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RESEARCH ARTICLE

SYNTHESIS AND CHARACTERIZATION OF PYRAZOL-3-YLTHIADIAZOLE AND THIADIAZOLINE DERIVATIVES FROM DEHYDRO-L-ASCORBIC ACID

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ABSTRACT

The pyrazol-3-yl-1,3,4-thiadiazole and thiadiazolines were prepared from the reaction of 3-formyl-4,5(1H)pyrazolinedione 4-(phenylhydrazone) with thiosemicarbazide followed by oxidation with $FeCl_3$, Br_2 in water or treatment with Ac_2O; in case of bromine the cyclization was carried out with bromination of the phenyl group in p-position. Similarly, treatment of 3-formyl-1-phenyl-4,5-pyrazolinedione 4-(phenylhydrazone) with thiosemicarbazide. Phenylthiosemicarbazide, or S-benzylhydrazine-carbodithiolate, afforded the corresponding hydrazone derivatives, which were also converted into the thiadiazole and the thiadiazolines. The p-nitrophenylhydrazone , gave 3-(2-p-nitrophenyl-4-acetyl-1,4-oxazol-5-yl)-1-phenyl-4,5-pyrazolinedione 4-(phenylhydrazone) upon acetylation with Ac_2O.

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INTRODUCTION

Dehydro-L-ascorbic acid, obtained by mild oxidation of L.ascorbic acid, is considered an excellent precursor for the synthesis of many nitrogen and Sulphur heterocycles through its reactions with hydrazines or diamines. Dehydro-L-ascorbic acid has two carbonyl groups of different activity; this enable us to synthesize mono- , bis-and mixed bishydrazones. In this connection, the synthesis of pyrazol -3-ylthiadiazole and thiadiazoline derivatives is described.

RESULTS AND DISCUSSION

It is known that pyrazoles exhibit pharmacological properties as antipyretic, analgesic and antiflamatory properties (Wellinga, 1977; Grossurt, 1979; Menozzi *et al*., 1997; Haufel, 1974). For these reasons and in continuation of our interest for the synthesis of N and S heterocyclic compounds from dehydro-L-ascorbic acid and its analogs, we have synthesized different heterocycles like triazoles, imidazolines, quinoxalines and pyrazolinediones ((El Sekily *et al*., 1994; El Sekily, 2000; El Sekily, 2006; El Sekily, 2008; El Sekily, 2011).

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We now describe the synthesis of some new heterocycles containing pyrazole nucleus attached to thiadiazole and thiadiazolines in the quest of producing more effective therapeutic compounds. Thus, treatment of 3-formyl-4,5(1H) pyrazolinedione 4- (phenylhydrazone) **1** with thiosemicarbazide, afforded the 3-formylthiosemicarbazone **2** which upon oxidation with $FeCl_3$, afforded 3-(2-amino-1,3,4-thiadiazol-5-yl)-4,5(1H) pyrazolinedione 4-(phenylhydrazone) **3** whose structure was confirmed from its elemental analysis and spectral data. Acetylation of **3** with boiling Ac_2O, afforded 3-(2-acetylamino-1,3,4- thiadiazol-5-yl)-1-acetyl-4,5-pyrazolinedione 4-(phenylhydrazone) **5**. The NMR spectrum of **5** showed two singlets of three proton intensity each at δ 2,20, 2,53 in addition to the expected signals. On the other hand, acetylation of **3** with Ac_2O in pyridine, afforded a triacetyl derivative **6** whose NMR spectrum showed three assignments of acetyl groups at δ 2.16, 2.51, 2.65. It seems that compound **3** exists in keto enol forms, and the enol form **4** being favoured in presence of base like pyridine. The cyclization of 3-formylthiosemicarbazone **2** to the thiadiazole derivative **7** was affected by treatment with Br_2 in water, which upon acetylation with Ac_2O in pyridine, gave the triacetyl **8**. Furthermore, treatment of **2** with boiling Ac_2O, afforded 3-(2-acetylamino- 4-acetyl-1,3,4-thiadiazolin-5-yl)-1-acetyl-4,5-pyrazolinedione 4- (phenylhydrazone) **9**.

