

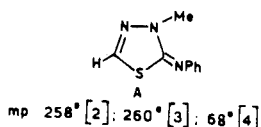
Francesco Buccheri, Giuseppe Cusmano, Renato Noto,  
Rosina Rainieri and Giuseppe Werber\*

Istituto di Chimica Organica, Università di Palermo,  
Via Archirafi 20, 90133 Palermo, Italy  
Received July 14, 1986

The true identity of the 4-methyl-5-phenylimino- $\Delta^2$ -1,3,4-thiadiazoline (**A**) has been demonstrated. The reactions, previously reported in the literature to give **A** have been repeated and the structure of the compounds obtained has been established.

*J. Heterocyclic Chem.*, **24**, 521 (1987).

In the course of our research on the reactivity of the A-CH=N-NR-CX-B system towards cyclizing agents [1], we became aware of a debate about the true identity of the 4-methyl-5-phenylimino- $\Delta^2$ -1,3,4-thiadiazoline (**A**).



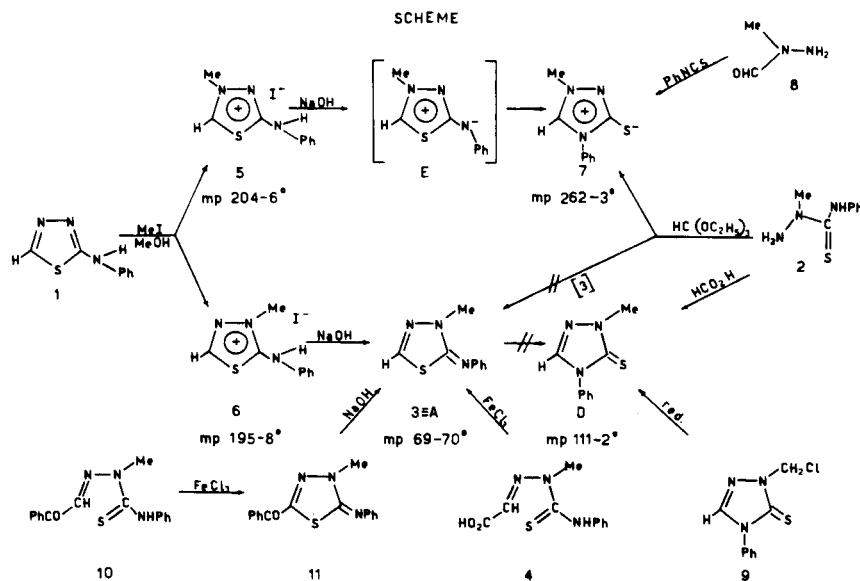
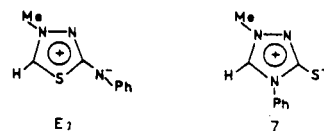
Pulvermacher [2] claimed that combining the 2-phenylamino-1,3,4-thiadiazole (**1**) with methyl iodide in methanol gave only one iodide derivative with mp 203-204° and this, by treatment with alkaline hydroxide solution, furnished a compound with mp 258°. The same compound was obtained by Stanovnik [3] from ethyl orthoformate and 2-methyl-4-phenylthiosemicarbazide (**2**). For this compound the structure of 4-methyl-5-phenylimino- $\Delta^2$ -1,3,4-thiadiazoline (**A**) was proposed by both authors.

Menin [4] later stated that 4-methyl-5-phenylimino- $\Delta^2$ -1,3,4-thiadiazoline (**A**) was a compound with mp 68°, obtained by oxidative cyclization [5] of the 2-methyl-4-phenylthiosemicarbazone (**4**) of glyoxylic acid with ferric

chloride. The evidence put forward by Menin in support of the structural assignments came from the synthetic methods used, the melting points determined, and the basicity of reaction products.

