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Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713618290>

THE STRUCTURE AND REACTIONS OF 4-PHENYL-5-HYDROXY-5,6-DIHYDRO-1,3,4-THIADIAZINE

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To cite this Article Matsubara, Yoshio, Yamada, Shigeji, Yoshihara, Masakuni and Maeshima, Toshihisa (1985) 'THE STRUCTURE AND REACTIONS OF 4-PHENYL-5-HYDROXY-5,6-DIHYDRO-1,3,4-THIADIAZINE', *Phosphorus, Sulfur, and Silicon and the Related Elements*, 22: 1, 41 – 47

To link to this Article: DOI: 10.1080/03086648508073353

URL: <http://dx.doi.org/10.1080/03086648508073353>

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THE STRUCTURE AND REACTIONS OF 4-PHENYL-5-HYDROXY-5,6-DIHYDRO- 1,3,4-THIADIAZINE

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(Received July 12, 1984; in final form September 17, 1984)

4-Phenyl-5-hydroxy-5,6-dihydro-1,3,4-thiadiazine **1** was prepared by the reduction of 4-phenyl-5-oxo-5,6-dihydro-1,3,4-thiadiazine **4** using lithium aluminum hydride (LAH). The structure of **1** was investigated by ^1H -NMR, ^{13}C -NMR and UV spectroscopies and X-ray analysis. Treatment of **1** with alcohols, thiols and amines gave the corresponding 5-alkyloxy-, 5-alkylthio- and 5-alkylamino-4-phenyl-5,6-dihydro-1,3,4-thiadiazines **2** in almost quantitative yields. The mechanism of formation of **2** is discussed.

INTRODUCTION

Recently we reported that methyl phenylhydrazonomethylthioacetate **3** is in an equilibrium with 4-phenyl-5-oxo-5,6-dihydro-1,3,4-thiadiazine **4** by the treatment with triethylamine in methanol.¹ The results of X-ray analysis of **3** and **4** suggest that the π -electrons of the thioformimidate group ($-\text{N}=\text{CH}-\text{S}-$) in **3** and **4** may be delocalized by a through-space interaction between the sulfur and carbonyl carbon atoms.

A question arises whether the resonance stabilization is caused by the electron-accepting carbonyl group at the 5-position of the ring. Thus, the title compound **1**, in which the 5-carbon has an sp^3 instead of an sp^2 configuration as in **4**, was subjected to X-ray analysis and reaction with several nucleophiles. The results are discussed in terms of the resonance stabilization of the ring.

RESULTS AND DISCUSSION

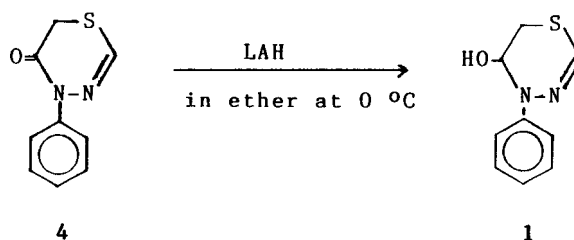
Structure of 4-phenyl-5-hydroxy-5,6-dihydro-1,3,4-thiadiazine 1

The compound **1** was prepared by the reduction of 4-phenyl-5-oxo-5,6-dihydro-1,3,4-thiadiazine **4** using lithium aluminum hydride (LAH) in good yield. Table I summarizes the data of the ^1H -NMR, ^{13}C -NMR and UV spectra of **1** and **4**. The data of ^1H -NMR and ^{13}C -NMR spectra supported the assigned structure. It is noted that the λ max value of **1** at 285 nm is much greater than that of **4** at 300 nm.