Treatment of **9** with Br_2 in water, resulted in removal of the acetyl group from the thiadiazoline nucleus with bromination of the phenyl group in p-position to give **10**; compound **10** has been also obtained from**7** when acetylated with boiling Ac_2O. Furthermore, treatment of **1** with phenylthiosemicarbazide, afforded the phenylthiosemicarbazone **11** which upon acetylation with Ac_2O in pyridine, gave 3-(2-phenylamino-4-acetyl-Δ^2-1,3,4-thiadiazolin-5-yl)-3-acetoxypyrazol-4-one 4-(2-acetyl-2-phenylhydrazone) **12** whose structure was confirmed from its NMR spectrum which showed 3-singlets of three proton intensity each at δ 2.22, 2.35, 2.54 corresponding to three acetyl groups. In addition, treatment of 3-formyl-1-phenyl-4,5-pyrazolinedione 4-(phenylhydrazone) **13** with thiosemicarbazide, afforded the 3-thiosemicarbazone **14a** which was cyclized to the thiadiazoline derivative **15a** upon oxidation with $FeCl_3$ and converted into monoacetyl derivative **15b** when acetylated with boiling Ac_2O. Similarly, the phenylthiosemicarbazone 14b was cyclized to the thiadiazoline **16** when acetylated with Ac_2O in pyridine.

The 3-formylthiosemicarbazone **14a** upon treatment with Br_2 in water, afforded the pyrazole thiadiazole **17a**, namely, 3-(2-amino- 1,3,4- thiadiazol-5-yl) -1-*p*-bromophenyl-4,5-pyrazolinedione 4-(p-bromophenylhydrazone) which was also acetylated to **17b**. In addition, treatment of compound **13** with S-benzylhydrazinecarbodithiolate, gave 3-formylhydrazone **18** which was also converted into the pyrazole thiadiazoline **19**, namely, 3-(4-acetyl-2-S-benzyl-Δ^2-1,3,4-thiadiazolin-5-yl)-1-phenyl-4,5-pyrazolinedione 4-(phenylhydrazone). Finally, treatment of **13** with p-nitrobenzoylhydrazine, afforded the 3-p-nitrobenzoylhydrazone **20** which was cyclized into pyrazole oxazole derivative **21**, namely, 3-(2-p-nitrophenyl-4-acetyl-1,4-oxazol-5-yl)-1-phenyl-4,5- pyrazolinedione 4-(phenylhydrazone) upon boiling with Ac_2O whose structure was established from its IR, elemental analysis and NMR data.

Experimental

M.ps. were recorded on a Tottoli (Büchi) apparatus and are not corrected. IR (KBr) were recorded on a Perkin-Elmer 580B spectrophotometer and ^1H NMR spectra (DMSO-d_6) on a Cameca 250 MHz spectrometer using TMS as an internal standard. Microanalyses were performed in the microanalytical Units, Department of Chemistry, Faculty of Science, Cairo University, Cairo. Mass spectra were recorded with an LKB model 2091 mass spectrometer and intensities are given in parantheses as a percentage of the base peak.

3-(2-Amino-1,3,4-thiadiazol-5-yl)-4,5(1H)pyrazolinedione 4-(phenylhydrazone) (3)

A solution of 3-carboxaldehyde-4,5(1H)pyrazolinedione 4-(phenylhydrazone)-3-thiosemi-carbazone 2(0.44 g; 2 mmol) in ethanol-dioxane mixture (1:1) (40 ml) was treated with $FeCl_3$ (1 g) and the mixture was heated on a steam bath for 2h, concentrated and left to cool. The resulting solid was filtered off, washed with ethanol and dried (0.3g; 75%). It was recrystallized from ethanol as red needles, m.p. 270-271°C. (Found: C, 45.83; H, 3.40; N, 34.38. $C_{11}H_9N_7SO$ Calcd. For: C, 46.00; H, 3.13; N, 34.14%); ν_{max} 3101 (NH), 1681 cm^{-1} (OCN); NMR: δ(DMSO-d_6): 3.94(s, 2H, NH_2, D_2O exchangeable), 7.22-8.12 (m, 6H, aromatic-H and 1H, NH, D_2O exchangeable), 12.42 (s, 1H, NH (hydrazone), D_2O exchangeable).

