

# The Crystal Structures of 2-Isopropylamino-6-methyl-5-phenyl-6*H*-1,3,4-thiadiazine and 2-Isopropylamino-6-methyl-5-phenyl-6*H*-1,3,4-selenadiazine

Klaus Szulzewsky,<sup>a</sup> Wolf-Diethard Pfeiffer,<sup>b</sup> Ehrenfried Bulka,<sup>b,\*</sup> Harald Rossberg<sup>b</sup> and Burghard Schulz<sup>a</sup>

<sup>a</sup> Central Institute of Physical Chemistry, formerly Academy of Sciences, D-O-1199 Berlin, Germany and <sup>b</sup> Department of Chemistry, University of Greifswald, D-O-2200 Greifswald, Germany

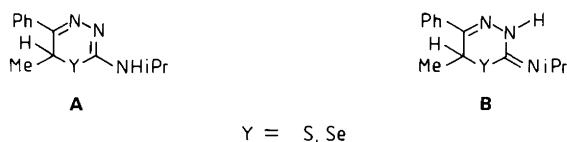
Szulzewsky, K., Pfeiffer, W.-D., Bulka, E., Rossberg, H. and Schulz, B., 1993. The Crystal Structures of 2-Isopropylamino-6-methyl-5-phenyl-6*H*-1,3,4-thiadiazine and 2-Isopropylamino-6-methyl-5-phenyl-6*H*-1,3,4-selenadiazine. – Acta Chem. Scand. 47: 302–306.

The structures of the title compounds have been determined by single-crystal X-ray methods. C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>S: *P*2<sub>1</sub>/*a*, *a* = 15.019(3), *b* = 9.918(3), *c* = 9.341(2) Å, β = 109.85(3)°, *V* = 1308.7(9) Å<sup>3</sup>, *Z* = 4, *D*<sub>x</sub> = 1.255 Mg m<sup>-3</sup>, final *R* = 0.077 for 3013 unique reflections. C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>Se: *P*2<sub>1</sub>/*a*, *a* = 19.523(3), *b* = 6.073(2), *c* = 12.241(2), β = 107.70(2)°, *V* = 1382.6(9) Å<sup>3</sup>, *Z* = 4, *D*<sub>x</sub> = 1.413 Mg m<sup>-3</sup>, final *R* = 0.067 for 2681 unique reflections.

1,3,4-Thiadiazines and 1,3,4-selenadiazines undergo ring contraction with remarkably different rates. The X-ray crystal structure analyses were undertaken in order to account for this behaviour. The molecular structures of both compounds differ in the position of one hydrogen atom which is localized on different nitrogen atoms. Correlation of the different hydrogen positions in both structures with the ring contraction is possible.

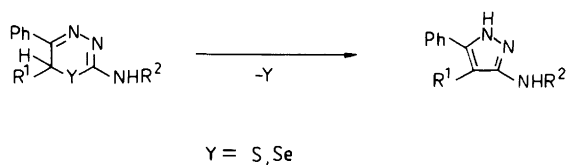
Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

1,3,4-Thiadiazines and 1,3,4-selenadiazines undergo, in the presence of acids or bases, ring contraction with extrusion of sulphur and selenium, respectively, and formation of pyrazoles (Scheme 1).<sup>1–14</sup> The rates of ring contraction for the compounds differ considerably; 1,3,4-thiadiazines split faster than 1,3,4-selenadiazines.<sup>13, 14</sup> This unexpected observation indicates a higher stability of 1,3,4-selenadiazines than of 1,3,4-thiadiazines. The present X-ray crystal structure analysis of the title compounds with the structural formulas **A** and **B** were undertaken in order to determine the reason for the different stabilities.



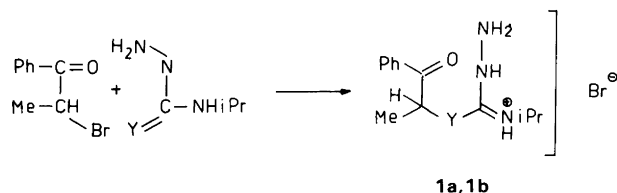
**Syntheses.** The ring-opened intermediates 3-(1-benzoyl-ethyl)-4-isopropylisothiosemicarbazide hydrobromide **1a** and 3-(1-benzoyl-ethyl)-4-isopropyliselenosemicarbazide hydrobromide **1b** were formed by reaction of α-bromopropiophenone with 4-isopropylthiosemicarbazide and 4-isopropylselenosemicarbazide, respectively

\* To whom correspondence should be addressed.