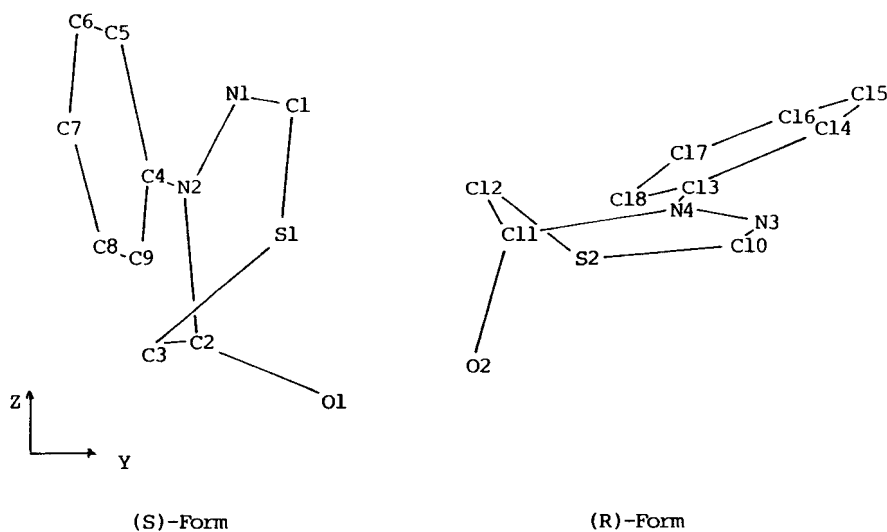
The X-ray analysis of **1** was carried out and the results are given in Figures 1, 2 and Tables II-V. Figures 1 and 2 indicate that a unit is built up as a pair of (S)- and (R)-stereomers by the hydrogen-bonding interaction, and the O(1)-O(2) distance is

TABLE I
 ^1H -, ^{13}C -NMR and UV spectra of **1** and **4**

Compound	^1H -NMR (ppm)		^{13}C -NMR (ppm)			UV (cyclohexane)	
	—CH=	—CH—	C-5	C-2	C-6	λ_{max} (nm)	ϵ_{max}
1	7.10	3.04	71	124	29	250	10 200
4	7.73	3.75	153	136	27	285	14 640
						240	12 000
						300	2 800



2.72 Å. One unit cell of the crystal contains four pairs of (S)- and (R)-forms ($Z = 4$). The S(1)–C(1)–N(1)–N(2) and S(2)–C(10)–N(3)–N(4) planes are coplanar. Furthermore, although the last cycle of refinement factor is $R = 0.109$, the standard deviations of O(1)–C(2), S(2)–C(10), S(2)–C(12), N(3)–N(4) and N(4)–C(11) distances are quite large (0.63–0.83), indicating that each bond length in the ring of **1** varies even in the crystal.


 FIGURE 1 A unit of crystal structure **1** viewed looking onto the Z-Y plane.

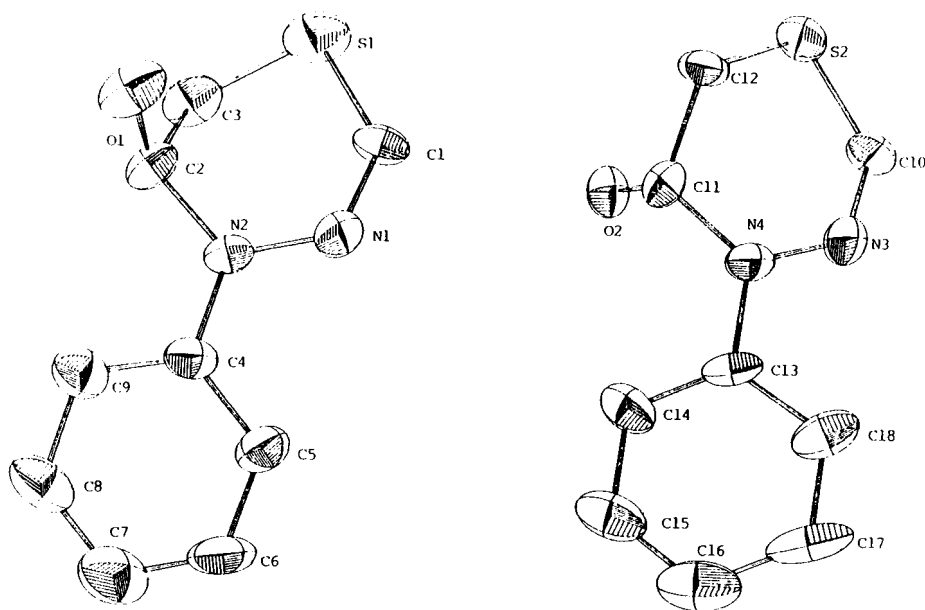


FIGURE 2 ORTEP drawing of compounds (S)- and (R)-1.

5-Substituted-4-phenyl-5,6-dihydro-1,3,4-thiadiazine 2 from 1

The reaction of **1** with alcohols, thiols and amines proceeded easily to give the corresponding 5-alkoxy-, 5-alkylthio- and, 5-alkylamino-4-phenyl-5,6-dihydro-1,3,4-thiadiazines **2** in almost quantitative yields and the results of these conversions are summarized in Table II.