Moreover Menin repeated the reactions carried out by Pulvermacher and obtained the same compounds. He assigned the structure **B** to the iodide and erroneously gave a "mesoionic" formulation **C** to the compound with mp 264-265°. Later [6], he repeated Stanovnik's experiment, obtaining once again the compound with mp 264-265°, but at that time he proposed neither a new structure nor confirmed the old one.

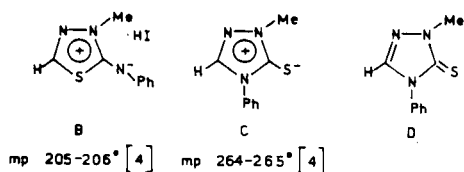
In contrast, Sandstrom [7] proposed the structure of 1-methyl-4-phenyl-1,2,4-triazoline-5-thione (**D**) for the above compound.



In order to confirm or to rectify the structures proposed, we have repeated the syntheses reported (Scheme).

When we repeated the Pulvermacher's experiment we obtained the *two* different iodides **5** and **6**. That with mp 204-206° was really the iodide **5** reported by Pulvermacher as **6**. The nmr spectra of the iodides are diagnostic for the structure of the two compounds. The singlets at  $\delta$  10.15 and  $\delta$  8.78 relative to the heterocycle-H of the iodides **5** and **6**, respectively, reveal the methylation position. Thus we assigned to the iodide with mp 204-206° the structure of the 2-phenylamino-4-methyl-1,3,4-thiadiazolium iodide (**5**). The second iodide, mp 195-198°, has the isomeric structure of 2-phenylamino-3-methyl-1,3,4-thiadiazolium iodide (**6**).

When **5** was treated with bases the mesoionic 2-methyl-4-phenyl-1,2,4-triazolium-5-thiolate (**7**) was obtained.



The isomeric mesoionic structure **E** for the Pulvermacher's compound was excluded because according to Ollis [8] compounds like **E** usually have a low melting point. Moreover, they change easily to the corresponding mesoionic triazolium thiolates. In contrast, compound **7** has a high melting point and is very stable. The ir spectrum of compound **7** shows a characteristic ( $1345\text{ cm}^{-1}$ ) very strong band relative to the C=S stretching [8]. This band is absent in the ir spectra of the iodides **5** and **6**. In the mass spectrum of compound **7** there is an ion with a mass number of 104 ( $\text{C}_6\text{H}_5\text{NCH}$ ) which fragment shows the position of the  $\text{C}_6\text{H}_5\text{N}$  group. Compound **7** has also been synthesized by Lazaris [9] from the 1-formyl-1-methylhydrazine (**8**) and phenylisothiocyanate. The above data for compound **7** agree with those reported by Lazaris.

The ring transformation for thiadiazole **5** to triazole **7** is consistent with other similar transformations reported in the literature [10].

When the iodide **6** was treated with bases it gave compound **3**  $\equiv$  **A** with mp 69-70° (*cf* ref [4], mp 68°). We have also synthesized compound **3** as follows: the 2-methyl-4-phenylthiosemicarbazone of phenylglyoxal (**10**) was cyclized by ferric chloride under the usual conditions (see Experimental section). The compound obtained (**11**) was hydrolyzed with sodium hydroxide and gave sodium benzoate and compound **3**.

The iodides **5** and **6** show a different behaviour towards sodium hydroxide. We think that while the compound **6** give the stable thiadiazoline **3** [11], **5** gives former the instable mesoionic thiadiazolium aminide **E** which rear-

ranges into stable triazolium thiolate **7**.

The spectral and analytical data for **3** are fully consistent with the assigned structure of the 4-methyl-5-phenylimino- $\Delta^2$ -1,3,4-thiadiazoline (**A**) and match Menin's data [4]. The cyclization of **4** or **10** with ferric chloride is a highly regioselective reaction; indeed, we were not able to obtain the triazolonic compound. This is in accord with our previous observations [12].