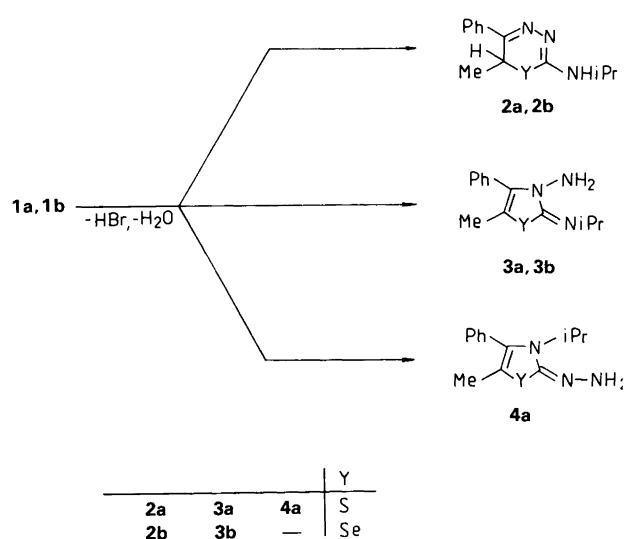


Scheme 1.

(Scheme 2). The mixtures were stirred at –20°C for 4 h. The 2-isopropylamino-6-methyl-5-phenyl-6*H*-1,3,4-thiadiazine **2a** and 2-isopropylamino-6-methyl-6*H*-selenadiazine **2b** were prepared by heating the corresponding ring-opened intermediates **1a** and **1b**, in ethanol. In addition, about 1% of 2-isopropylimino-3-amino-5-methyl-4-phenyl-4-thiazoline **3a**, 17.4% 2-isopropylimino-3-amino-5-methyl-4-phenyl-4-selenazoline **3b** and traces of the corresponding hydrazone derivate **4a** were formed (Scheme 3).



Scheme 2.



Scheme 3.

### Experimental

*3-(1-Benzoyl-ethyl)-4-isopropylisothiosemicarbazide hydrobromide 1a and 3-(1-benzoyl-ethyl)-4-isopropylselenosemicarbazide hydrobromide 1b. General procedure.* 4-Isopropylthiosemicarbazide (0.1 mol) and 4-isopropylselenosemicarbazide (0.1 mol), respectively, were dissolved in 40 ml of ethanol and cooled to  $-20^{\circ}\text{C}$ . A solution of  $\alpha$ -bromopropiophenone (0.1 mol), 30 ml ethanol and 30 ml ether was added dropwise with vigorous stirring. After 4 h colourless crystals of **1a** or **1b** precipitated. The products were washed with a chilled ethanol-ether mixture.

**1a**: yield, 68%, m.p.  $205^{\circ}\text{C}$ , IR:  $\nu_{\text{CO}}$   $1645\text{ cm}^{-1}$ . Anal.  $\text{C}_{13}\text{H}_{20}\text{BrN}_3\text{OS}$ : C, H, N, S.

**1b**: yield, 74%, m.p.  $135\text{--}136^{\circ}\text{C}$ , IR:  $\nu_{\text{CO}}$   $1650\text{ cm}^{-1}$ . Anal.  $\text{C}_{13}\text{H}_{20}\text{BrN}_3\text{OSe}$ : C, H, N, Se.

*2-Isopropylamino-6-methyl-5-phenyl-6H-1,3,4-thiadiazine 2a and 2-isopropylamino-6-methyl-5-phenyl-6H-1,3,4-selenadiazine 2b. Hydrobromide.* Each ring-opened intermediate **1a** or **1b** (0.01 mol), was refluxed in 30 ml ethanol for 5 min. The filtered and ice-cooled reaction mixtures were diluted carefully with ether, whereupon the hydrobromides of **2a** and **2b** separated as the main products.

