5)
C11	−.2927(2)	−.04739(7)	.3125(2)	.0247(5)
C12	−.1366(2)	−.02149(7)	.2831(2)	.0202(4)
N13	.2633(2)	.24615(7)	.3985(2)	.0258(4)
O14	.3662(2)	.19383(7)	.4643(2)	.0393(4)
O15	.2970(2)	.30675(7)	.4613(2)	.0424(5)
C16	−.2868(2)	.14751(9)	−.1184(2)	.0289(5)
O17	.0127(2)	−.06134(5)	.2844(2)	.0276(4)
H5	−.240(3)	.2912(11)	−.078(3)	.032(5)
H9	−.513(3)	.1047(11)	.280(3)	.037(5)
H10	−.537(3)	−.0154(10)	.337(3)	.031(5)
H11	−.294(3)	−.0985(10)	.343(2)	.026(5)
H16A	−.215(3)	.1058(13)	−.142(3)	.046(6)
H16B	−.385(3)	.1352(11)	−.079(3)	.037(5)
H16C	−.342(3)	.1713(12)	−.226(3)	.049(6)
H17	.002(3)	−.1037(13)	.304(3)	.040(6)

[a] For anisotropic atoms, the U value is U_{eq}, calculated as

$$U_{eq} = \frac{1}{3}\Sigma_i\Sigma_jU_{ij}a_ia_jA_{ij}$$

where A_{ij} is the dot product of the ith and j^{th} direct space unit cell vectors.

one (4). The solution turned bright red upon addition of the imidazole solution, was stirred at room temperature for one hour and was then brought to reflux for 16 hours.

On cooling, the reaction mixture was worked up to yield a yellow crystalline material melting at 260-262° which analyzed correctly for 5-(3'-hydroxypyridyl-2'-thio)-4-nitro-1-methylimidazole (6) rather than the desired pyrid[1,4]oxathiinoimidazole (7).

Failure of the intermediate phenolate sulfide 5 to undergo cyclization to afford 7 has several possible explanations. First, it could be argued that the phenolate anion of 5 is a weaker nucleophile than that available in the ethanolic ammonia reaction cited above [9,10] and is consequently unable to displace the 4-nitro substituent. This contention may, however, be ruled out as a possibility since the anion of o-mercaptoaniline also reacted to form the corresponding sulfide but again failed to cyclize [12]. A second possibility was that of a strong intramolecular interaction between the sulfur atom and one of the oxygen atoms of the nitro group which are common to o-nitroaryl sulfides [13-18] and which further have been shown to exert a strong influence on the direction of cyclization during the synthesis of 9-chloro-1-azaphenoxathiin [19]. To test this hypothesis, we undertook the examination of the crystal structure of 6.

The crystal structure of 6 was solved by the heavy atom method as described below. Final positional and thermal parameters are contained in Table I. Atomic labeling, bond distances and bond angles appear in Figures 1 and 2; least-squares planes are given in Table II. Figure 3 illustrates the molecular packing in which molecules are linked by chains parallel to the b axis through fairly strong hydrogen bonds (N4···H17 is 1.97(2) Å).

Although a potentially strong interaction between the sulfur atom and a nitro group oxygen atom was anticipa-

