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STUDY ON SYNTHESES AND STRUCTURE OF A NEW KIND OF BIS-HETEROCYCLIC THIADIAZINE DERIVATIVES CONTAINING PYRAZOLONE

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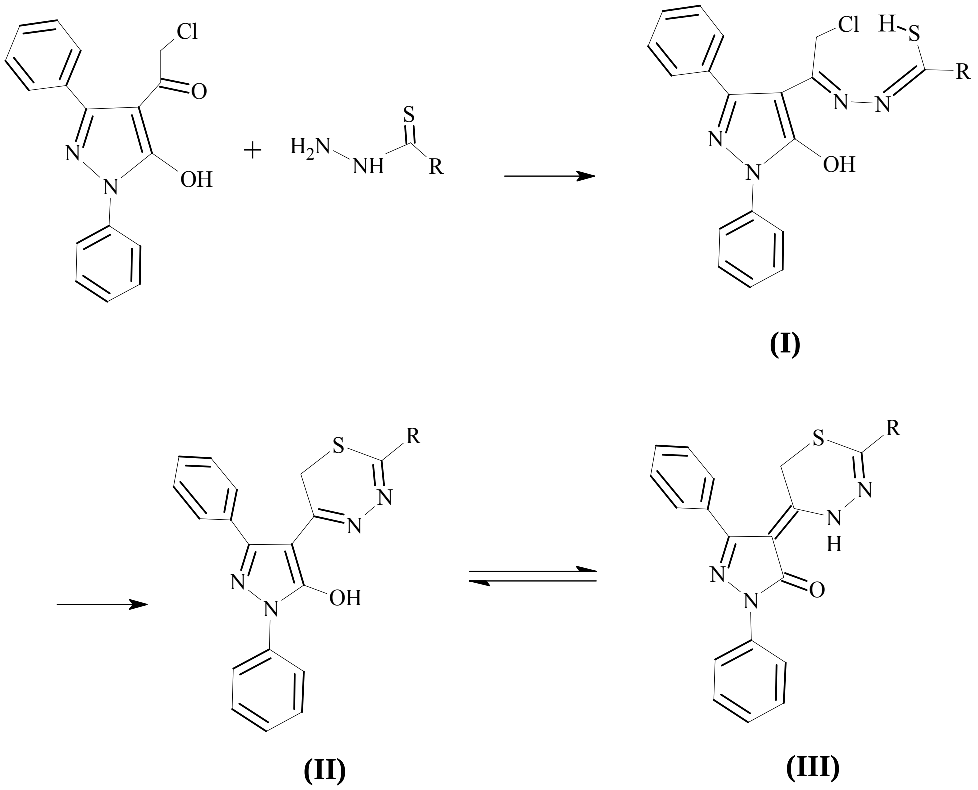
Abstract – A new kind of *bis*-heterocyclic thiadiazine derivatives containing pyrazolone were synthesized and characterized. 2-Methylthio-5-(1,3-diphenyl-5-pyrazolone-4-ylidene)-5,6-dihydro-4*H*-1,3,4-thiadiazine (DPCP-MTTSC) (**5**) was determined by X-Ray crystallographical analysis.

INTRODUCTION

Syntheses and studies on biological activities of *bis*-heterocyclic compounds have become an important area of heterocyclic pesticide.[1, 2] The derivatives of thiadiazine and pyrazole have attracted an interest because of their many advantages such as high efficiency, low toxicity, and variety of structures. Especially, the thiadiazines are useful as herbicides, insecticides[3] and antimicrobial drugs.[4] Though investigations on these compounds and their derivatives have been increased in recent years.[5-7]

Few works on *bis*-heterocyclic compounds containing pyrazolone-ring[8-10] especially the condensed products of 1,3-diphenyl-4-chloroacetyl-5-pyrazolone with thiosemicarbazide (TSC) and its derivatives, such as 4-methyl-3-thiosemicarbazide (MTSC), 4-ethyl-3-thiosemicarbazide (ETSC), 4-phenyl-3-thiosemicarbazide (PTSC) and methylthio thiosemicarbazide (MTTSC) were reported before. In the previous work, the structure and properties of *bis*-heterocyclic compound 2-amino-5-(1-phenyl-3-methyl-5-pyrazolone-4-ylidene)-5,6-dihydro-4*H*-1,3,4-thiadiazine (PMCP-TSC)[11] has been reported. As the continuing work with 4-acyl pyrazolones and their derivatives, this paper mainly deals with the syntheses, spectroscopy and solid-state structures of five new *bis*-heterocycles compounds.