**2a**: yield, 95%, m.p.  $189^{\circ}\text{C}$ . Anal.  $\text{C}_{13}\text{H}_{18}\text{BrN}_3\text{S}$ : C, H, N, S.

**2b**: yield, 75%, m.p.  $212^{\circ}\text{C}$ . Anal.  $\text{C}_{13}\text{H}_{18}\text{BrN}_3\text{Se}$ : C, H, N, Se.

*Free bases.* A small excess of diluted aqueous ammonia was added to the solutions of the hydrobromides, until light yellow crystals precipitated. The bases of **2a** and **2b** were purified by repeated recrystallization from ethanol: **2a** m.p.  $153^{\circ}\text{C}$ ; **2b** m.p.  $148^{\circ}\text{C}$ .

The crystals, used for X-ray crystal structure determination were obtained by slow evaporation of the saturated solutions in a desiccator ( $T = 293\text{ K}$ ). Anal.  $\text{C}_{13}\text{H}_{17}\text{N}_3\text{S}$ : C, H, N, S. Anal.  $\text{C}_{13}\text{H}_{17}\text{N}_3\text{Se}$ : C, H, N, Se.

*X-Ray crystallography.* Details from the crystal analysis, data collection and structure refinement are given in Table 1. The atomic coordinates are given in Tables 2 and 3. Conditions applied to both crystal structure determinations: Hilger & Watts diffractometer settings,  $\omega$ - $2\theta$  step scan with 40 steps of 1 s and  $\Delta\omega = 0.03^{\circ}$  up to  $\theta_{\text{max}} = 27.5^{\circ}$ , graphite monochromatized  $\text{Mo K}_{\alpha}$  radi-

Table 1. Crystal data and experimental details of the structure determination of 2-isopropylamino-6-methyl-5-phenyl-6H-1,3,4-thiadiazine **2a** and 2-isopropylamino-6-methyl-5-phenyl-6H-1,3,4-thiadiazine **2b**.

	$\text{C}_{13}\text{H}_{17}\text{N}_3\text{S}$	$\text{C}_{13}\text{H}_{17}\text{N}_3\text{Se}$
Formula	$\text{C}_{13}\text{H}_{17}\text{N}_3\text{S}$	$\text{C}_{13}\text{H}_{17}\text{N}_3\text{Se}$
$M_r$	247.3	294.3
Space group	$P2_1/a$	$P2_1/a$
Cell parameters at 296 K		
$a/\text{\AA}$	15.019(3)	19.533(3)
$b/\text{\AA}$	9.918(3)	6.079(2)
$c/\text{\AA}$	9.341(2)	12.241(2)
$\beta/^\circ$	109.85(3)	107.79(2)
$V/\text{\AA}^3$	1308.7(9)	1382.6(9)
$Z$	4	4
$D_x/\text{Mg m}^{-3}$	1.255	1.413
$\lambda_{\text{Mo K}\alpha}/\text{\AA}$	0.71069	0.71069
$\mu(\text{Mo K}\alpha)/\text{cm}^{-1}$	2.28	29.02
Crystal description	yellow prisms	yellow prisms
Crystal size/mm	$0.28 \times 0.55 \times 0.48$	$0.30 \times 0.60 \times 0.65$
Instrument	Hilger & Watts	Hilger & Watts
Data collection	$\omega/2\theta$	$\omega/2\theta$
Maximum $2\theta/^\circ$	55	55
Reflections collected	3107	3263
Reflection used in refinement $I > 2.5\sigma(I)$	3013	2681
$R = \Sigma( F_o  -  F_c )/\Sigma F_o $	0.077	0.067
$F(000)/e$	528	600

**Table 2.** 2-Isopropylamino-6-methyl-5-phenyl-6*H*-1,3,4-thiadiazine **2a**: fractional coordinates ( $\times 10^4$ ),  $U_{\text{eq}}$  values for non-hydrogen atoms and  $U_{\text{iso}}$  values for hydrogen atoms (all thermal parameters  $\text{\AA}^2 \times 10^3$ ).