Table IS

Anisotropic Thermal Parameters Expressed as U_{ij} [a] for $C_9H_8N_4O_3S$

Atom	U11	U22	U33	U12	U13	U23
S1	.0188(2)	.0133(2)	.0379(2)	.00164(11)	.01050(14)	.00374(13)
C2	.0182(6)	.0130(5)	.0232(6)	−.0003(4)	.0079(5)	.0014(5)
C3	.0220(6)	.0155(6)	.0231(7)	−.0025(5)	.0089(5)	−.0007(5)
N4	.0305(6)	.0135(5)	.0331(7)	.0000(5)	.0134(5)	.0021(5)
C5	.0278(7)	.0173(6)	.0296(8)	.0030(5)	.0090(6)	.0067(5)
N6	.0211(5)	.0160(5)	.0222(6)	−.0007(4)	.0058(4)	.0016(4)
C7	.0193(6)	.0135(6)	.0222(6)	−.0015(4)	.0063(5)	−.0007(4)
N8	.0218(5)	.0145(5)	.0305(6)	−.0003(4)	.0093(5)	−.0012(4)
C9	.0233(7)	.0214(7)	.0367(8)	−.0010(5)	.0129(6)	−.0039(6)
C10	.0263(7)	.0245(7)	.0320(8)	−.0070(6)	.0136(6)	−.0032(6)
C11	.0292(7)	.0156(6)	.0273(7)	−.0056(5)	.0090(6)	−.0000(5)
C12	.0235(6)	.0123(5)	.0219(6)	−.0005(5)	.0060(5)	−.0001(5)
N13	.0248(6)	.0261(6)	.0256(6)	−.0084(5)	.0089(5)	−.0043(5)
O14	.0298(6)	.0353(6)	.0372(7)	−.0021(5)	−.0032(5)	.0028(5)
O15	.0471(8)	.0311(6)	.0425(7)	−.0155(6)	.0109(6)	−.0169(5)
C16	.0261(7)	.0296(7)	.0237(7)	−.0042(6)	.0023(6)	−.0034(6)
O17	.0294(6)	.0116(4)	.0423(7)	.0032(4)	.0148(5)	.0037(4)

[a] The U_{ij} are the mean-square amplitudes of vibration in Å² from the general temperature factor expression.
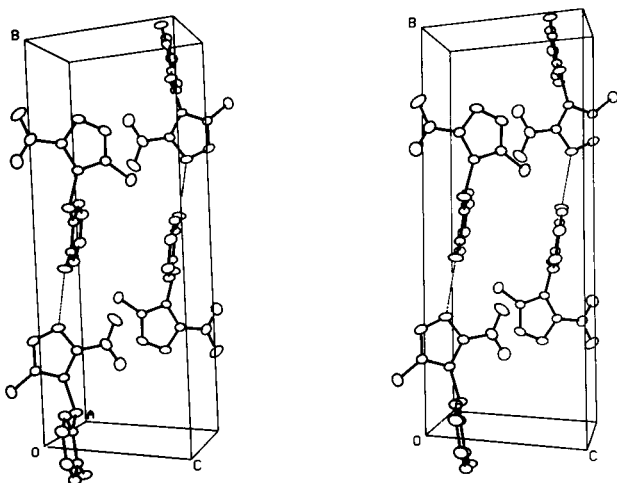
Figure 3. Packing diagram illustrating the hydrogen bonded chain of moelcules parallel to the *b* axis.

Table IIS

Bond Lengths (Å) and Angles (°) Involving Hydrogen Atoms in $C_9H_8N_4O_3S$

1	2	3	1 - 2	1 - 2 - 3
H5	C5	N4	.916(18)	125.7(12)
H5	C5	N6		121.9(12)
H9	C9	N8	.964(24)	117.6(14)
H9	C9	C10		119.6(14)
H10	C10	C9	.925(24)	119.6(12)
H10	C10	C11		121.1(12)
H11	C11	C10	.992(19)	122.0(13)
H11	C11	C12		118.7(13)
H16A	C16	N6	1.011(26)	107.7(12)
H16A	C16	H16B		115.2(20)
H16A	C16	H16C		105.4(21)
H16B	C16	N6	.944(28)	110.1(12)
H16B	C16	H16C		108.5(20)
H16C	C16	N6	.927(23)	109.8(14)
H17	O17	C12	.820(24)	112.8(19)

Table II

Least Squares Planes and the Deviations of Individual Atoms from the Calculated Planes

Plane 1:   composed of C7,N8,C10,C11,C12 (pyridine ring)
$-0.8027x - 2.8724y - 7.0436z = -1.8247$ $x^2 = 46.08$
Deviations:

C7	0.0032(13)	N8	−0.0058(13)	C9	0.0029(17)
C10	0.0025(16)	C11	−0.0051(15)	C12	0.0022(14)
S1	−0.0065(4)	O17	−0.0125(12)	H9	−0.0379(201)
H10	−0.0703(195)	H11	−0.0749(184)	H17	−0.0193(211)

Plane 2:   composed of C2,C3,N4,C5,N6 (imidazole ring)
$6.4339x - 0.3669y - 6.7194z = -1.0956$ $x^2 = 19.62$
Deviations:

C2	−0.0039(15)	C3	0.0026(15)	N4	−0.0001(15)
C5	−0.0025(18)	N6	0.0039(14)	S1	0.0757(4)
N13	0.0167(15)	O14	0.2568(14)	O15	−0.2123(16)
C16	−0.0114(19)	H5	−0.0367(223)		