Based on the experimental results, the stoichiometric equations are shown in Scheme **1**. It seems plausible to suggest a three-stage mechanism comprising two intermediates.



1 R = NH_2, **2** R = $NHCH_3$, **3** R = NHC_2H_5, **4** R = NHPh, **5** R = SCH_3

Scheme 1

X-Ray crystallographic The single crystal of the compound (**5**) suitable for X-Ray analysis was obtained by evaporating tetrahydrofuran solution slowly. A yellowish single crystal with dimensions of 0.54 mm × 0.44 mm × 0.24 mm was mounted on a Siemens *P*4 four-circle diffractometer with graphite monochromated Mo Kα radiation (λ = 0.71073 Å) at 296(2)K. The structure was solved and refined using *SHELXS*97 and *SHELXL*97 program,[15] respectively. A summary of crystal data, experimental details and refinement results are listed in Table 1. Cell constants and orientation matrix for data collection were obtained with least-squares refinement. The structures were solved by direct methods. All non-hydrogen atoms were refined anisotropically, and the hydrogen atoms were located by difference Fourier syntheses and refined isotropically.

Table 1. Crystal data and structure refinement for **5**

Empirical formula	$C_{19}H_{16}N_4OS_2$
Formula weight	380.48
Temperature	296(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic

Space group	$P2_1/c$
Unit cell dimensions	$a = 11.085(2)$ Å
	$b = 6.882(1)$ Å $\beta = 101.82(2)$ °
	$c = 24.240(5)$ Å
Volume, Z	$1810.0(5)$ Å^3, 4
Density (calculated)	1.396 g/cm^3
Absorption coefficient	0.310 mm^{-1}
$F(000)$	792
Crystal size	0.54 × 0.44 × 0.24 mm
Theta range for data collection	1.72 to 25.00°
Limiting indices	$0 \le h \le 13$, $0 \le k \le 8$, $-28 \le l \le 28$
Reflections collected	3790
Independent reflections	3186 [$R_{\text{int}} = 0.0121$]
Absorption correction	Empirical
Max. and min. transmission	0.9810 and 0.9262
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3186 / 1 / 241
Goodness-of-fit on F^2	1.020
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0367$, $wR_2 = 0.0927$
R indices (all data)	$R_1 = 0.0546$, $wR_2 = 0.0980$
Extinction coefficient	0.0022(8)
Largest diff. peak and hole	0.211 and -0.229 e·Å^{-3}

RESULTS AND DISCUSSION

Selected bond distances and angles for **5** are listed in Table 2. Perspective views, packing diagram and connection of hydrogen bond of **5** are shown in Figures 1, 2 and 3, respectively.