It must have been noticed that in the reaction between **1** and methyl iodide both nitrogen atoms of the ring undergo methylation. This has already been observed for some 2,5-disubstituted-1,3,4-thiadiazoles [13].

The **5:6** ratio obtained (see Experimental) is consistent with the substituent effect of the phenylamino group.

We synthesized compound **D** in order to demonstrate that this derivative is different from **3** (Sandstrom's attribution was wrong). Compound **D** was obtained [14] by reduction of the 1-chloromethyl-4-phenyl-1,2,4-triazoline-5-thione (**9**) as well as by **2** and formic acid [15]. Indeed the melting point of **D** ( $111\text{-}112^\circ$ ) and the spectral data allow us to exclude the structure **D** for the compound with mp  $262\text{-}263^\circ$  (see Experimental). We claim that all the structures previously assigned to compound **7**, **A** (Pulvermacher [2] and Stanovnik [3]), **C** (Menin [4]), and **D** (Sandstrom [7]) are incorrect. In fact the so-called Pulvermacher's compound is really the 2-methyl-4-phenyl-1,2,4-triazolium-5-thiolate (**7**).

Our data confirm that compound **3** has the structure of the 4-methyl-5-phenylimino- $\Delta^2$ -1,3,4-thiadiazoline (**A**).

## EXPERIMENTAL

All melting points (Kofler) are uncorrected. The spectra were recorded as follows: ir (nujol mull), Perkin-Elmer Infracord 137 Spectrophotometer;  $^1\text{H-nmr}$ , Varian EM 360 spectrometer (TMS as the internal reference); uv (95% ethanol), Varian Superscan 3 spectrophotometer; mass spectra (ionization potential 75 eV), Jeol-01SG-2 spectrometer. All compounds had analytical data consistent with the assigned structures.

### Methylation of 2-Phenylamino-1,3,4-thiadiazole (**1**).

A suspension of **1** (4.9 g, 28 mmoles) in anhydrous methanol (50 ml) and methyl iodide (5 ml) were refluxed for 12 hours. After cooling the 2-phenylamino-4-methyl-1,3,4-thiadiazolium iodide (**5**) (4.6 g) was collected and crystallized from ethanol, mp  $204\text{-}206^\circ$  (lit  $203\text{-}204^\circ$  [2],  $205\text{-}206^\circ$  [4]); ir:  $1555, 1595\text{ cm}^{-1}$  (C=N);  $^1\text{H-nmr}$  ( $\text{DMSO-d}_6$ ):  $\delta$  4.23 (3H, s, N-CH<sub>3</sub>), 6.90-7.75 (5H, m, Ar-H), 10.16 (1H, s, CH), 11.12 (1H, s, NH) ppm.

The methanol mother liquors were concentrated under reduced pressure and 1.85 g of the 2-phenylamino-3-methyl-1,3,4-thiadiazolium iodide (**6**) were obtained. After recrystallization from water or ethanol the product had mp  $195\text{-}198^\circ$ ; ir:  $1570, 1600\text{ cm}^{-1}$  (C=N);  $^1\text{H-nmr}$  ( $\text{DMSO-d}_6$ ):  $\delta$  3.88 (3H, s, N-CH<sub>3</sub>), 7.37 (5H, s, Ar-H), 8.78 (1H, s, CH), 8.13 (1H, s, NH) ppm.

*Anal.* Calcd. for  $\text{C}_9\text{H}_{10}\text{IN}_3\text{S}$ : C, 33.87; H, 3.15; N, 13.17. Found: C, 34.00; H, 3.10; N, 13.20.

Reaction of the Iodides (**5**) and (**6**) with Sodium Hydroxide: 2-Methyl-4-phenyl-1,2,4-triazolium-5-thiolate (**7**) and 4-Methyl-5-phenylimino- $\Delta^2$ -1,3,4-thiadiazoline (**3**).