3-(2-Acetamido-1,3,4-thiadiazol-5-yl)-1-acetyl-4,5(1H) pyrazolinedione 4-(phenyl-hydrazone) (5)

A solution of 3-(2-amino-1,3,4-thiadiazol-5-yl)-4,5(1H)pyrazolinedione 4-(phenylhydrazone) **3** (0.1 g; 0.35 mmol) in Ac_2O (10 ml) was heated under reflux for 1h. The mixture was poured onto crushed ice, and the solid that separated was collected, washed with water, ethanol and dried (0.1 g; 78%). It was recrystallized from chloroform-ethanol mixture in red needles, m.p. 231-232°C (Found: C, 48.34; H, 3.61; N, 26.28 $C_{15}H_{13}SN_7O_3$ Calcd. for: C, 48.52; H, 3.53; N, 26.41%), ν_{max} 3106 (NH), 1732, 1672 ($NCOCH_3$), 1660 cm^{-1} (OCN). NMR: δ (DMSO-d_6): 2.25 (s, 3H, $NCOCH_3$), 2.50 (s, 3H, $N_{1'}$, $COCH_3$), 7.11-7.86 (m, 5H, aromatic-H), 12.21 (s, 1H, exchangeable, hydrazone NH). MS: *m/z* (%): 372 (M^+ + 1, 68), 371 (M^+, 70.3), 328 (M^+ - C_2H_3O), 313 (M^+ - C_2H_4NO, 32), 285 (M^+ - $C_4H_6O_2$, 42.6), 230 (M^+ - $C_4H_7NO_2$, 58), 229 (M^+ - $C_4H_4N_3SO$, 17), 186 (M^+ - $C_6H_7N_3SO_2$, 32), 142 (M^+ - $C_{11}H_9N_4O_2$, 11), 106 ($C_6H_6N_2$, 22), 921 (C_6H_6N, 21), 77 (C_6H_5, 100).