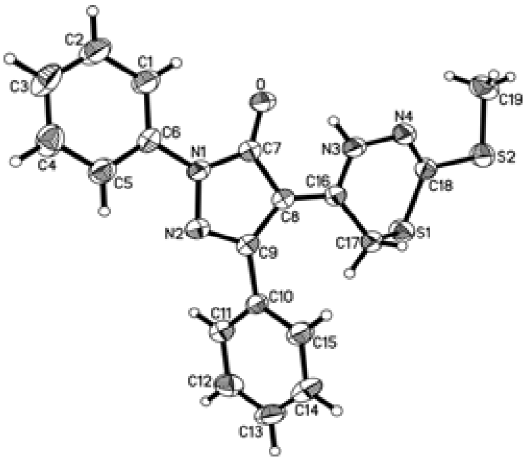


Figure 1. The stereo ORTEP drawing of **5**

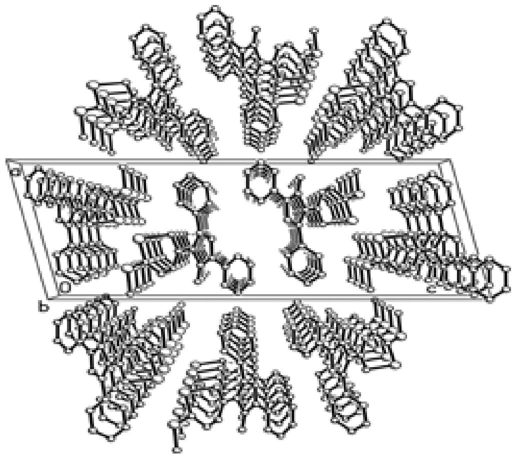


Figure 2. Arrangement of **5** in the unit cell along the *b*-axis

The structure of a new kind of *bis*-heterocyclic thiadiazine compound containing pyrazolone is shown in Figure 1. Changes of electronic distribution have taken place in the thiadiazine ring due to the conjugation effect of pyrazolone ring (the atoms in pyrazolone ring have the mean plane deviation of

0.0050 Å), which make the bond lengths of C18-N4 (1.279 Å) be close to C=N double bond and C-S (1.749 Å and 1.807 Å) be close to the C-S single bond, respectively. So the results suggest that Schiff base (I) in Scheme **1** was formed firstly in the reaction, and then the intermediate product (II) was obtained by ring-closure reaction. Finally the other tautomer (III) was formed by intramolecular proton transfer, accordingly, the electronic cloud between N3 and C16 delocalized to C8 and C16, this may be the reason why the N3-C16 (1.337 Å) bond lengths is in the mediate of C=N double bond length (1.28 Å) and C-N single bond length (1.47 Å), the same as the C8-C16 bond length.[16] Therefore, we can conclude that the new thiadiazine ring was formed during the condensed reaction and it has the extensive electron delocalization. However, its detail mechanism is on further study. The crystal exists in keto-form in the solid state for the simple reason that the bond lengths of C7-O (1.244 Å) is the typical C=O double bond.[17] These can further confirm our presumption of the three-stage reaction mechanism for the compound (**5**).

Table 2. Selected bond lengths (Å) and angles (˚) for **5**

S(1)-C(18)	1.749(2)	N(3)-C(16)	1.337(3)
S(1)-C(17)	1.807(2)	N(3)-N(4)	1.388(2)
S(2)-C(18)	1.741(2)	N(4)-C(18)	1.279(3)
S(2)-C(19)	1.795(2)	C(7)-C(8)	1.453(3)
O-C(7)	1.244(2)	C(8)-C(16)	1.385(3)
N(1)-C(7)	1.374(2)	C(8)-C(9)	1.435(3)
N(1)-N(2)	1.401(2)	C(9)-C(10)	1.482(3)
N(1)-C(6)	1.419(2)	C(16)-C(17)	1.489(3)
N(2)-C(9)	1.312(3)		
C(18)-S(1)-C(17)	96.48(10)	C(16)-C(8)-C(9)	132.93(19)
C(18)-S(2)-C(19)	101.91(12)	C(16)-C(8)-C(7)	122.10(18)
C(7)-N(1)-N(2)	112.08(16)	C(9)-C(8)-C(7)	104.96(18)
C(7)-N(1)-C(6)	129.62(17)	N(2)-C(9)-C(8)	111.68(17)
N(2)-N(1)-C(6)	118.21(16)	N(2)-C(9)-C(10)	117.31(18)
C(9)-N(2)-N(1)	106.51(16)	C(8)-C(9)-C(10)	130.97(19)
C(16)-N(3)-N(4)	128.67(18)	N(3)-C(16)-C(8)	117.94(18)
C(18)-N(4)-N(3)	117.47(18)	N(3)-C(16)-C(17)	117.30(19)
C(1)-C(6)-N(1)	120.70(19)	C(8)-C(16)-C(17)	124.67(18)
C(5)-C(6)-N(1)	118.84(18)	C(16)-C(17)-S(1)	110.71(14)
O-C(7)-N(1)	126.66(18)	N(4)-C(18)-S(2)	121.04(17)
O-C(7)-C(8)	128.59(19)	N(4)-C(18)-S(1)	125.77(17)
N(1)-C(7)-C(8)	104.75(17)	S(2)-C(18)-S(1)	113.19(12)

Symmetry transformations used to generate equivalent atoms.

