METHYLATION OF PYRIDAZINES. THE CRYSTAL AND MOLECULAR STRUCTURE OF 4,5-DIAMINO-1-METHYL-3-METHYLTHIOPYRIDAZINIUM IODIDE

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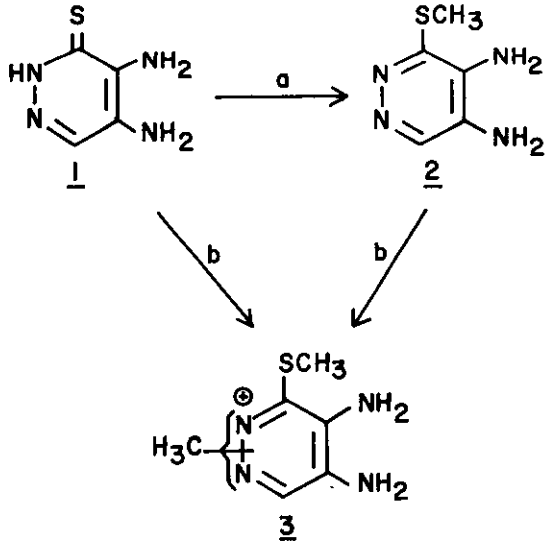
Abstract - The crystal and molecular structure of 4,5-diamino-1-methyl-3-methylthiopyridazinium iodide (3) has been determined. This X-ray crystallographic study corroborates the suggested course of methylation of substituted pyridazines and established the direction of ring closure of mucochloric acid with methylhydrazine.

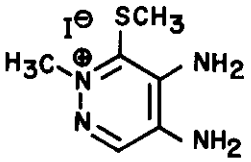
We were exploring synthetic pathways to certain 4-substituted imidazo- and v-triazolo[4,5-d]-pyridazines in anticipation that these derivatives might serve as possible chemotherapeutic agents. One possible route which could provide either bicyclic ring system required 4,5-diamino-3-methylthiopyridazine (2) as a precursor. This key intermediate had been synthesized[2] by methylating 4,5-diaminopyridazin-3-thione (1) with methyl iodide under basic conditions. Following the published procedure which called for a 60% excess of methyl iodide we obtained a dimethylated heterocycle (3) rather than the desired 2 (Scheme 1). Elemental analysis confirmed the occurrence

Scheme 1

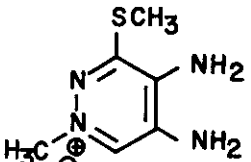


[a]Methyl iodide (1 equiv.) 0.5 N KOH, [b]methyl iodide (excess) 0.5 N KOH

of dimethylation and spectral data (uv and ^{1}H nmr) strongly suggested that methylation took place on sulfur and on one of the two ring nitrogens. Thus, only two structures were possible: structure A and structure B.



A

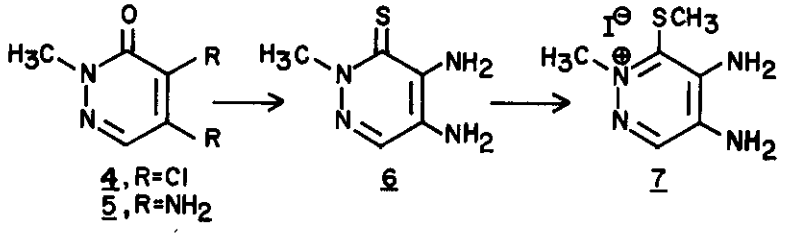


B

Chemical intuition and our preliminary data favored structure B. The course of methylation of 3-substituted pyridazines had been examined[3] and experimental evidence suggested that certain functional groups could influence the site of alkylation as a result of their inductive effect. Those groups which activated the adjacent nitrogen, e.g., methyl (+I), gave rise to N(2)-methylated derivatives whereas those substituents which deactivate this position, e.g., methylthio(-I), favored alkylation on N(1). When exactly one equivalent of methyl iodide was used (Scheme 1), the sole product of the reaction was 2. Reacting 2 with methyl iodide in a basic medium afforded 3. Therefore, based on the aforementioned substituent arguments, 2 should give rise to B. We exercised caution, however, in making such an assignment since the pyridazines examined in this earlier study were only substituted on C(3). We were not certain what effect other substituents on the pyridazine ring could have on the course of methylation and realized that a structural assignment made only on electronic arguments would be equivocal. In addition, it had been pointed out that the structures of the N-methylated, 3-substituted pyridazines were based solely on physical evidence (mainly uv spectra) and had never been confirmed by an unambiguous synthesis.[4]

Realizing that an unequivocal synthesis of B would be difficult, we turned our attention to the preparation of A. Treatment of mucochloric acid with methylhydrazine provided 4,5-dichloro-

