Fused polycyclic nitrogen-containing heterocycles
13.* Synthesis of 6-phenyl-2-phenylimino-6*H*-1,3,4-thiadiazine-5-carboxylic acid and its intermolecular cyclodehydration accompanied by sulfur extrusion to form dipyrazolo[1,5-*a*,1′,5′-*d*]pyrazine

V. A. Mamedov, I. Z. Nurkhametova, A. T. Gubaidullin, I. A. Litvinov, and Ya. A. Levin*

A. E. Arbuzov Institute of Organic and Physical Chemistry,
Kazan Research Center of the Russian Academy of Sciences,
8 ul. Akad. Arbuzova, 420088 Kazan, Russian Federation.
Fax: +7 (843 2) 73 2253. E-mail: mamedov@iopc.kcn.ru

Condensation of methyl phenylchloropyruvate with 4-phenylthiosemicarbazide proceeds as the Bose reaction to form 5-methoxycarbonyl-6-phenyl-2-phenylimino-6*H*-1,3,4-thiadiazine, which is hydrolyzed to give carboxylic acid. In the presence of polyphosphoric acid, the latter undergoes intermolecular cyclodehydration accompanied by sulfur extrusion to yield dipyrazolo[1,5-*a*,1′,5′-*d*]pyrazine.

Key words: phenylchloropyruvates, 4-phenylthiosemicarbazide, 5-methoxycarbonyl-6-phenyl-2-phenylimino-6*H*-1,3,4-thiadiazine, Bose reaction, dipyrazolo[1,5-*a*,1′,5′-*d*]pyrazine.

Earlier, we have demonstrated that the reactions of phenylchloropyruvic acid esters and amides with *N*,*N*′-diphenylthiourea produce 4-hydroxythiazolidines, which are stable intermediates of the Hantzsch reaction,[2,3] whereas their reactions with thiosemicarbazide afford stable intermediates of the Bose reaction,[4] *viz.*, 5-hydroxyperhydrothiadiazines.[5,6]

In this connection, the reaction of methyl phenylchloropyruvate (**1**) with 4-phenylthiosemicarbazide containing fragments of both *N*,*N*′-diphenylthiourea and thiosemicarbazide would be expected to give either thiazolidine derivatives **2** and **3** or thiadiazine derivatives **4**. However, it appeared that the reaction affords one product regardless of the nature of the solvent, acidity of the reaction mixture, the order of addition of the reagents, temperature, *etc.*, including the known conditions.[2—6] The elemental composition of this product corresponds to isomeric structures **5**—**7**, which are dehydration products of compounds **2**—**4**, respectively. However, the ^{1}H NMR spectrum shows a singlet for the methine proton at δ 5.63, which unambiguously supports structure **7** and argues against structures **5** and **6** (Scheme 1). Therefore, the reaction of 4-phenylthiosemicarbazide with chloroketone **1** proceeds as the Bose reaction rather than as the Hantzsch reaction.

Taking into account the presence of the ester and phenyl groups at the adjacent C atoms in heterocycle **7**, we examined the possibility of indenoannelation of carboxylic acid **8** prepared by hydrolysis of ester **7** (Scheme 2).

Like intramolecular dehydration of 2-substituted 5-phenylthiazole-4-carboxylic acids with polyphosphoric acid,[7] the Friedel—Crafts reaction of acid **8** under these conditions would be expected to give indeno[2,1-*e*]-1,3,4-thiadiazine **9**. However, the reaction afforded a sulfur-free product rather than indenothiadiazine **9**. Based on the results of elemental analysis and spectroscopy, we assigned structure **10** to this product. Structure **10** corresponds to the dehydration product of pyrazolecarboxylic acid **11**, which can be derived from acid **8** through sulfur extrusion (Scheme 3). This result is consistent with the well-known instability of 1,3,4-thiadiazines in acidic medium. Under these conditions, the latter are transformed into pyrazoles with sulfur extrusion and ring contraction.[6—9]