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{eq}}/U_{\text{iso}}^a$
S	2246(1)	2341(1)	6369(1)	59
N(1)	1607(2)	584(3)	3581(3)	55
N(2)	1012(2)	625(3)	4454(3)	56
N(3)	753(2)	1109(3)	6675(3)	57
C(1)	2204(2)	2842(3)	4481(4)	54
C(2)	2152(2)	1578(3)	3561(3)	48
C(3)	1250(2)	1285(3)	5727(3)	50
C(4)	2699(2)	1487(3)	2500(3)	52
C(5)	3365(2)	2453(4)	2486(4)	68
C(6)	3832(3)	2382(4)	1436(5)	75
C(7)	3640(3)	1355(4)	395(4)	77
C(8)	2986(2)	387(4)	407(4)	73
C(9)	2525(2)	445(4)	1448(4)	61
C(10)	688(2)	2085(3)	7804(4)	57
C(11)	105(3)	3303(4)	7045(6)	80
C(12)	281(3)	1402(5)	8886(5)	75
C(13)	1397(3)	3799(4)	3699(6)	75
H(N3)	280(20)	640(40)	6330(40)	73(12)
H(1)	2800(20)	3300(30)	4720(30)	63(9)
H(5)	3540(20)	3240(40)	3230(40)	92(12)
H(6)	4350(30)	3070(40)	1580(50)	126(14)
H(7)	3920(30)	1190(40)	-330(50)	100(14)
H(8)	2870(30)	-340(50)	-270(50)	118(17)
H(9)	2100(20)	-240(30)	1490(40)	75(11)
H(10)	1350(20)	2340(30)	8390(40)	95(11)
H(11)	350(20)	3770(30)	6350(40)	76(10)
H(111)	80(30)	3990(40)	7820(50)	128(15)
H(211)	-580(30)	2890(40)	6500(50)	120(14)
H(12)	320(30)	1950(40)	9690(40)	104(14)
H(112)	-390(20)	1170(30)	8300(40)	82(11)
H(212)	660(30)	550(40)	9300(50)	125(15)
H(13)	1430(20)	4090(40)	2660(4)	97(13)
H(113)	1400(30)	4500(40)	4320(40)	91(14)
H(213)	790(30)	3290(40)	3590(40)	126(14)

$$^a U_{\text{eq}} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j.$$

tion, temperature during the measurement 296 K, Lp correction, no absorption correction. The number of measured unique reflections (*hkl* and  $\bar{h}\bar{k}\bar{l}$ ) from **2a** was 3107 and from **2b** was 3263. In each case two standard reflections measured every 50 reflections showed no

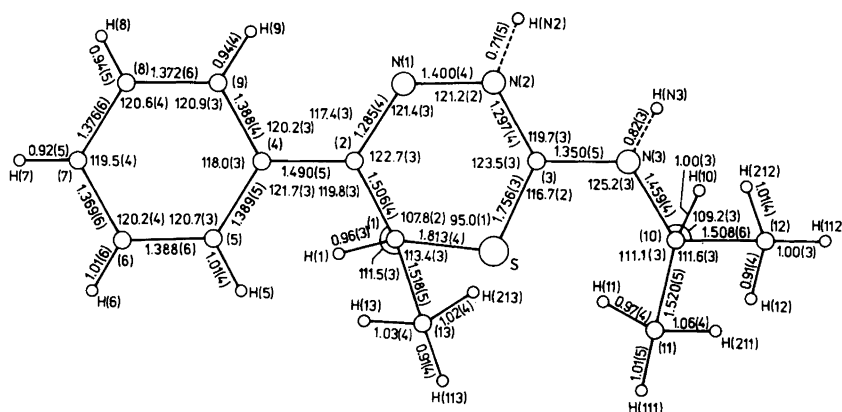
**Table 3.** 2-Isopropylamino-6-methyl-5-phenyl-6*H*-1,3,4-selenadiazine **2b**: fractional coordinates ( $\times 10^4$ ),  $U_{\text{eq}}$  values for non-hydrogen atoms and  $U_{\text{iso}}$  values for hydrogen atoms (all thermal parameters  $\text{\AA}^2 \times 10^3$ ).