5-(2-Acetamido-1,3,4-thiadiazol-5-yl)-3-acetoxypyrazol-4-one 4-(2-acetyl-2-phenylhydrazone) (6)

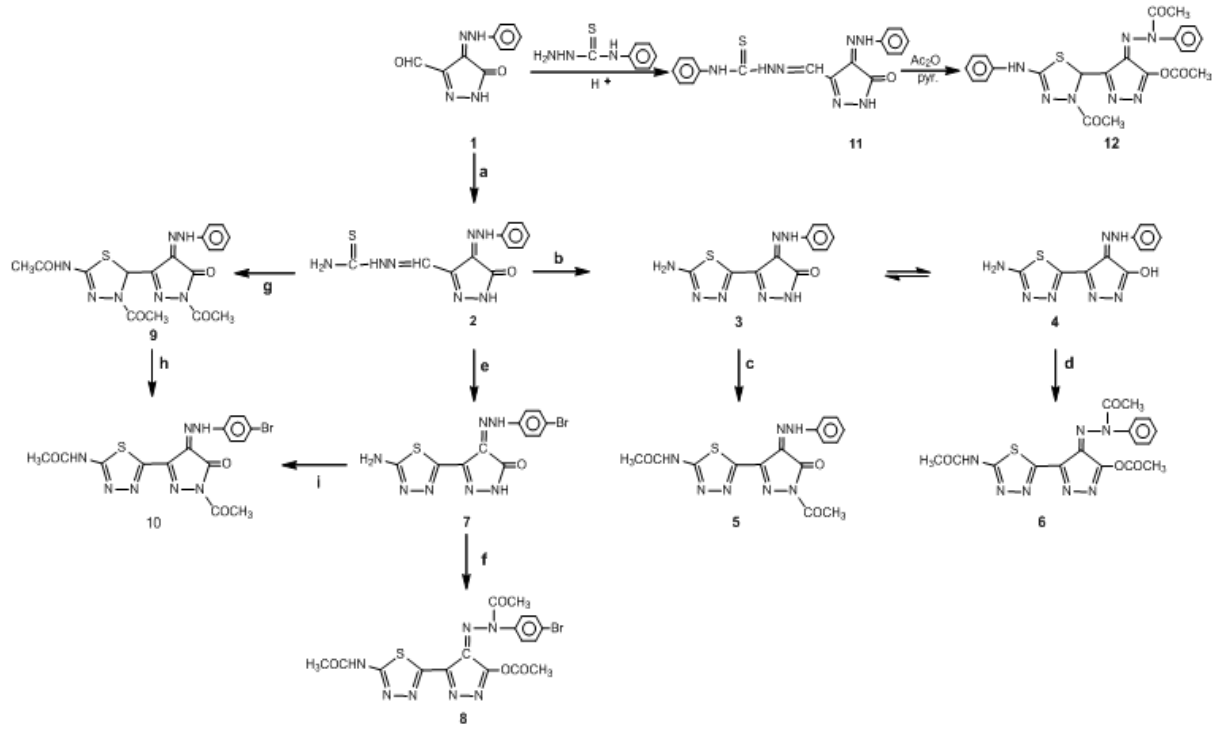
A solution of **3** (0.1 g; 0.3 mmol) in dry pyridine (10 ml) was treated with Ac_2O (5 ml) and the mixture was kept overnight at room temperature, and then poured onto crushed ice. The product was filtered off, washed with water, and ethanol and dried (0.1g; 71%). It was recrystallized from ethanol-dioxane in red needles, m.p. > 270°C (Found: C, 49.24; H. 3.42; N, 23.46. $C_{17}H_{15}SN_7O_4$ Calcd.for: C, 49.35; H, 3.63; N, 23.71%), ν_{max} 2901 (NH) 1702, 1745 cm^{-1} (acetyl groups). NMR: δ (DMSO-d_6) 2.16, 2.54, 2.57 (3s, 9H, 3 $COCH_3$), 7.12 (s, 1H, NH), 7.42-7.86 (m, 5H, Ar-H). MS: *m/z* (%): 414 (M^+ + 1, 100), 413 (M^+, 66), 370 (M^+ - C_2H_3O, 62), 322 (M^+ - C_6H_5N, 22), 321 (M^+ - C_6H_3NH, 12), 312 (M^+ - 1 – $C_4H_6NO_2$, 44), 91 (C_6H_5N, 21), 77 (C_6H_5, 98). δ(DMSO-d_6) 2.16 (s, 3H, $N_2.COCH_3$), 2.54 (s, 3H, $N_{1'}$-$COCH_3$), 2.57 (s, 3H, $NCOCH_3$-hydrazone), 7.12 (s, 1H, exchangeable NH), 7.42-7.86 (m, 5H, aromatic-H).