A suspension of **5** (2.4 g, 7.5 mmoles) in water (25 ml) was treated with

10% sodium hydroxide (6 ml). The mixture was left overnight at room temperature. The product **7** separated and was filtered, washed with water and crystallized from ethanol (1.15 g), mp 262-263° (lit 258° [2], 260° [3], 264-265° [4]); ir: 1346 cm<sup>-1</sup> (C=S); <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ 3.86 (3H, s, N-CH<sub>3</sub>), 7.40-7.85 (5H, m, Ar-H), 9.71 (1H, s, CH) ppm; (TFA-d): 4.26 (3H, s, N-CH<sub>3</sub>), 7.50-7.80 (5H, m, Ar-H), 9.60 (1H, s, CH) ppm; ms: m/e 191 (M<sup>+</sup>), 190, 132, 118, 104, 91, 77, 51, 42.

Compound **6** (1.60 g, 5 mmoles) was dissolved by heating, in water (15 ml). The solution was diluted with water (15 ml) and made alkaline with aqueous 10% sodium hydroxide (3 ml). The solid **3** obtained (0.85 g) was crystallized from ligroin had mp 69-70° (lit 68° [4]). This compound in mixture with a pure sample had not any depression of the melting point; ir: 1570, 1600 cm<sup>-1</sup> (C=N); uv λ max (ε) 246 nm (7110), 279 nm (7580); <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ 3.54 (3H, s, N-CH<sub>3</sub>), 6.65-7.45 (5H, m, Ar-H), 8.12 (1H, s, CH) ppm.

#### 1-Methyl-4-phenyl-1,2,4-triazoline-5-thione (**D**).

A mixture of **2** (2.5 g, 14 mmoles) and 99% formic acid (10 ml) was refluxed for ½ hour. The acid excess was removed under reduced pressure and the residue was treated with diethylether and the resultant solid collected. The product **D** was recrystallized from methanol (1.45 g), mp 111-112° (lit 110-111° [6,14]). Mixed melting point with an authentic specimen of 1-methyl-4-phenyl-1,2,4-triazoline-5-thione (**D**) [14] was undepressed; ir: 1600 cm<sup>-1</sup> (C=N), 1345 cm<sup>-1</sup> (C=S); <sup>1</sup>H-nmr (DMSO-d<sub>6</sub>): δ 3.69 (3H, s, N-CH<sub>3</sub>), 7.48 (5H, s, Ar-H), 8.65 (1H, s, CH) ppm; <sup>1</sup>H-nmr (deuteriochloroform): δ 3.90 (3H, s, N-CH<sub>3</sub>), 7.47 (5H, s, Ar-H), 7.86 (1H, s, CH) ppm.

#### 2-Methyl-4-phenylthiosemicarbazone of Phenylglyoxal (**10**).

To a solution of phenylglyoxal hydrate (7.6 g, 5 mmoles) in a mixture of ethanol:water (40:60) (70 ml) an hydroalcoholic solution (100 ml) of 2-methyl-4-phenylthiosemicarbazide (**2**) (9 g, 5 mmoles) was added. The mixture was allowed to stand at room temperature for 24 hours. The thiosemicarbazone **10** (12.9 g) was collected, crystallized from benzene-ligroin had mp 109-111°; <sup>1</sup>H-nmr (deuteriochloroform): δ 3.80 (3H, s, N-CH<sub>3</sub>), 6.90-8.00 (11H, m, 2Ar-H and C-H), 9.50 (1H, br s, N-H) ppm.

*Anal.* Calcd. for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>OS: C, 64.63; H, 5.09; N, 14.14. Found: C, 64.75; H, 4.98; N, 14.22.

#### Oxidative Cyclization of the 2-Methyl-4-phenylthiosemicarbazone of Phenylglyoxal (**10**). 2-Benzoyl-4-methyl-5-phenylimino-Δ<sup>2</sup>-1,3,4-thiadiazoline (**11**).