Plane 3:   composed of C3,N13,O14,O15 (nitro group)
$6.1590x + 3.5952y - 6.7693z = -0.1909$ $x^2 = 0.0001$
Deviations:

C3 = N13 = 0.15	0.0000(15)	O14	0.0000(14)

Dihedral Angles Formed by Planes:
Plane 1-2   64.48°
Plane 2-3   12.46°

ted when the determination of the crystal structure was undertaken, the S1···O14 interatomic distance at 3.1157(14) Å, is only slightly less than the sum of the van der Waals radii of 3.25 Å. Regardless of the apparent weakness of this interaction, it is interesting to note that the orientation of the pyridine and imidazole rings with respect to each other (dihedral angle, 64.5(2)°) allows a lone pair placed at an idealized position on S to lie 0.09 Å from the plane of the imidazole ring. The final difference map shows a density of 0.29 e/Å³ near this position which is 2.52 Å from O14. This suggests that an S1···O14 inter-

action plays a role in the orientation of the rings in this compound. This conformation could be a contributing factor to the failure of **5** to undergo cyclization.

Finally, it is possible that electronic factors may be largely or solely responsible for the failure of **5** to undergo cyclization. Evidence in support of this possibility is provided by observations that nitro-substituents at the 4-position of imidazole rings are the least susceptible to nucleophilic displacement [20,21].

Alternative strategies to induce the displacement of 4-nitro groups from imidazole rings are at present under investigation in these laboratories. Results of these studies will be forthcoming.

EXPERIMENTAL

Melting points were obtained in open capillary tubes using a Thomas-Hoover melting point apparatus and are reported uncorrected. Infrared spectra were determined as potassium bromide pellets on a Perkin-Elmer Model 283 spectrophotometer. Microanalysis was performed by Atlantic Microlab, Inc., Atlanta, GA.

5-(3'-Hydroxypyridyl-2'-thio)-4-nitro-1-methylimidazole (**6**).

A solution containing 1.833 g (0.011 mole) of 5-chloro-4-nitro-1-methyl-imidazole (**2**) which was prepared according to the procedure of Sarasin and Wegmann [11] in 40 ml of dry, distilled DMF was added dropwise with stirring over a period of 45 minutes to a solution containing 1.444 g (0.012 mole) of the disodium salt of 3-hydroxypyridine-2(1H)-thione (**4**) in 40 ml of dry, distilled DMF. During the course of the addition, the solution turned a bright red color. After stirring for 1 hour at room temperature, the reaction mixture was brought to reflux temperature for 16 hours. Upon cooling, the DMF was removed *in vacuo*, the remaining residue washed thoroughly with distilled water and then with methylene chloride. The remaining crude product, which was insoluble in methylene chloride, was crystallized from hot methanol to give 2.01 g (73% yield) of yellowish crystals which melted at 260-262°. The infrared spectrum of the material showed strong absorptions at 3300 (OH) and 1325 (NO_2) cm^{-1}.

Anal. Calcd. for $C_9H_8N_4O_3S$: C, 42.85; H, 3.20; N, 22.21; S, 12.71. Found: C, 42.82; H, 3.21; N, 22.14; S, 12.70.