3-(2-amino-1,3,4-thiadiazol-5-yl)-4,5(1H) pyrazolinedione 4-(p-bromophenyl-hydrazone) (7)

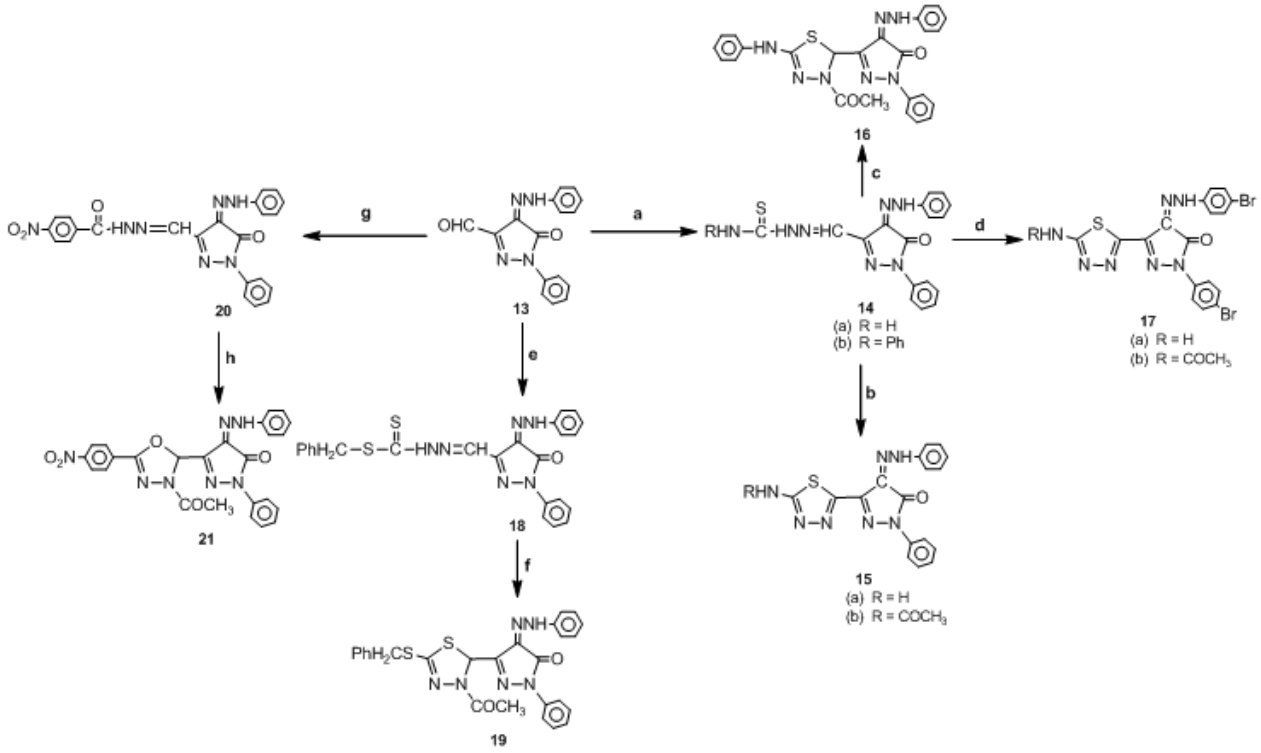
A suspension of 3-carboxaldehyde-4,5(1H) pyrazolinedione 4-(phenyl-hydrazone)-3-thiosemicarbazone 2(0.2g; 1 mmol) in water (30 ml) was treated with bromine (1 ml) in water (10 ml) and the mixture was kept overnight at room temperature with stirring. Excess of bromine was removed by passing a stream of air, and the solid that separated was filtered off, washed with water, ethanol and dried (0.15 g; 54%). It was recrystallized from ethanol as orange needles, m.p. 209-210°C . (Found: C, 36.41; H, 2.10; N, 26.52. $C_{11}H_8BrSN_7O$ Calcd. For: C, 36.07; H, 2.20; N, 26.79%), ν_{max} 3159 (NH). 1660 cm^{-1} (OCN), MS: *m/z* (%) 367 (M^+, 63.3), M^+, 68.0), 350 (M^+ - NH_2, 22.8), 266 (M^+ -1- $C_2H_2SN_3$, 34.5), 264 (M^+ -1- $C_2H_2SN_3$, 28.0) 210 (M^+ - C_6H_4Br, 22.4), 196 (M^+- C_6H_5BrN, 62.2), 181 (M^+ -1, $C_6H_5BrN_2$, 8.2), 172 (C_6H_5BrN, 14.0), 170 (C_6H_5-BrN, 10.6), 100 ($C_2H_2SN_3$, 16.6).

5-(2-Acetamido-1,3,4-thiadiazol-5-yl)-3-acetoxypyrazol-4-one 4-(2-acetyl-2-p-bromophenylhydrazone (8)

A solution of **7** (0.1 g; 0.27 mmol) in dry pyridine (10 ml) and Ac_2O (5 ml) and the mixture was kept overnight at room temperature and then poured onto crushed ice.



Scheme 1. Reagents and conditions: (a) $NH_2NHCSNH_2$, H^+, Δ1h; (b) $FeCl_3$, EtOH-dioxane, Δ2h; (c) Ac_2O, Δ1h; (d) Ac_2O, pyr. overnight; (e) Br2 in water, overnight ., (f) Ac_2O, pyr. overnight; (g) Ac_2O, Δ1h; (h) Br_2 in water; (i) Ac_2O, Δ1h



Scheme 2. Reagents and conditions: (a) $RNHCSNHNH_2$, H^+, EtOH Δ3h; (b) $FeCl_3$, EtOH, Δ1h; (c) Ac_2O, pyr. overnight; (d) Br_2 in

The solid was filtered off, washed with water ethanol and dried (0.1 g, 76%). It was recrystallized from ethanol in red needles, m.p. 253-254°C (Found: C, 41.29; H, 2.74; N, 19.71. Calcd for $C_{17}H_{14}BrN_7SO_4$ C, 41.46; H, 2.87; N, 19.92%). ν_{max} 2986 (NH), 1700, 1742 cm^{-1} (acetyl groups), NMR: δ (DMSO-d_6): 2.14 (s, 3H, N_2COCH_3), 2.50 (s, 3H, $OCOCH_3$), 2.54 (s, 3H, hydrazone $NCOCH_3$), 7.16 (s, 1H, N_2-H), 7.40-7.88 (m, 4H, aromatic-H).