	<i>x</i>	<i>y</i>	<i>z</i>	$U_{\text{eq}}/U_{\text{iso}}^a$
Se	230(0)	1820(1)	2966(1)	48
N(1)	1375(2)	3064(8)	1711(4)	43
N(2)	653(2)	3103(9)	1054(4)	48
N(3)	-516(2)	3865(9)	878(4)	52
C(1)	1099(3)	268(10)	2941(6)	49
C(2)	1580(3)	1833(9)	2587(5)	44
C(3)	72(3)	3031(9)	1462(5)	41
C(4)	2355(3)	1981(10)	3261(5)	46
C(5)	2678(3)	304(12)	4019(6)	63
C(6)	3415(3)	485(15)	4642(7)	75
C(7)	3803(3)	2201(15)	4493(6)	69
C(8)	3485(3)	3933(13)	3753(6)	65
C(9)	2763(3)	3770(11)	3134(6)	53
C(10)	-1156(3)	3822(13)	1262(6)	63
C(11)	-1785(3)	2916(14)	312(8)	79
C(12)	-1298(4)	6075(16)	1620(9)	96
C(13)	929(4)	-1779(10)	2202(8)	74
H(1)	1288(31)	-58(107)	3725(57)	60

$$^a U_{\text{eq}} = \frac{1}{3} \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j.$$

significant variation in intensity. Systematic extinctions of **2a** as well as **2b**: for *h0l* reflections with *h* odd and for *0k0* reflections with *k* odd.

**Structure determination of 2a.** Structure from direct methods, refinement by full-matrix least-squares methods, anisotropic thermal parameters, function minimized  $\Sigma \omega \Delta F^2$ , unit weights, H atoms from three-dimensional difference Fourier synthesis. It was not possible to ascertain whether one hydrogen atom is attached at N(2) or N(3) (atom numbering see Fig. 1). The difference synthesis revealed electron density maxima of nearly equal height at both positions, anisotropic (non-hydrogen) and isotropic (H) refinement gave  $R = 0.077$  for 3013 reflections, 94 reflections were omitted, difference synthesis showed no significant features.



**Fig. 1.** Bond lengths ( $\text{\AA}$ ) and angles ( $^\circ$ ) of 2-isopropylamino-6-methyl-5-phenyl-6*H*-1,3,4-thiadiazine **2a**.

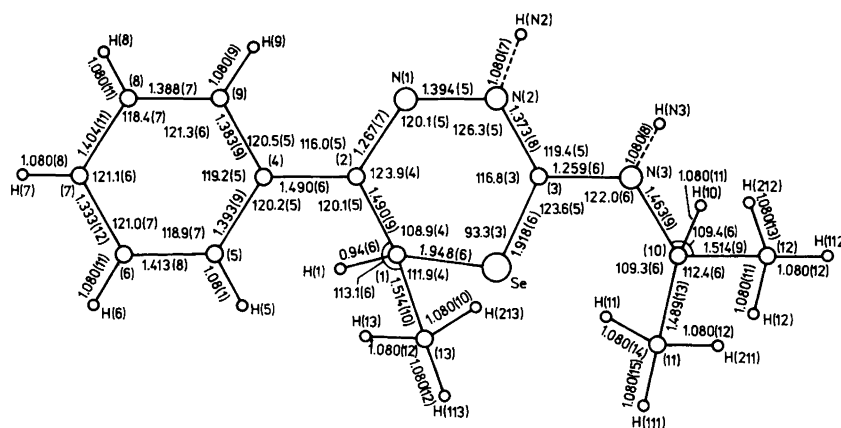


Fig. 2. Bond lengths (Å) and angles ( $^{\circ}$ ) of 2-isopropylamino-6-methyl-5-phenyl-6H-1,3,4-selenadiazine **2b**.

*Structure determination of 2b.* Se position from three-dimensional Patterson synthesis, remaining non-hydrogen atoms from subsequent Fourier map, refinement by full-matrix least-squares methods, anisotropic thermal parameters, function minimized  $\Sigma \omega \Delta F^2$ , unit weights, H atoms in calculated positions. It was not possible to ascertain whether one hydrogen atom is attached at N(2) or N(3) (atom numbering see Fig. 2). The difference synthesis revealed electron density maxima of nearly equal height at both positions, anisotropic (non-hydrogen) refinement with constrained hydrogen positions gave  $R = 0.067$  for 2681 reflections. 582 reflections were omitted, difference synthesis showed remaining maxima with the same height as hydrogen atoms.

All calculations were carried out with the SHELX-system (Sheldrick, BESM 6 computer<sup>15</sup>). Scattering factors from Ref. 16.

## Discussion

Bond distances of **2a** and **2b** are given in Figs. 1 and 2, respectively. Stereoscopic views of the packing of the molecules in the crystals of **2a** and **2b** are shown in Figs. 3 and 4, respectively. Not all hydrogen atoms could be localized unambiguously.