It seems worthy of note that the hydroxy group of **1** can easily be substituted by other nucleophiles without catalysis, because no reaction occurred during treatment of 3-hydroxy-dihydropyridazine **5** with alcohols, thiols and amines and also because rather strong acids such as Lewis acids and superacids are usually applied for the dehydroxylation of alcohols. The possibility of an S_N2 process may also be excluded because both the leaving ability and nucleophilicity of alkoxyl and hydroxyl groups are similar and also the tertiary butyl group has a large steric requirement (Table I). One possible assumption may be that the carbonium-ion intermediate, 5,6-dihydro-1,3,4-thiadiazinium cation, is formed by the unimolecular fission of the carbon-oxygen bond of **1**, perhaps via stabilization of the resulting iminium ion by electron donation from sulfur into the hydrazono function, and is then attacked by the nucleophiles to give the corresponding substituted products. Another possibility may be that the carbonium-ion intermediate thus formed has six π -electrons, namely homoaromaticity, in the ring via an anchimeric through-space interaction between the sulfur atom and the carbon atom at the 5-position. A possible example of homoaromaticity was recently observed for the 1,1,4-trimethyl-1,4-dihydro-1,2,4,5-tetrazinium cation.²⁻⁶

TABLE II
Reaction of **1** with several alcohols, thiols and amines

1

2

Reagent RXH	Product RX—	Yield (%)	¹ H-NMR spectra (ppm)			
			Ha	Hb	Hc	R
—	HO—	—	3.04		5.58	3.18 (d, 1 H, —OH)
MeOH	MeO—	≈ 100	3.13		5.39	3.31 (s, 3 H, —CH ₃)
EtOH	EtO—	≈ 100	3.17		5.51	1.16 (t, 3 H, —CH ₃), 3.55 (q, 2 H, —CH ₂ —)
Allyl-OH	Allyl-O—	≈ 100	3.20		5.55	4.04 (d, 2 H, —CH ₂ —), 5.15 (m, 2 H, CH ₂ =), 5.80 (m, 1 H, =CH—)
EtSH	EtS—	≈ 100	3.77	3.20	5.53	1.12 (t, 3 H, —CH ₃), 2.48 (q, 2 H, —CH ₂ —)
<i>n</i> -BuSH	<i>n</i> -BuS—	≈ 100	3.73	3.17	5.50	0.79 (t, 3 H, —CH ₃), 1.30–1.50 (m, 4 H, —CH ₂ CH ₂ —)
<i>s</i> -BuSH	<i>s</i> -BuS—	≈ 100	3.82	3.18	5.49	0.80–1.70 (m, 8 H, —CH ₂ CH ₃ , —CH ₃), 2.63 (m, 1 H, CH)
<i>t</i> -BuSH	<i>t</i> -BuS—	≈ 100	3.97	3.12	5.22	1.12 (s, 9 H, <i>t</i> -Bu)
PhSH	PhS—	≈ 100	3.36	3.15	5.64	7.10 (s, 5 H, —Ph)
<i>n</i> -BuNH ₂	<i>n</i> -BuNH—	91		3.16	5.13	0.84 (t, 3 H, —CH ₃), 1.20–1.40 (m, 4 H, —CH ₂ CH ₂ —), 2.58 (t, 2 H, —CH ₂ —)
HOCH ₂ CH ₂ NH ₂	HOCH ₂ CH ₂ NH—	≈ 100		3.15	5.12	2.68 (t, 2 H, —CH ₂ —), 3.48 (t, 2 H, —CH ₂ —)

^aAll products were oily compound and gave satisfactory microanalyses: (C ± 0.20, H ± 0.25, N ± 0.12).

EXPERIMENTAL

General Data. Melting points were obtained on a Yanaco hot-stage apparatus and are uncorrected. The ¹H-NMR spectra were recorded on a JEOL FX-200 NMR spectrometer at 200 MHz with TMS as an internal standard. Infrared spectra were run on a JASCO IR-A1 spectrometer with the samples in potassium bromide pellets. UV-absorption spectra were recorded on a Hitachi 124 spectrometer.