3-(2-Acetamido-4-acetyl-Δ^2-1,3,4-thiadiazolin-5-yl)-1-acetyl-4,5(1H)pyrazolinedione 4-(phenylhydrazone) (9)

A suspension of **2** (0.1g, 0.34 mmol) in Ac_2O (10 ml) was heated under reflux for 1H, and the mixture was worked as in the general procedure (0.1g, 85%)/ It was recrystallized from ethanol as red needles, m.p. 272-273°C. (Found: C, 49.0; H, 4.34; N, 23.35. Calc. for $C_{17}H_{17}SN_7O_4$: C, 49.15; H, 4.12; N, 23.20%), ν_{max} 3170 (NH), 1734. 1644 ($NCOCH_3$), 1687 cm^{-1}

(OCN), NMR: δ (DMSO-d_6): 2.07 (s, 3H, N_2COCH_3), 2.20 (s, 3H, N_4COCH_3), 2.48 (s, 3H, N_1COCH_3), 6.92 (s, 1H, C_5H), 7.28-7.67 (m, 5H, aromatic-H), 7.72 (s, 1H, exchangeable NH), 12.68 (s, 1H, exchangeable hydrazone NH). MS *m/z* (%) 416 (M^+ + 1, 32), 415 (M^+,16), 372 (M^+- $COCH_3$, 8.6), 356 (M^+- $OCOCH_3$, 6.7), 313 (M^+- $2COCH_3$, 38.2), 270 (M^+- $3COCH_3$, 12.9) 229 (M^+- $C_6H_8SN_3O_2$, 43), 186 (M^+- $C_{11}H_9N_4O_2$, 12.6), 111 ($C_6H_6N_2$, 28.3), 97 (C_6H_6N, 18.2), 77 (C_6H_5, 100).

5-(2-Acetamido-1,3,4-thiadiazol-5-yl)-1-acetyl-4,5 (1H) pyrazolinedione 4-(p-bromophenylhydrazone (10) (a)

A suspension of compound (7) (0.1 g; 0.27 mmol) in Ac_2O (10 ml) was heated under reflux for 1h. The mixture was poured onto crushed ice, and the solid that separted was filted off, washed with water, ethanol and dried (0.08 g; 80%). It was recrystallized from ethanol as orange needles, m.p. 261-262°C. (Found: C, 40.12; H, 2.43; N, 21.94. $C_{15}H_{12}BrSN_7O_3$. Calcd. For : C, 40.01; H, 2.68; N, 21.77%); ν_{max} 3154 (NH), 1740, 1674 ($NCOCH_3$), 1660 cm^{-1} (OCN). NMR: δ (DMSO-d_6): 2.25 (s, 3H, N_2-$COCH_3$), 2.27 (s, 2H, N'_1-$COCH_3$), 7.22 (s, 1H, exchangeable N_2-H), 7.25-7.66 (m, 4H, aromatic-H), 12.50 (s, 1H, exchangeable C_4-hydrazone NH). MS *m/z* (%) 452 (M^+ + 1, 50), 450 (M^+ + 1, 42.6), 451 (M^+ , 8.3) 449 (M^+ , 6.2), 408 (M^+ - $COCH_3$, 12.4), 406 (M^+ - $COCH_3$, 10.2), 392 (M^+ - $OCOCH_3$, 22.4), 390 (M^+ - $OCOCH_3$, 17.3), 349 (M^+ - $2COCH_3$, 16). 347 (M^+ - $2COCH_3$, 18.2), 309 (M^+- $C_4H_4SN_3O$, 36.4), 307 (M^+ - $C_4H_4SN_3O$, 6.2), 186 ($C_6H_5BrN_2$, 18.2), 184 ($C_6H_5BrN_2$, 14.9), 142 ($C_4H_4SN_3O$, 10.4).A suspension of 3-(2-acetamido-4-acetyl-Δ^2-1,3,4-thiadiazolin-5-yl)-1-acetyl-4,5-(1H)pyrazolinedione 4-(phenylhydrazone) (**9**) (0.3 g; 0.7 mmol) in water (30 ml) was treated with bromine (1 ml) in water (10 ml) and the mixture was kept over night at room temperature with stirring. Excess of bromine was removed by passing a stream of air, and the solid that separated was filtered off, washed with water, ethanol and dried (0.3 g; 93%). It was recrystallized from ethanol as orange needles, m.p. 261-262°C alone or mixed with the compound from (a), both compounds had identical IR, mass, and NMR data.