To a suspension of the thiosemicarbazone **10** (3 g, 10 mmoles) in ethanol (50 ml) was added an ethanol solution (2M) of ferric chloride hexahydrate (10 ml). The mixture was allowed to stand at room temperature for 3 days. When the compound was all dissolved, the solution was refluxed for 5 minutes and then concentrated under reduced pressure. Water (30 ml) was added dropwise. The mixture was allowed to stand overnight.

The solid **11** was collected, washed with water and crystallized from ethanol (2.6 g), mp 76-77°; ir: 1570, 1600 cm<sup>-1</sup> (C=N); <sup>1</sup>H-nmr (deuteriochloroform): δ 3.78 (3H, s, N-CH<sub>3</sub>), 6.80-8.30 (10H, m, 2Ar-H) ppm.

*Anal.* Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>OS: C, 65.00; H, 4.40; N, 14.30. Found: C, 65.08; H, 4.44; N, 14.27.

#### 4-Methyl-5-phenylimino-Δ<sup>2</sup>-1,3,4-thiadiazoline (**3**).

To a solution of **11** (1.5 g, 5 mmoles) in ethanol (20 ml) aqueous 10% sodium hydroxide (5 ml) was added. The solution was refluxed for ½ hour, the solvent removed under reduced pressure and water (15 ml) was added. After extraction with chloroform (3 x 30 ml) the organic layer was dried and the chloroform distilled off, yielding **3** (0.9 g). The mother liquors upon acidification gave benzoic acid (0.4 g).

## REFERENCES AND NOTES

- [1] G. Werber, F. Buccheri, N. Vivona and M. Gentile, *J. Heterocyclic Chem.*, **16**, 145 (1979) and references cited therein.
- [2] G. Pulvermacher, *Chem. Ber.*, **27**, 619 (1894).
- [3] B. Stanovnik and M. Tisler, *J. Org. Chem.*, **25**, 2234 (1960). The behaviour of substituted thiosemicarbazides with orthoesters will be the subject of our next communication.
- [4] J. Menin, J. F. Giudicelli and H. Najer, *Compt. Rend.*, **261**, 766 (1965).
- [5] G. Werber and F. Maggio, *Ann. Chim. (Rome)*, **51**, 944 (1961).
- [6] J. F. Giudicelli, J. Menin and H. Najer, *Bull. Soc. Chim. France*, 874 (1969).
- [7] J. Sandstrom, in "Advances in Heterocyclic Chemistry", Vol **9**, A. R. Katritzky, ed, Academic Press, New York, NY, 1968, p 205.
- [8] W. D. Ollis and C. A. Ramsden, *J. Chem. Soc., Perkin Trans. I*, 633 (1974).
- [9] A. Ya. Lazaris, A. N. Egorochkin, S. M. Smhuilovich and A. I. Burov, *Chem. Heterocyclic Compd. (USSR)*, **9**, 1048 (1973).
- [10] W. D. Ollis and C. A. Ramsden, *loc. cit.*; R. Noto, F. Buccheri, G. Werber, G. Consiglio and D. Spinelli, *J. Chem. Soc., Perkin Trans. II*, 537 (1984).
- [11] In fact, **3** does not isomerize into **D** when synthesized under basic condition, from **6** or **11**.
- [12] In order to explore further the substituent effect on the ring cyclization, is in progress a study about the oxidative cyclization of a series of substituted thiosemicarbazones.
- [13] H. Lund, *Acta Chem. Scand.*, **27**, 391 (1973); M. B. Kolesova, L. I. Maksimova, A. V. El'tsov, *Zh. Org. Khim.*, 2613 (1973); in "Advances in Heterocyclic Chemistry", Vol **22**, A. R. Katritzky and A. J. Boulton eds, Academic Press, New York, NY, 1978, p 116.
- [14] I. L. Shegal, I. Ya. Postovskii, *Chem. Heterocyclic Compd. (USSR)*, **1**, 92 (1965).
- [15] J. F. Giudicelli, J. Menin and H. Najer, *loc. cit.*