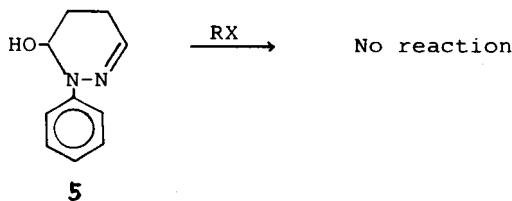


FIGURE 3

Preparation of Materials. 4-Phenyl-5-oxo-5,6-dihydro-1,3,4-thiadiazine **4**. This compound was prepared as described in the preceding papers.^{1,7}

4-Phenyl-5-hydroxy-5,6-dihydro-1,3,4-thiadiazine 1. To a solution of 61 mg of LAH in 5 ml of THF was added dropwise a solution of 1 g of **4** in 10 ml of THF at -10°C under dry nitrogen atmosphere. After the mixture was stirred for 6 hr, water and 1 g of Na_2SO_4 were added. After extraction of the water layer with ether, drying of the extract over Na_2SO_4 , and evaporation of the ether, **1** was obtained and purified by recrystallization from hexane in 93% yield, mp $73\text{--}75^{\circ}\text{C}$. For $^1\text{H-NMR}$ spectroscopic data see Table I. The compound must be stored below 0°C .

General procedure for conversion of 1 to 5-substituted-4-phenyl-5,6-dihydro-1,3,4-thiadiazines 2. A mixture of **1** (1 mmol) and alcohols, thiols or amines (1 ml) was stirred for 12 to 100 hr at room temperature. Progress of the reaction was monitored by TLC, and then the unreacted reagent was evaporated *in vacuo* to give **2** in almost pure form. The purification of **2** was by column chromatography (hexane-ether). The properties of **2** prepared in this way and $^1\text{H-NMR}$ spectroscopic data are summarized in Table VI.

TABLE III
Experimental data for the X-ray diffraction study

Parameter	
Formula	$\text{C}_{18}\text{H}_{20}\text{N}_2\text{OS} \cdot (\text{C}_9\text{H}_{10}\text{N}_2\text{OS})_2$
Formula weight	356.5 (178.25) ₂
Crystal system	Monoclinic
Space group	P 2 ₁ /C
a, Å	19.256(5)
b, Å	10.076(3)
c, Å	19.486(5)
α, β, γ , deg	150.76(2)
V, Å ³	1847.2
Z	4
D, g · cm ³	1.40
Cryst. dimension	0.25 × 0.15 × 0.23
Radiation	MoK α
R	0.109

TABLE IV
Atomic coordinates for nonhydrogen atoms with their standard deviation in parentheses

Atom	(S)-Form of 1			Atom	(R)-Form of 1		
	X	Y	Z		X	Y	Z
S1	0.1505(3)	0.0477(3)	0.0847(3)	S2	0.1622(2)	0.5377(2)	0.0952(2)
O1	0.3352(6)	−0.0989(6)	0.1382(6)	O2	0.4106(5)	0.4332(5)	0.2069(5)
N1	0.2419(8)	0.1961(6)	0.0554(8)	N3	0.1003(7)	0.5703(9)	−0.0926(7)
N2	0.2206(8)	0.0921(6)	−0.0088(8)	N4	0.2438(7)	0.5852(7)	0.0134(7)
C1	0.2161(10)	0.1855(9)	0.0980(10)	C10	0.0570(9)	0.5481(10)	−0.0694(10)
C2	0.2031(9)	−0.0448(8)	−0.0003(9)	C11	0.3628(8)	0.5681(7)	0.1644(8)
C3	0.0923(9)	−0.0517(9)	−0.0383(9)	C12	0.3260(9)	0.6171(8)	0.2045(9)
C4	0.2585(8)	0.1181(8)	−0.0452(8)	C13	0.2734(9)	0.6159(8)	−0.0310(8)
C5	0.2446(10)	0.2494(9)	−0.0822(9)	C14	0.4100(9)	0.5886(9)	0.0590(10)
C6	0.2806(10)	0.2720(10)	−0.2113(10)	C15	0.4365(10)	0.6179(10)	0.0133(11)
C7	0.3272(10)	0.1714(10)	−0.1247(10)	C16	0.3285(11)	0.6714(10)	−0.1215(10)
C8	0.3373(9)	0.0437(10)	−0.0899(9)	C17	0.1873(10)	0.6997(10)	−0.2146(10)
C9	0.3053(9)	0.0146(9)	−0.0484(8)	C18	0.1594(10)	0.6712(9)	−0.1696(9)