Carboxaldehyde- 4,5 (1H) pyrazolinedione4-(phenylhydrazone)-3-phenylthiosemicarbazone) (11): A solution of compound **1** (0.22 g; 1 mmol) in ethanol (20 ml) was treated with phenylthiosemicarbazide (0.17 g; 1 mmol) and AcOH (2 ml) and the mixture was heated under reflux for 3h, and left to cool. The solid was filtered off, washed with ethanol and dried (0.22 g; 60%) It was recrystallized from ethanol as red needles, m.p. 232-233°C. (Found: C, 55.64; H, 4.33; N, 26.52. $C_{17}H_{15}SN_7O$ Calcd. for : C, 55.84; H, 4.11; N, 26.82%), ν_{max} 3125 (NH), 1655 (OCN), 1237 cm^{-1} (C=S).

(2-Phenylamino-4-acetyl-Δ^2 -1,3,4 -thiadiazolin-5-yl)-3-acetoxypyrazol-4-one-4-(2-acetyl-2-phenylhydrazone (12)

A solution of **11** (0.1 g; 0.27 mmol) in dry pyridine (10 ml) was treated with Ac_2O (5 ml) and the mixture was kept overnight at room temperature. The mixture was poured onto crushed ice, and the product was filtered off, washed with water, ethanol and dried (0.1 g; 76%). It was recrystallized from ethanol as orange needles, m.p. 270-272 °C (Found: C, 56.32; H, 4.38; N, 19.84. $C_{23}H_{21}SN_7O_4$ Calcd. for: C, 56.16; H, 4.27; N, 19.94%), NMR: δ (DMSO-d_6): 2.22 (s, 3H, N_4.$COCH_3$), 2.35 (s, 3H, $NCOCH_3$, (hydrazone), 2.54 (s, 3H, $OCOCH_3$), 4.94 (s, 1H, C_5-H), 7.32-7.88 (m, 10H, aromatic-H), 8.18 (s, 1H, C_2NH). MS: *m/z* (%): 492 (M^+ + 1, 100), 491 (M^+, 47), 448 (M^+ - C_2H_3O, 42), 429 (M^+ - $C_2H_6O_2$, 18), 370 (M^+ - $C_4H_9O_4$, 32), 371 (M^+ - $C_{10}H_{10}N_3SO$, 26), 269 (M^+ - 2, $C_{10}H_{10}SN_3O_2$, 16), 220 (M^+ - , $C_6H_{11}N_4O_3$, 13), 178 (M^+ + 1 – $C_{15}H_{14}N_4O_4$, 46), 105 ($C_6H_5N_2H$, 18), 92 (C_6H_5NH, 13), 77 (C_6H_5, 21) .

Carboxaldehyde-1-phenyl-4, 5-pyrazolinedione 3-phenylthiosemicarbazone 4-(phenylhydrazone) (14b)

A solution of **13** (13 g; mmol) in ethanol (30 ml) was treated with phenylthiosemicarbazide (1.2 g; 7.18 mmol) and acetic acid (1 ml), and the mixture was heated under reflux for 3h, and left to cool. The resulting solid was filtered off, washed with ethanol and dried (0.83 g; 76%). It was recrystallized from ethanol to give orange needles, m.p. 210-112°C. (Found: C, 62.70; H, 4.69; N, 22.62. $C_{23}H_{19}N_7SO$. Calcd. for : C, 62.57; H, 4.34; N, 22.21%), ν_{max} 3124 (NH), 1694 (OCN), 1594 (C=N), 1101 cm^{-1} (C=S).