Scheme 2



4, R=Cl
5, R=NH2

6

7

2-methylpyridazin-3-one[5] (4). Then a four-step sequence furnished 4,5-diamino-2-methylpyridazin-3-thone (6) which in turn was reacted with methyl iodide to provide a quantitative yield of 4,5-diamino-2-methyl-3-methylthiopyridazinium iodide (7, A). A spectral comparison (see Tables 1 and 2)of 7 and 3 indicated that the two heterocycles were different. Of particular interest were the carbon-13 chemical shift data. An investigation[6] involving pyridine and pyridine methiodide, in a neutral solvent, showed that the carbon chemical shift of the carbon adjacent to the site of methylation, i.e., α or C(2),experienced a shielding effect (-4.1 ppm) going from pyridine to pyridine methiodide whereas the β (C(3)) and γ (C(4)) carbon chemical shifts reflected a de-shielding effect (+ 3.5 ppm and + 8.3 ppm, respectively). An inspection of our data (Table 2) shows that the carbon chemical shifts for those carbons adjacent (α) to the suspected site of methylation were shielded, but, in each case, so were those carbon chemical shifts of the respective β carbon. Although the magnitudes of the carbon chemical shifts for the α carbons were larger, an assignment based entirely on this spectral feature would again be equivocal.

Even though the preparation of 7 was straightforward, we were still somewhat reluctant to finalized the structural assignments of these heterocycles. A range of melting points have been reported[5] for 4 and ring closures with methylhydrazine have been known[7,8,9] to produce the unexpected product. If the mode of annulation with methylhydrazine and mucochloric acid occurred in the opposite manner, this could account for the difference in the reported melting points of 4. In view of these documented anomalies and in order to avoid misassigning these heterocycles, we subjected 3 to an X-ray crystallographic analysis. Diffraction data were collected on an Enraf-Nonius CAD4 automatic diffractometer equipped with molybdenum radiation [$\lambda(MoK\bar{\alpha})$ = 0.7107 Å] and a graphite monochromator. Accurate cell constants were obtained by least squares refinement of the diffractometer angle settings for 25 reflections. The cell constants and other crystal information are listed in Table 3. The crystal is in space group $P2_1/n$ of the monoclinic system. A total of 2904 independent, observed reflections was processed of which 2035 had $I \geq \sigma(I)$. Only these latter data were used in the solution and refinement of the structure. Complete details of data collection and structure solution and refinement will be published elsewhere.[10]

The most important feature of the structure of 3 is the confirmation that the ring methyl group is attached to N(1) rather than N(2). A view of the pyridazinium cation is shown in Figure 1. The molecular dimensions, which are listed in Table 4, revealed no uncharacteristic features; all distances and angles fell within the ranges observed in other pyridazine structures.[11-17] The pyridazine ring is planar with no atom deviating from the 6-atom least squares plane by more than 0.013 Å, which is typical for pyridazines. All substituent atoms lie no further than 0.10 Å from the ring plane. This includes the methylthio carbon atom, C(7), which lies toward N(2)

TABLE 1. Ultraviolet Spectral Data for Certain 4,5-Diaminopyridazines[a]

	Compound[b]	solvent	λmax(nm)	ε x 10^{-3}
1	4,5-Diaminopyridazin-3-thione	H_2O	342.0	9.29
			263.5	12.39
			242.5	11.94
2	4,5-Diamino-3-methylthiopyridazine	H_2O	339.5 sh[c]	3.06
			300.0	7.19
			259.5 sh	8.44
			241.5	13.47
3	4,5-Diamino-1-methyl-3-methylthio-pyridazinium iodide (B)	H_2O	336.0	8.94
			303.5 sh	6.38
			260.0	16.85
			225.0	23.85
6	4,5-Diamino-2-methylpyridazin-3-thione	H_2O	341.0	11.36
			263.5	15.89
			244.0	15.50
7	4,5-Diamino-2-methyl-3-methylthio-pyridazinium iodide (A)	H_2O	342.0	11.60
			278.5 sh	2.74
			229.0	24.90

[a]Spectra were recorded on a Beckman DB-GT Spectrophotometer. [b]Satisfactory analyses (C, H, N) were obtained for all compounds. [c]sh = shoulder.

TABLE 2. Carbon-13 Chemical Shifts[a] of Certain Methylated 4,5-Diaminopyridazines

Compound	Solvent	C6[b]	C4/C5	C3	NCH_3	SCH_3
7(A)	DMSO-d_6	132.5_0	137.5_4, 137.0_5	134.8_9	49.7_0	16.1_5
2	DMSO-d_6	137.2_1	130.2_7, 128.4_6	144.8_7		13.1_8
3(B)	DMSO-d_6	128.9_2	133.2_7, 132.1_5	143.8_7	49.6_4	13.4_1

[a]Chemical shifts are in parts per million with respect to TMS. Spectra were obtained on a Varian CFT-20 Spectrometer at ambient temperature. A flip angle (α) of 42.5° was employed. [b]Off-resonance decoupling experiments verified the assignment of C6.