Table III

Bond Distances (Å), Bond Angles (°) and Torsion Angles (°) in $C_9H_8N_4O_3S$

1	2	3	4	1 - 2	1 - 2 - 3	1 - 2 - 3 - 4
S1	C2	C3	N4	1.7388(13)	132.53(9)	176.43(15)
C2	C3	N4	C5	1.381(2)	112.29(11)	− .3(2)
C3	N4	C5	N6	1.361(2)	104.19(11)	− .2(2)
N4	C5	N6	C2	1.315(2)	112.35(12)	.6(2)
C5	N6	C2	C3	1.353(2)	107.83(11)	− .7(2)
N6	C2	C3	N4	1.378(2)	103.35(11)	.6(2)
C5	N6	C2	S1			− 177.00(14)
N6	C2	S1	C7		123.98(9)	− 64.7(2)
C2	S1	C7	N8		100.51(7)	− 6.78(12)
S1	C7	N8	C9	1.786(2)	120.37(11)	179.96(11)
C7	N8	C9	C10	1.324(2)	117.93(13)	.9(2)
N8	C9	C10	C11	1.343(2)	122.7(2)	− .1(2)
C9	C10	C11	C12	1.383(2)	119.1(2)	− .7(2)
C10	C11	C12	C7	1.389(2)	119.17(14)	.6(2)
C11	C12	C7	N8	1.384(2)	117.42(14)	.2(2)
C12	C7	N8	C9	1.409(2)	123.71(15)	− .9(2)
C11	C12	C7	S1			179.32(10)
C12	C7	S1	C2		115.91(11)	174.05(10)
C7	S1	C2	C3			120.2(2)
O14	N13	C3	C2	1.235(2)	118.29(12)	12.3(3)
N13	C3	C2	S1	1.433(2)	127.90(12)	− 3.3(3)
N13	C3	C2	N6			− 179.1(2)
O15	N13	C3	C2	1.230(2)	117.70(12)	− 167.7(2)
O14	N13	C3	N4			− 167.4(2)
N13	C3	N4	C5		119.81(12)	179.5(2)
O15	N13	C3	N4			12.6(3)
O14	N13	O15			124.01(12)	
C16	N6	C5	N4	1.465(2)	125.36(11)	179.3(2)
C16	N6	C2	C3		126.80(12)	− 179.4(2)
C16	N6	C2	S1			4.4(3)
O17	C12	C11	C10	1.351(2)	125.07(12)	179.55(13)
O17	C12	C7	N8		117.51(14)	− 178.82(12)
O17	C12	C7	S1			.3(2)

X-Ray Crystallography.

A crystal of approximately 0.35 × 0.30 × 0.59 mm was used to measure lattice parameters and intensity data on a Syntex P2₁ diffracto-meter at 173°K, employing graphite monochromated MoKα radiation (λ = 0.71069 Å). The lattice paramaters determined by a least-squares refinement of the 2θ angles of 60 reflections (24° < 2θ < 30°) were a = 7.5728 (13), b = 18.725 (4) and c = 8.1894 (18) Å, β = 113.342 (17)°. The volume was 1066.2 (4) Å³, giving a density of 1.57 g cm⁻¹ for Z = 4. Systematic extinctions (0k0, k odd and h0ℓ, ℓ odd) established the space group as P2₁/c.

Intensities for 3115 unique, non-absent reflections were collected by the ω-scan procedure (Δω = 1.0°, scan rate = 3-6° min⁻¹, $2\theta_{max}$ = 60°). Backgrounds were counted at ω_{peak} ± 1.0° such that each background time equalled half the scan time. Four check reflections (004; 0,10,0; 300; 112) were counted every 96 reflections to measure crystal and instrument stability. The data were corrected for Lorentz and polarization effects, absorption (μ = 3.02 cm⁻¹, correction factor: 1.088-1.107) and crystal and instrument stability (correction factor: 0.999-1.055). The σ(I) and σ(F₀) were determined as described by Stout and Jensen [22] where ϱ = 0.04.

The S position, obtained from a Patterson map, gave an R = 0.552. Twelve additional atoms found in a ΔF map refined by full-matrix least-squares (Σω(|F₀| − |F₀|)² minimized, ω = 1/σ²) to an R = 0.323. The po-sitions for the remaining four non-hydrogen atoms were determined from a second ΔF map. Refinement of all positional and isotropic ther-mal parameters resulted in R = 0.119. After refinement of positions and anisotropic thermal parameters (R − 0.054), all hydrogens were located

in a ΔF map as peaks of 0.64-0.82 e Å⁻³. Refinement of all atomic posi-tions, anisotropic thermal parameters for non-hydrogen atoms and iso-tropic thermal parameters for hydrogen atoms converged at R = 0.036 (R_ω = 0.049) with parameter shifts less than 0.02σ. The goodness of fit was 1.84 for m = 2565 (I > 3σ(I)) and n = 186 [23]. All peaks in the final difference map greater than 0.11 e Å⁻³ (maximum 0.39 e Å⁻³) were loca-ted in expected regions of bonding and lone pair electrons. Scattering factor tables for C, O, S were taken from Cromer and Waber [24]; H-tables were taken from Stewart, Davidson and Simpson [25]. Anoma-lous dispersion corrections for S were taken from the International Tables for X-ray Crystallography [26]. Computational details were car-ried out with programs listed elsewhere [27].

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