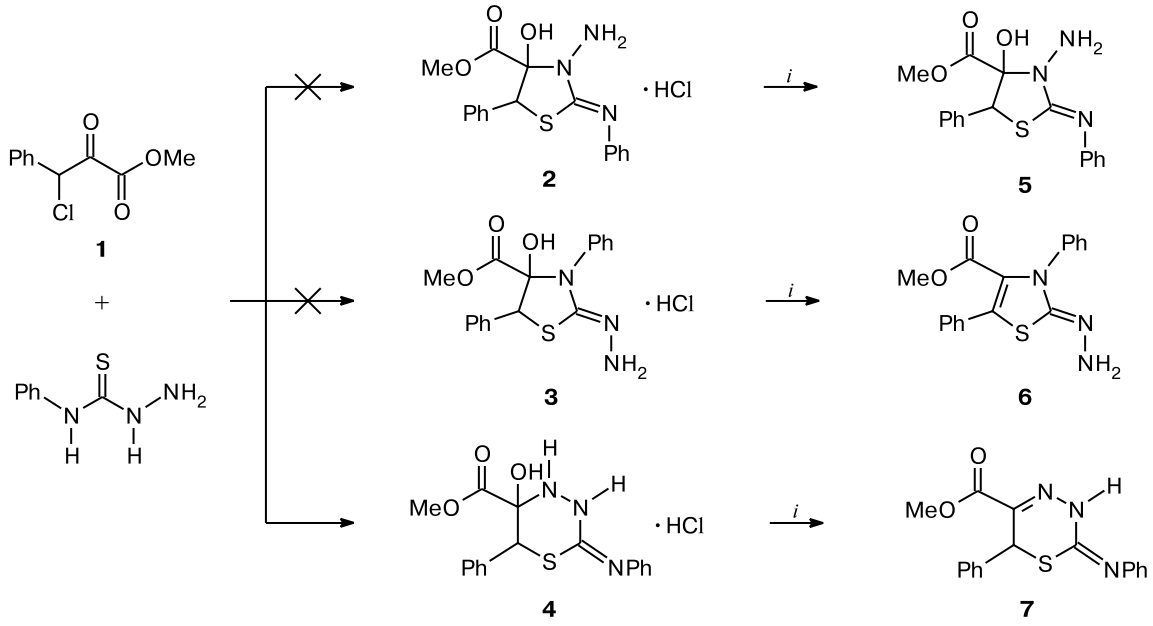
X-ray diffraction study of compound **10** confirmed its structure (Fig. 1). Compound **10** crystallizes in the triclinic space group. The unit cell contains DMSO solvate molecules. In the crystal, molecule **10** occupies a special position (see Fig. 1), so that there are four DMSO molecules per molecule **10**. The tricyclic fragment of the molecule is planar, and the phenyl substituent (C(21)—C(26) atoms) lies virtually in the plane of the tricyclic system (the dihedral angle between the planes is 4.8°). The second phenyl substituent is twisted with respect to the plane of the molecule by 57.1°. The molecular packing in the crystal is characterized by an extensive system of intermolecular interactions involving the

* For Part 12, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 2, pp. 432—435, February, 2005.

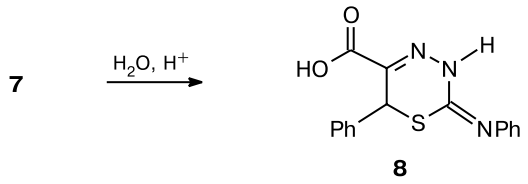
1066-5285/05/5402-0441

Scheme 1



Reagents and conditions: *i.* 5% aqueous $NaHCO_3$ solution.

Scheme 2



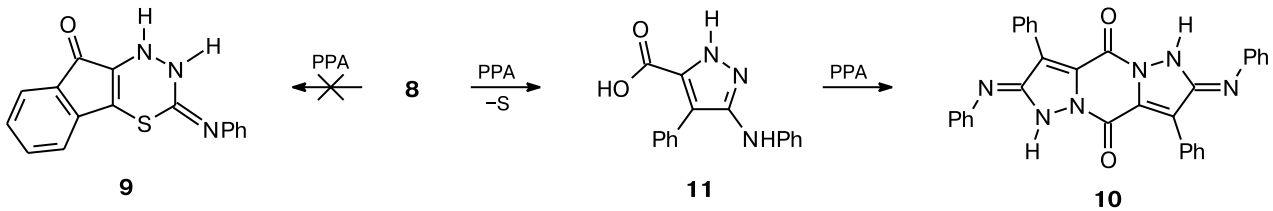
solvate molecules. The molecular and supramolecular structures of compounds **7** and **10** in the crystals will be described in detail elsewhere.