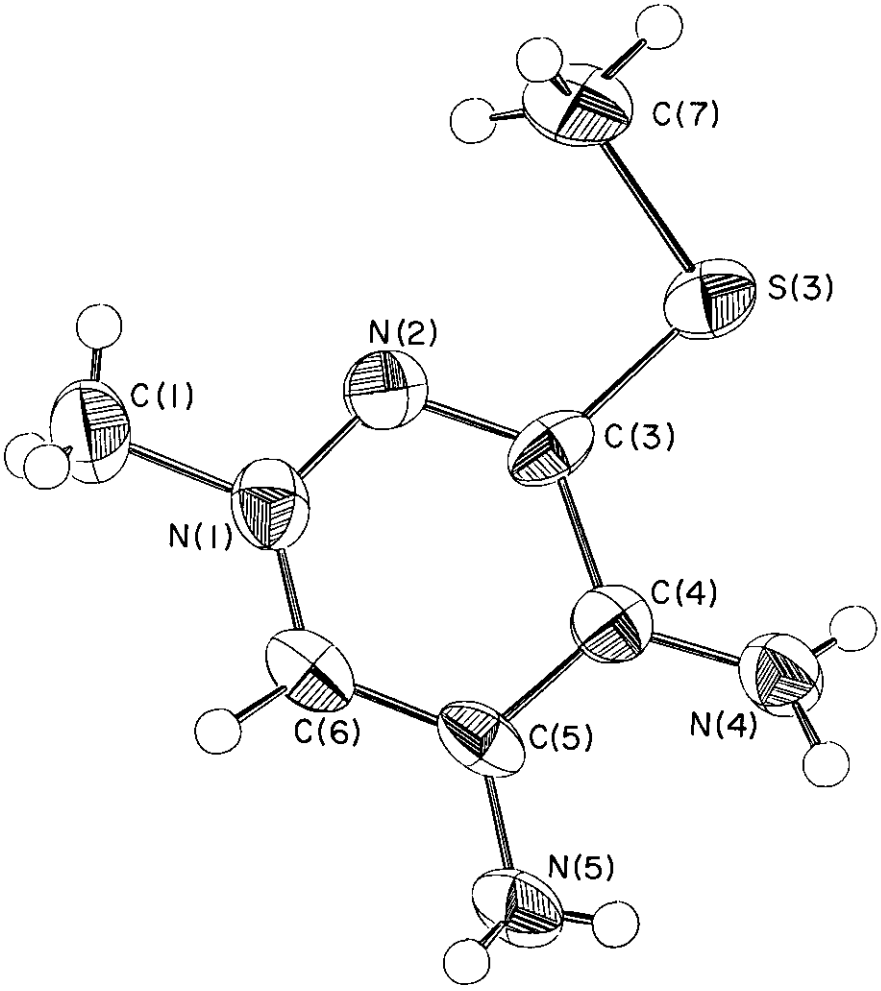


Figure 1. The Pyridazinium Cation as Viewed Along $\underline{a}^*$ and the Numbering Scheme Employed.

TABLE 3. Crystal Data for 4,5-Diamino-1-methyl-3-methylthiopyridazinium Iodide

Formula	$C_6H_{11}N_4S^+I^-$	Space group	$P2_1/n$
Mol. wt.	298.15 g $mole^{-1}$	Z	4
	a = 7.549(2) Å	D_o (THF/$CHBr_3$)	1.861 g cm^{-3}
	b = 9.605(2) Å	D_c	1.875 g cm^{-3}
	c =14.568(2) Å	$\mu(MoK\bar{\alpha})$	32.14 cm^{-1}
	β =89.11(2)°		

TABLE 4. Distances and Angles Involving Non-hydrogen Atoms in 4,5-Diamino-3-methylthio-1-methylpyridazinium Iodide

Atoms	Distance, Å	Atoms	Angle, deg.
N(1) - C(1)	1.487(5)	C(1) - N(1) - C(6)	121.0(3)
N(1) - N(2)	1.345(4)	C(1) - N(1) - N(2)	114.7(3)
N(2) - C(3)	1.328(4)	C(6) - N(1) - N(2)	124.3(3)
C(3) - S(3)	1.763(4)	N(1) - N(2) - C(3)	116.8(3)
S(3) - C(7)	1.782(5)	N(2) - C(3) - S(3)	118.5(2)
C(3) - C(4)	1.425(4)	C(3) - S(3) - C(7)	101.2(3)
C(4) - N(4)	1.333(5)	S(3) - C(3) - C(4)	116.8(3)
C(4) - C(5)	1.422(5)	N(2) - C(3) - C(4)	124.7(3)
C(5) - N(5)	1.349(4)	C(3) - C(4) - N(4)	121.8(3)
C(5) - C(6)	1.400(5)	N(4) - C(4) - C(5)	122.7(3)
C(6) - N(1)	1.326(5)	C(3) - C(4) - C(5)	115.5(3)
		C(4) - C(5) - N(5)	121.3(3)
		N(5) - C(5) - C(6)	120.7(3)
		C(4) - C(5) - C(6)	118.0(3)
		C(5) - C(6) - N(1)	120.7(3)

and away from the amino group at C(4).

The purpose of this X-ray crystallographic study was threefold: (1) it established the structure of 3 as B; (2) it reaffirmed the suggested course[3] of methylation of substituted pyridazines; and (3) it proved that ring closure of mucochloric acid with methylhydrazine occurred in the proper manner to furnish 4 and thus establishes 7 as A.

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