The H atom at N(3) corresponds to structure formula A and the H atom at N(2) corresponds to structural for-

mula B. The bond lengths N(2)–C(3) [**2a**: 1.297(4), **2b**: 1.373(8) Å] and C(3)–N(3) [**2a**: 1.350(5), **2b**: 1.259(6) Å] indicate that **2a** is consistent with structure formula A and that **2b** conforms to structure formula B. Statistical occupancy of the both hydrogen positions should not be excluded, particularly as the Fourier difference maps revealed maxima at both positions. Nevertheless the configuration mentioned above should be valid in each case because of the unambiguity of the bond lengths. The alternation of the bond lengths N(2)–C(3) and C(3)–N(3) corresponds to a difference in the angles  $\angle$  N(1)–N(2)–C(3) [**2a**: 121.2(2) $^{\circ}$ , **2b**: 126.3(5) $^{\circ}$ ] and  $\angle$  C(3)–N(3)–C(10) [**2a**: 125.2(3) $^{\circ}$ , **2b**: 122.0(6) $^{\circ}$ ] in the two structures.

The more space-requiring selenium favours the arrangement with a large N(1)–N(2)–C(3) angle [distance C(1)  $\cdots$  C(3) of **2b** 2.811(7) Å], i.e., structure formula B, whereas **2a** favours the structural formula A [distance C(1)  $\cdots$  C(3) 2.631(4) Å]. The structure of the 1,3,4-thiadiazine and 1,3,4-selenadiazine ring, respectively, may be described as distorted boat forms, with C(1) and N(2) forming the bow and stern of the boat. C(1), C(2), N(1) and N(2) are more or less in a plane, whereas S(Se), C(3) and N(3) are situated well out of the plane.

In both crystal structures intermolecular hydrogen bonds exist between the atoms N(2) and N(3). The hydrogen-bonded molecules are related by a centre

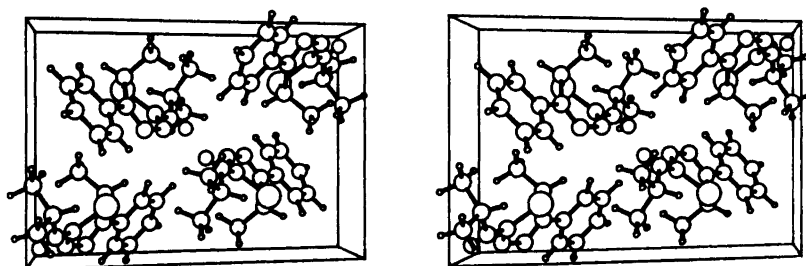


Fig. 3. Stereoscopic view of the packing of the molecules in the crystal structure of 2-isopropylamino-6-methyl-5-phenyl-6H-1,3,4-thiadiazine **2a**.

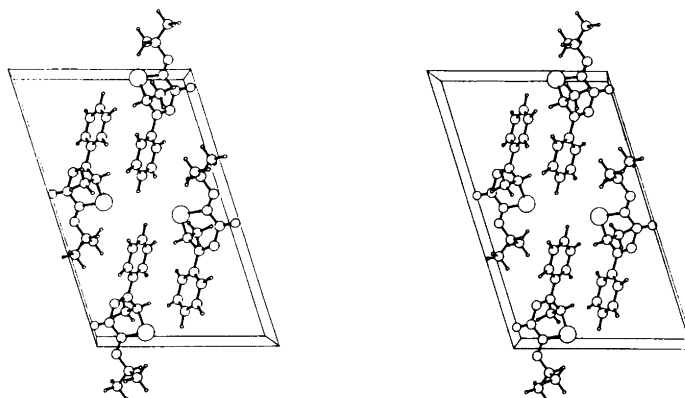


Fig. 4. Stereoscopic view of the packing of the molecules in the crystal structure of 2-isopropylamino-6-methyl-5-phenyl-6H-1,3,4-selenadiazine **2b**.