The pyrazinedione ring in tricyclic structure **10** is formed through two nucleophilic substitutions involving the carboxy group of one molecule of biphilic pyrazolecarboxylic acid **11** and the nucleophilic N atom of the pyrazole fragment of another molecule **11**. Data on cyclization of pyrazoles containing the carbonyl group at position 3, which affords dipyrazolo[1,5-*a*,1′,5′-*d*]pyrazines, are available in the literature. For example, two 3-chlorocarbonyl-5-methoxycarbonyl-4-trimethylsilylpyrazole molecules eliminate two HCl molecules to form the dipyrazolo[1,5-*a*,1′,5′-*d*]pyrazine system.[10] The reaction of 3-carboxy-4-(α-hydroxybenzyl)pyrazole proceeds analogously and gives rise to the pyrazinedione ring accompanied by elimination of two water molecules.[11] 3-Formylpyrazoles also undergo dimerization to dipyrazolo[1,5-*a*,1′,5′-*d*]pyrazines.[11–14] An analogous behavior was observed for 5-acyl-2-pyrazolines.[15,16]

Experimental

The melting points were determined on a Boetius hot-stage microscope. The IR spectra were recorded in Nujol mulls on a UR-20 spectrometer. The ^1H NMR spectra were recorded on a Bruker MW-250 spectrometer (250 MHz). Methyl phenylchloropyruvate (**1**) was prepared according to a known procedure.[17]

Scheme 3



PPA is polyphosphoric acid

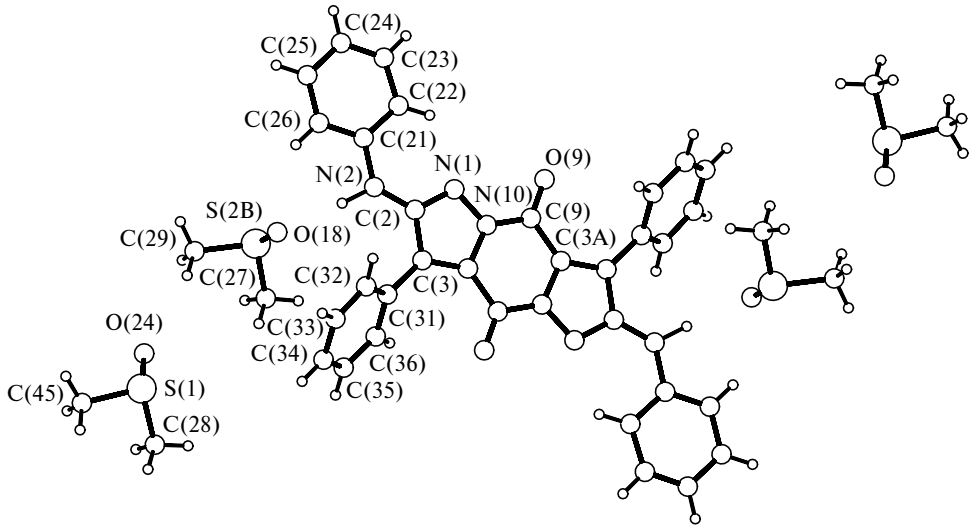


Fig. 1. Molecular structure of compound **10** in the crystal.

5-Methoxycarbonyl-6-phenyl-2-phenylimino-6*H*-1,3,4-thiadiazine (7). A solution of chloropyruvate **1** (2.12 g, 0.01 mol) in CH_2Cl_2 (10 mL) was added carefully dropwise to a solution of 4-phenylthiosemicarbazide (1.67 g, 0.01 mol) in CH_2Cl_2 (30 mL) under argon at 0±2 °C. The reaction mixture was stirred at this temperature for 3 h, warmed to ~20 °C, and poured into water. The organic layer was separated, and the aqueous solution was extracted with CH_2Cl_2 (3×15 mL). The organic layer and the extract were combined and dried with $MgSO_4$. The solvent was removed, the residue was treated with a 5% aqueous $NaHCO_3$ solution, and the precipitate was filtered off and recrystallized from MeOH. Compound **7** was obtained in a yield of 2.75 g (84.6%) as pale-yellow crystals, m.p. 209—210 °C. Found (%): C, 62.70; H, 4.75; N, 12.65; S, 9.97. $C_{17}H_{15}N_3O_2S$. Calculated (%): C, 62.78; H, 4.61; N, 12.92; S, 9.86. IR, ν/cm^{-1}: 3286 (NH), 1714 (C=O), 1590 (C=N). ^{1}H NMR (DMF-d_7), δ: 3.80 (s, 3 H, Me); 5.63 (s, 1 H, CH); 6.70 (dd, 1 H, *p*-H (NPh), J = 7.05 Hz, J = 7.43 Hz); 7.01—7.44 (m, 9 H, Ph, 2 *o*-H, 2 *m*-H (NPh)); 7.63 (br.s, 1 H, N(3)H).