The short distance between O atom and N3 atom strongly suggests the presence of an intramolecular hydrogen bond involving the N3H proton and the lone pair of electrons on O atom (O···N3 = 2.6702 Å, N3-H = 0.867 Å, O···H = 1.920 Å; N3-H···O = 144º). As in other pyrazolone derivatives containing thiadiazine heterocycles,[11,18] this intramolecular hydrogen bond must stabilize the six member-ring comprised by O, C7, C8, C16, N3 and H atoms (Figure 1).

However, besides the only intramolecular hydrogen bond mentioned above, it is interesting that the intermolecular hydrogen bond is observed between N2 and C17 [C17···N2 = 3.450(3) Å, C17-H = 0.97 Å, N2···H = 2.54 Å; C17-H···N2 = 156.3°], which links the molecules together to form one-dimensional catenulate structure along the *b*-axis (Figure 3). No other intermolecular hydrogen bonds between heteroatoms were observed.

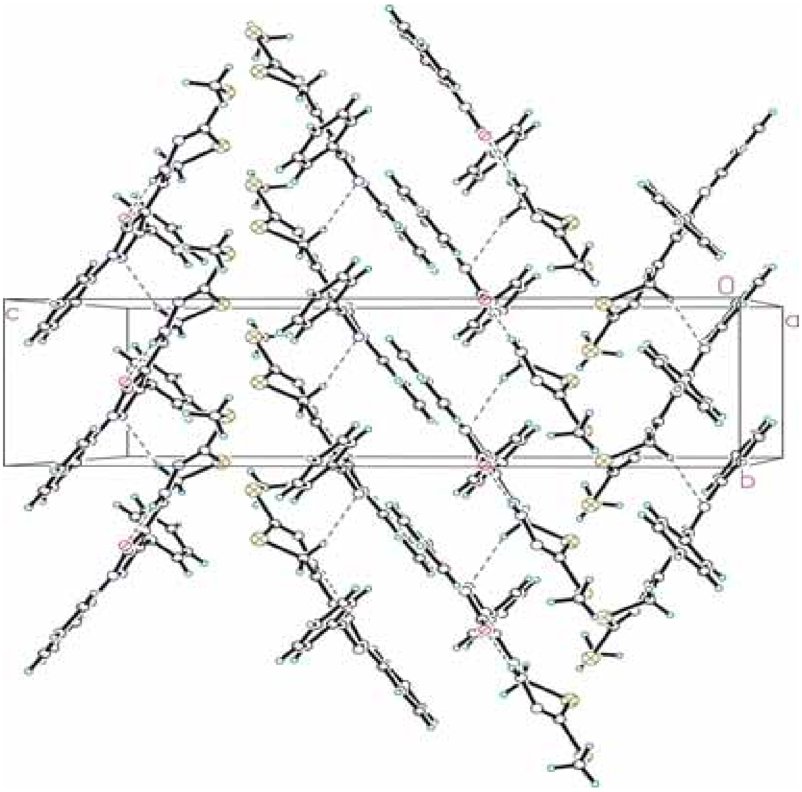


Figure 3. View of the unit-cell packing with the hydrogen-bonding scheme shown as dashed lines for **5**

The least-squares plane defined by the pyrazolone-ring makes an angle of 7.4° with that defined by C (1)-C (6) phenyl ring (rms deviation of fitted atoms = 0.0028 Å), and an angle of 1.7° with plane defined by O, C7, C8, C16, N3 and HN3 (rms deviation of fitted atoms = 0.0091 Å), respectively, which indicate these three least-squares planes are almost co-planar. In the new thiadiazine heterocycle, the least-squares plane defined by C16, N3, N4, C18 (rms deviation of fitted atoms = 0.0738 Å) is slightly deviate from the pyrazolone-ring with dihedral angle of 10.9°. However, the atom C17 has the deviation of 0.4551 Å, and S1 is -0.3995 Å, which shows that the six atoms of the new heterocycle is not in the same plane, and the torsion angle 48.88° of C18-S1-C17-C16 indicates that the thiadiazine heterocycle is a semi-chair conformation.