of symmetry: in **2a**  $N(2) \cdots H(N3')-N(3')$  with  $N(2) \cdots N(3') = 3.034(4) \text{ \AA}$  (i:  $\bar{x}, \bar{y}, 1-z$ ) and in **2b**  $N(2)-H(N2) \cdots N(3')$  with  $N(2) \cdots N(3') = 2.945(7) \text{ \AA}$  (ii:  $\bar{x}, 1-y, \bar{z}$ ). Thus hydrogen-bonded molecules form dimers. Transfer of the hydrogen atom from the donor to the acceptor nitrogen atom would transform the compound into the corresponding tautomer. UV-spectroscopic analysis indicates that similar tautomeric proportions, as already found by X-ray structure analysis, exist in solution, too. The amino and imino structures of 1,3,4-thiadiazines and 1,3,4-selenadiazines, which are fixed by methyl groups, were compared with **2a**, **2b** and other 2-alkylamino-1,3,4-thiadiazines and -selenadiazines. A tautomeric equilibrium of stable 2-methylamino-5-phenyl-6H-1,3,4-thiadiazine favours the imino structure in ethanol.<sup>17</sup> The kinetic measurements in glacial acetic acid confirmed that all compounds with a fixed exocyclic N-atom in the amino structure (2-dimethylamino-, 2-morpholino-, 2-piperidino-derivatives) or without an N(3)-atom (CN, Ph, SMe), are exceptionally susceptible to ring contraction with extrusion of sulphur or selenium and formation of pyrazoles. 3-Methyl-2,3-dihydro-6H-1,3,4-thiadiazines or -selenadiazines also undergo ring contraction but not as fast as the unsubstituted thia- and selenadiazines in the 3-position.<sup>13</sup> The ring contractions of 1,3,4-thiadiazines and 1,3,4-selenadiazines are not simple processes. Substituent effects, 2-amino-2-imino tautomerism, 4H-6H tautomerism and differences in the distance  $C(1) \cdots C(3)$  of 1,3,4-thiadiazines or 1,3,4-selenadiazines may influence the valence isomerization to thia- or selenadiazines, respec-

tively, followed by chalcogen extrusion and the formation of pyrazoles.

#### References

1. Sandström, J. *Ark. Kemi* 8 (1955) 523.
2. Beyer, H. and Wolter, G. *Chem. Ber.* 89 (1956) 1652.
3. Sandström, J. *Acta Chem. Scand.* 16 (1962) 2395.
4. Beyer, H., Honeck, H. and Reichelt, L. *Liebigs Ann. Chem.* 741 (1970) 45.
5. Bulka, E. and Pfeiffer, W. D. *J. Prakt. Chem.* 318 (1976) 971.
6. Pfeiffer, W. D., Dilk, E. and Bulka, E. *Z. Chem.* 17 (1977) 173.
7. Pfeiffer, W. D., Dilk, E. and Bulka, E. *Z. Chem.* 17 (1977) 218.
8. Pfeiffer, W. D., Dilk, E. and Bulka, E. *Z. Chem.* 18 (1978) 65.
9. Bulka, E., Pfeiffer, W. D., Trölsch, C., Dilk, E., Gärtner, H. and Daniel, D. *Collect. Czech. Chem. Commun.* 43 (1978) 1227.
10. Pfeiffer, W. D., Dilk, E. and Bulka, E. *Synthesis* (1977) 196.
11. Pfeiffer, W. D. and Bulka, E. *Synthesis* (1977) 485.
12. Pfeiffer, W. D., Dilk, E. and Bulka, E. *Wiss. Z. Ernst-Moritz-Arndt-Univ. Greifswald, Math.-nat.-wiss. Reihe* 27 (1978) 135.
13. Rossberg, H., Pfeiffer, W. D. and Bulka, E. *Wiss. Z. Ernst-Moritz-Arndt-Univ. Greifswald, Math.-nat.-wiss. Reihe* 34 (1985) 75.
14. Pfeiffer, W. D., Bulka, E. and Miethchen, R. *Z. Chem.* 27 (1987) 296.
15. Sheldrick, G. M. *SHELX 76. A Computer Program for Crystal Structure Determination*, Univ. of Cambridge, England 1976.
16. *International Tables for X-Ray Crystallography*, Kynoch Press, Birmingham 1974, Vol. IV.
17. Pfeiffer, W. D., Rossberg, H., Zaumseil, A. and Bulka, E. *Unpublished results*.

Received March 31, 1992.