6-Phenyl-2-phenylimino-6*H*-1,3,4-thiadiazine-5-carboxylic acid (8). 1,3,4-Thiadiazine **7** (2.9 g, 0.01 mol) was refluxed in 20% hydrochloric acid (25 mL) for 2 h. The hot reaction mixture was filtered and the crystals that precipitated upon cooling were filtered off and recrystallized from Pr^{i}OH. Acid **8** was isolated in a yield of 2.7 g (97%), m.p. 227—229 °C. Found (%): C, 62.51; H, 4.25; N, 13.65; S, 10.27. $C_{16}H_{13}N_3O_2S$. Calculated (%): C, 61.74; H, 4.18; N, 13.50; S, 10.30. IR, ν/cm^{-1}: 3380, 3340 (NH); 3060 (C(5)H); 1685 (C=O); 1640 (C=N). ^{1}H NMR (CD_3OD), δ: 5.68 (s, 1 H, CH); 7.01—7.45 (m, 10 H, 2 Ph).

3,8-Diphenyl-2,7-diphenylimino-1*H*,6*H*-dipyrazolo[1,5-*a*,1′,5′-*d*]pyrazine (10). A mixture of P_2O_5 (35 g) and H_3PO_4 (10 mL) was heated with stirring at 240 °C for 1.5 h. Then polyphosphoric acid that formed was cooled, and acid **8** (2.05 g, 0.01 mol) was dissolved in polyphosphoric acid with stirring. The reaction mixture was kept at 100—140 °C for 1.5 h, cooled, and diluted with water. The crystals that precipitated were filtered off and dried in air. Compound **10** was obtained in a yield of 0.8 g (61%), m.p. >360 °C. Found (%): C, 73.42; H, 4.05; N, 16.14. $C_{32}H_{22}N_6O_2$. Calculated (%): C, 73.57; H, 4.21; N, 16.09. IR, ν/cm^{-1}: 3250 (br), 1700, 1600, 1550, 1510, 1485, 1380, 1345, 1290, 1250. ^{1}H NMR (CD_3OD), δ: 6.95 (br.t, 1 H, H(4′), NPh, J = 7.85 Hz); 7.10—7.58 (m, 9 H, NPh, CPh); 7.90 (br.s, 1 H, NH). Crystals suitable for X-ray diffraction study were prepared by recrystallization from DMSO. Found (%): C, 57.32; H, 5.81; N, 9.76; S, 15.05. $C_{32}H_{22}N_6O_2 \cdot 4Me_2SO$. Calculated (%): C, 57.56; H, 5.51; N, 10.07; S, 15.36.

X-ray diffraction study of compound **10** was performed on an automated four-circle Enraf-Nonius CAD-4 diffractometer. Red platelet-like crystals are triclinic, $C_{32}H_{22}N_6O_2 \cdot 4Me_2SO$, crystal dimensions 0.1×0.2×0.3 mm. At 20 °C, a = 6.142(6) Å, b = 13.392(8) Å, c = 14.4580(10) Å, α = 65.53(2)°, β = 85.34(4)°, γ = 87.77(6)°, V = 1079(1) Å^3, Z = 1, d_{calc} = 1.29 g cm^{-3}, space group $P\bar{1}$. The unit cell parameters and the intensities of 1514 reflections, of which 1443 reflections were with $I \geq 2\sigma$, were measured at 20 °C (λ(Cu-Kα), graphite monochromator, ω/2θ scanning technique, θ ≤ 73.7°). The intensities of three check reflections showed no decrease in the course of X-ray data collection. The absorption correction was applied (μ(Cu) = 23.98 cm^{-1}). The structure was solved by direct methods using the SIR program[18] and refined first isotropically and then anisotropically using the SHELXL-97 program package.[19] Subsequently, the position of the H atom at the N(1) atom was revealed from difference electron density maps. The coordinates of other H atoms were calculated based on stereochemical criteria and refined using a riding model. The final R factors were R = 0.065, R_w = 0.168 using 1443 reflections with $F^2 \geq 4\sigma$. All calculations were carried out using the MolEN[20] and WinGX[21] program packages. The figure was drawn using the PLATON program.[22]

This study was financially supported by the Russian Foundation for Basic Research (Project Nos 03-03-32865 and 02-03-32280) and the Charity Foundation for Support of Russian Science.