TABLE V
Bond distance (Å) with their standard deviations
in parentheses

(S)-Form of 1		(R)-Form of 1	
S(1)–C(1)	1.74(10)	S(2)–C(10)	1.75(63)
S(1)–C(3)	1.82(21)	S(2)–C(12)	1.84(64)
O(1)–C(2)	1.44(83)	O(2)–C(11)	1.43(15)
N(1)–C(2)	1.40(10)	N(3)–N(4)	1.40(70)
N(1)–C(1)	1.28(6)	N(3)–C(10)	1.26(6)
N(2)–C(2)	1.46(4)	N(4)–C(11)	1.47(78)
N(2)–C(4)	1.41(7)	N(4)–C(13)	1.43(7)
C(2)–C(3)	1.53(17)	C(11)–C(12)	1.52(7)
C(4)–C(5)	1.41(7)	C(13)–C(14)	1.42(5)
C(4)–C(9)	1.41(7)	C(13)–C(18)	1.44(7)
C(5)–C(6)	1.42(7)	C(14)–C(15)	1.39(7)
C(6)–C(7)	1.39(7)	C(15)–C(16)	1.41(7)
C(7)–C(8)	1.38(7)	C(16)–C(17)	1.47(6)
C(8)–C(9)	1.40(7)	C(17)–C(18)	1.47(7)

TABLE VI
Bond angles (°) with their standard deviation
in parentheses

(S)-Form of 1		(R)-Form of 1	
C(1)–S(1)–C(3)	100(10)	C(10)–S(2)–C(12)	100(37)
N(2)–N(1)–C(1)	123(4)	N(4)–N(3)–C(10)	124(64)
N(1)–N(2)–C(2)	121(4)	N(3)–N(4)–C(11)	124(33)
N(1)–N(2)–C(4)	116(5)	N(3)–N(4)–C(13)	116(19)
C(2)–N(2)–C(4)	120(4)	C(11)–N(4)–C(13)	119(14)
S(1)–C(1)–N(1)	127(4)	S(2)–C(10)–N(4)	126(23)
O(1)–C(2)–N(2)	111(20)	O(2)–C(11)–N(4)	111(16)
O(1)–C(2)–C(3)	109(22)	O(2)–C(11)–C(12)	111(4)
N(2)–C(2)–C(3)	110(28)	N(2)–C(11)–C(12)	112(14)
S(1)–C(3)–C(2)	110(18)	S(2)–C(12)–C(11)	111(32)
N(2)–C(4)–C(5)	118(4)	N(4)–C(13)–C(14)	120(19)
N(2)–C(4)–C(9)	120(3)	N(4)–C(13)–C(18)	117(11)
C(5)–C(4)–C(9)	120(4)	C(14)–C(13)–C(18)	123(30)
C(4)–C(5)–C(6)	117(4)	C(13)–C(14)–C(15)	119(20)
C(5)–C(6)–C(7)	122(4)	C(14)–C(15)–C(16)	120(11)
C(6)–C(7)–C(8)	118(5)	C(15)–C(16)–C(17)	120(21)
C(7)–C(8)–C(9)	121(4)	C(16)–C(17)–C(18)	119(19)
C(4)–C(9)–C(8)	119(4)	C(13)–C(18)–C(17)	118(11)

Reaction of **5** with alcohols, thiols or amines. A mixture of **5** (1 mmol) and alcohols, thiols or amines (1 ml) was stirred at room temperature for 100 hr. No reaction was found to take place by TLC and NMR spectral analyses.

X-ray Analysis of 1. A single crystal of compound **1** was prepared by slow crystallization from hexane. The measurement was performed on a Rigaku AFC-5 diffractometer using graphite-monochromated MoK α radiation ($\lambda = 0.7107$ Å). The cell parameters were determined by least-squares fitting of 25 reflections in the range of $28^\circ < 2\theta < 37^\circ$. The intensities of reflections with two values up to 50° were collected by the scan technique ($2\theta < 30^\circ$) or 2θ scan technique ($30^\circ < 2\theta < 50^\circ$) with a scan rate of 4/min. The structure was solved by the direct method using a MULTAN 78 program, and was refined by the full-matrix least-squares method, minimizing the function $\sum_w (F_o - F_c)^2$ with $w = \sigma^{-2}$. The last cycles of refinement, which included an isotropic thermal parameters converged the discrepancy factors $R = 0.109$ for the 3536 observed reflections. The crystal data are given in Table III.⁸

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8. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, UK. Requests should be accompanied by the full literature citation for this paper.