By contrasting the elemental analyses, ^{1}H NMR spectra, ^{13}C NMR spectra and IR spectra of the other four compounds with the compound (**5**), it can be obtained that the structure of the compounds (**1**, **2**, **3** and **4**) is very similar with that of compound (**5**), that is to say, these compounds in this paper have the same reaction mechanism. This is the new synthetic method of thiadiazine and *bis*-heterocycle.

Although the 3-position of the pyrazolone on *bis*-heterocyclic compounds mentioned in the literature[11, 18] is methyl, in this paper the group was changed to phenyl, the conclusion can also be obtained that the phenyl of 3-position does not hinder the ring-closure reaction to form a new kind of *bis*-heterocyclic compounds from the discussion above.

The compound reported in the literature[9] possesses the photochromism is due to the intramolecular hydrogen bond [between N (3) atom and O atom] and the solvent molecule which was incorporated with the master molecular, therefore the hydrogen bond, solvent molecule and irradiation of UV-light provide the condition of the intramloecular proton transfer, correspondingly, the color changes. However, the photochromism of these heterocyclic compounds (**1, 2**, **3**, **4** and **5**) was not observed both in solid state and in solution. By analyzing the molecular structures, it can be found that there is no solvent molecule take part in the crystal structure of the compounds synthesized in this paper, and this maybe the reason of the compounds which do not possess the photochromism.

EXPERIMENTAL

Materials and instruments: Materials were of commercial reagents and used without further purification. 4-methyl-3-thiosemicarbazide (MTSC), 4-ethyl-3-thiosemicarbazide (ETSC) and 4-phenthyl-3-thiosemicarbazide（PTSC）were obtained from Aldrich Chemical Co. and were not recrystallized before using. 1,3-Diphenyl-5-pyrazolone (DPP),[12] 1,3-diphenyl-4-chloroacetyl-5-pyrazolone (DPCP)[13] and methylthio-thiosemicarbazide (MTTSC)[14] were prepared according to the literatures, respectively. Elemental analyses were carried out with a model 2400-Perkin-Elmer elemental analyzer. IR spectra were recorded from KBr pellets on BRUKER EQUINOX 55 spectrophotometer. Crystal structure was determined by Siemens *P*4 four-circle diffractometer. ^{1}H NMR spectra were recorded with standard procedures on INOVA-400 NMR instrument. Melting point was measured using a TX-5 apparatus (uncorrected).

Syntheses of compounds: General procedure for the preparation of the compound. **2-Amino-5-(1,3-diphenyl-5-pyrazolone-4-ylidene)-5,6-dihydro-4*H*-1,3,4-thiadiazine (DPCP-TSC) (1):** A mixture of 1.414 g (3.0 mmol) of DPCP, 0.456 g of TSC, 15 mL of methanol and 1.5 mL of acetic acid were heated at reflux in round flask for 4 h, then methanol was evaporated slowly affording the yellowish solid. They were recrystallized with methanol. The same method was used to synthesize the compounds (**2, 3, 4** and **5**).

1 Yield: 82%, mp 227-228 °C. *Anal.* Calcd for $C_{18}H_{15}N_5OS$: C 61.88, H 4.33, N 20.04. Found: C 61.54, H 4.45, N 19.82. ^{1}H NMR ($CDCl_3$): δ 3.38 (s, 2H, -CH_2-), 7.18-7.98 (m, 10H, $2C_6H_5$), 8.06 (s, 2H, NH_2), 13.45 (w, 1H, -NH-); ^{13}C NMR (DMSO-d_6): δ 42.85, 96.50, 121.22, 122.72, 128.30, 128.72, 129.23, 129.62, 133.01, 138.75, 143.90, 153.21, 156.84, 168.27; IR υ (cm^{-1}): 3275, 3035, 1624, 1592, 1549, 1543, 1490, 1440, 1375, 1300, 1242, 1238, 1138, 575.