References

1. A. A. Kalinin, O. G. Isaikina, and V. A. Mamedov, *Khim. Geterotsikl. Soedin.*, 2004, 1741 [*Chem. Heterocycl. Compd.*, 2004, **40** (Engl. Transl.)].
2. V. A. Mamedov, I. Z. Nurkhametova, R. R. Shagidullin, A. V. Chernova, and Ya. A. Levin, *Khim. Geterotsikl. Soedin.*, 1999, 975 [*Chem. Heterocycl. Compd.*, 1999, **35** (Engl. Transl.)].
3. V. A. Mamedov, I. Z. Nurkhametova, I. Kh. Rizvanov, Yu. Ya. Efremov, and Ya. A. Levin, *Khim. Geterotsikl. Soedin.*, 1999, 1561 [*Chem. Heterocycl. Compd.*, 1999, **35** (Engl. Transl.)].
4. P. K. Bose and B. N. Nandi, *J. Indian Chem. Soc.*, 1930, 733; *Chem. Abstr.*, 1931, **25**, 1532.
5. V. A. Mamedov, E. A. Berdnikov, V. N. Valeeva, I. E. Ismaev, I. Kh. Rizvanov, L. A. Antokhina, I. A. Nuretdinov, and P. P. Chernova, *Izv. Akad. Nauk, Ser. Khim.*, 1993, 1962 [*Russ. Chem. Bull.*, 1993, **42**, 1879 (Engl. Transl.)].
6. V. A. Mamedov, L. V. Krokhina, E. A. Berdnikov, and Ya. A. Levin, *Khim. Geterotsikl. Soedin.*, 1996, 1266 [*Chem. Heterocycl. Compd.*, 1996, **32** (Engl. Transl.)].
7. V. A. Mamedov, A. T. Gubaidullin, I. Z. Nurkhametova, I. A. Litvinov, and Ya. A. Levin, *Zh. Org. Khim.*, 2004, **40**, 564 [*Russ. J. Org. Chem.*, 2004, **40** (Engl. Transl.)].
8. S. V. Usol´tseva, G. P. Andronikova, and V. S. Mokrushin, *Khim. Geterotsikl. Soedin.*, 1991, 435 [*Chem. Heterocycl. Compd.*, 1991, **27** (Engl. Transl.)].
9. A. P. Novikova, N. M. Perova, and O. N. Chupakhin, *Khim. Geterotsikl. Soedin.*, 1991, 1443 [*Chem. Heterocycl. Compd.*, 1991, **27** (Engl. Transl.)].
10. A. S. Medvedeva, M. M. Demina, L. P. Safronova, I. D. Kalikhman, V. Yu. Vitkovskii, and N. S. Vyazankin, *Zh. Obshch. Khim.*, 1983, **53**, 2251 [*J. Gen. Chem. USSR*, 1983, **53** (Engl. Transl.)].
11. J. Bastide, J. Lematre, and J. Soulier, *C. R. Acad. Sci.*, 1968, 1393.
12. E. J. Browne, *Aust. J. Chem.*, 1971, **24**, 2389.
13. A. S. Medvedeva, M. M. Demina, A. I. Borisova, O. M. Margorskaja, I. D. Kalikhman, E. I. Brodskaja, and N. S. Vyazankin, *J. Organomet. Chem.*, 1982, **231**, 109.
14. A. S. Medvedeva, O. I. Margorskaya, N. I. Golovanova, I. D. Kalikhman, M. M. Demina, and N. S. Vyazankin, *Zh. Obshch. Khim.*, 1983, **53**, 2247 [*J. Gen. Chem. USSR*, 1983, **53** (Engl. Transl.)].
15. I. E. S. El-Kholy, F. K. Rafla, and M. M. Mishrikey, *J. Chem. Soc. C*, 1970, 1578.
16. A. F. Noels, J. N. Braham, A. J. Hubert, and Ph. Teyssie, *J. Org. Chem.*, 1977, **42**, 1527.
17. V. A. Mamedov, I. A. Nuretdinov, and D. N. Sadkova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1990, 2854 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1990, **39**, 2591 (Engl. Transl.)].
18. A. Altomare, G. Cascarano, C. Giacovazzo, and D. Viterbo, *Acta Crystallogr., Sect. A*, 1991, **47**, 744.
19. G. M. Sheldrick, *SHELX-97*, *Release 97-2*, University of Göttingen, Göttingen, 1997.
20. L. H. Straver and A. J. Schierbeek, *MolEN. Structure Determination System 1*, Nonius B.V., 1994, **16**, 180.
21. L. J. Farrugia, *J. Appl. Crystallogr.*, 1999, **32**, 837.
22. A. L. Spek, *Acta Crystallogr., Sect. A*, 1990, **46**, 34.

Received May 26, 2004;
in revised form August 4, 2004