2-Methylamino-5-(1,3-diphenyl-5-pyrazolone-4-ylidene)-5,6-dihydro-4*H*-1,3,4-thiadiazine (DPCP-MTSC) (**2**), yield: 80%, mp 263-264 °C. *Anal.* Calcd for $C_{19}H_{17}N_5OS$: C 62.79, H 4.71, N 19.27. Found: C 63.03, H 4.60, N 19.52. ^{1}H NMR ($CDCl_3$): δ 2.99 (d, J = 5.2 Hz, 3H, -CH_3,), 3.48 (s, 2H, -CH_2-), 4.70 (w, 1H, -NH-), 7.16-8.09 (m, 10H, $2C_6H_5$), 13.50 (w, 1H, -NH-); ^{13}C NMR (DMSO-d_6): δ 28.23, 44.13, 97.22, 120.71, 123.70, 129.64, 133.80, 134.04, 134.20, 134.27, 139.53, 144.21, 153.52, 159.25, 169.64; IR υ (cm^{-1}): 3286, 3042, 1618, 1590, 1559, 1514, 1484, 1440, 1375, 1293, 1240, 1198, 1140, 575.

2-Ethylamino-5-(1,3-diphenyl-5-pyrazolone-4-ylidene)-5,6-dihydro-4*H*-1,3,4-thiadiazine (DPCP-ETSC) (**3**), yield: 85%, mp 238-239 °C. *Anal* Calcd for $C_{20}H_{19}N_5OS$: C 63.64, H 5.07, N 18.55; found C 63.82, H 5.25, N 18.74. ^{1}H NMR ($CDCl_3$): δ 1.15 (m, 3H, -CH_3), 3.28 (m, 2H, -$C\underline{H}_2$-CH_3), 3.75 (s, 2H, ring-CH_2-), 7.15-8.06 (m, 11H, $2C_6H_5$+NH), 13.45 (w, 1H, ring-NH-); ^{13}C NMR (DMSO-d_6): δ 18.24, 41.25, 43.20, 96.38, 122.67, 128.34, 132.70, 132.91, 133.07, 133.19, 138.16, 143.47, 152.44, 153.12, 157.23, 169.02; IR υ (cm^{-1}): 3288, 3030, 1629, 1590, 1558, 1525, 1493, 1460, 1333, 1350, 1293, 1235, 1176, 1120, 580.

2-Phenylamino-5-(1,3-diphenyl-5-pyrazolone-4-ylidene)-5,6-dihydro-4*H*-1,3,4-thiadiazine (**DPCP-PTSC**) (**4**), yield: 78%, mp 243-244 °C. *Anal.* Calcd for $C_{24}H_{19}N_5OS$: C 67.75, H 4.50, N 16.46, Found: C 67.68, H 4.42, N 16.43. ^{1}H NMR ($CDCl_3$): δ 3.52 (s, 2H, -CH_2), 7.12-8.05 (m, 16H, $3C_6H_5$+NH), 13.59 (w, 1H, -NH-); ^{13}C NMR (DMSO-d_6): δ 40.13, 94.80, 118.46, 119.60, 122.99, 124.32, 128.60, 128.88, 129.05, 132.68, 133.23, 134.09, 135.59, 137.28, 138.26, 139.22, 140.12, 146.23, 149.17, 150.36, 158.21, 164.87; IR υ (cm^{-1}): 3177, 3042, 1620, 1585, 1566, 1520, 1488, 1372, 1309, 1224, 1200, 1171, 1145, 570.

2-Methylthio-5-(1,3-diphenyl-5-pyrazolone-4-ylidene)-5,6-dihydro-4*H*-1,3,4-thiadiazine (DPCP-MTTSC) (**5**), yield: 82%, mp 192-193 °C. *Anal.* Calcd for $C_{19}H_{16}N_4OS_2$: C 59.98, H 4.24, N 14.73. Found: C 60.12, H 4.20, N 14.70. ^{1}H NMR ($CDCl_3$): δ 2.55 (s, 3H, -CH_3), 3.50 (s, 2H, -CH_2-), 7.18-8.08 (m, 10H, $2C_6H_5$), 13.67 (w, 1H, -NH-); ^{13}C NMR (DMSO-d_6): δ 15.11, 42.66, 95.28, 119.57, 124.99, 128.86, 128.93, 129.16, 129.48, 133.81, 138.89, 145.51, 149.56, 155.27, 165.65; IR υ (cm^{-1}): 2990, 1625, 1589, 1569, 1519, 1500, 1489, 1380, 1330, 1200, 1174, 1128, 573.

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