(2-Amino-1,3,4- thiadiazol-5-yl)- 1-phenyl-4,5-pyrazolinedione 4-(phenylhydrazone) (15a)

A solution of compound (Mancy, 1995) **(14a)** (0.3 g; 0.82 mmol) in ethanol (30 ml) was treated with ferric chloride (1 g) in ethanol (10 ml) and the reaction mixture was heated under reflux for 2h, and left to cool. The product was filtered off, washed with ethanol and dried (0.2 g; 63%). It was recrystallized from chloroform-ethanol as red needles, m.p. 283-284°C. (Found: C, 53.18; H, 4.32; N, 25.34. $C_{17}H_{13}N_7SO.H_2O$ Calcd. for : C, 53.19; H, 3.99; N, 25.60%), ν_{max} 3124 (NH), 1673 cm^{-1} (OCN).

3-(2-Acetamido-1 ,3,4-thiadiazol-5-yl)-1-phenyl-4,5 pyrazolinedione 4-(phenylhydrazone) (15b)

A solution of **15a** (0.2 g; 0.5 mmol) in Ac_2O (10 ml) was heated under reflux for 1h. The mixture was poured onto crushed ice, and the product was filtered off, washed with water, ethanol and dried (0.18 g; 75%). It was recrcystallized from ethanol as red needles, m.p. > 280°C. (Found: C, 56.41; H, 3.50; N, 24.48. $C_{19}H_{15}N_7SO_2$ Calcd. for : C, 56.29; H, 3.73; N, 24.18%). ν_{max} 3149 (NH), 1698 ($NCOCH_3$), 1672 (OCN), 1593 cm^{-1} (C=N). NMR: δ (DMSO-d_6): 2.22 (s, 3H, C_2NCOCH_3), 7.21-7.91 (m, 10H, aromatic – H), 7.72 (s, 1H, NH), 12.76 (s, 1H, hydrazone NH). MS: *m/z* (%): 406 (M^+ + 1, 100), 405 (M^+, 68), 362 (M^+ - C_2H_3O, 42), 347 (M^+ - C_2H_4NO, 16), 263 (M^+ - $C_4H_4N_3SO$, 36), 250 (M^+ - $C_8H_{10}N_2O$, 21), 143 (M^+ + 1 - $C_{15}H_{11}N_4O$, 16), 105 (M^+ - 1 - $C_{13}H_9N_5SO_2$, 22), 91 (M^+ – $C_{13}H_{10}N_6SO_2$, 100).

3-(2-phenylamino-4-acetyl-Δ^2-1,3,4-thiadiazol in-5-yl)-1-phenyl-4,5-pyrazolinedione 4-(phenylhy drazone) (16)

A solution of **14b** (0.1 g; 0.23 mmol) in dry pyridine (10 ml) was treated with Ac_2O (5 ml) and the mixture was left overnight at room temperature. The mixture was poured onto crushed ice, and the product was filtered off, washed with water ethanol and dried (65 mg; 59%). It was recrystallized from ethanol as red needles, m.p. 170-172°C (Found: C, 62.28; H, 4.11; N, 20.62. $C_{25}H_{21}N_7SO_2$. Calcd. for: C, 62.11; H, 4.34 N, 20.29%) , ν_{max} 3120 (NH), 1682 (OCN), 1664 cm^{-1} ($NCOCH_3$), NMR: δ (DMSO-d_6): 2.22 (s, 3H, N_4COCH_3), 6.84 (s, 1H, NH), 7.21-7.92 (m, 15H, Ar-H), 8.18 (s, 1H, C_5-H), 12.86 (s, 1H, NH).

3-(2-Amino-1,3, 4-thiadiazol-5-yl) -1-p-bromophenyl-4,5-pyrazolinedione 4-(p-bromophenylhydrazone) (17a)

A suspension of 14a (0.3 g; 0.82 mmol) in water (20 ml) was treated with bromine (1 ml) in water (10 ml) and the mixture was stirred for 24h at room temperature . Excess of bromine was removed by passing a stream of air and the resulting product was filtered off, washed with water, ethanol and dried (0.32 g; 74%). It was recrystallized from ethanol as orange needles, m.p. 172-173 ^{o}C (Found: N, 18.59. $C_{17}H_{11}Br_2N_7SO$ Calc. for: N, 18.80%), ν_{max} 3234 (NH), 1665 (OCN), 1600 cm^{-1} (C=N), $\lambda_{max}^{dioxane}$ 279, 422 nm (log ε 4.33, 4.19), λ_{min} 362 nm (log ε 3.22).

(2-Acetamido-1,3,4-thiadiazol-5-yl)-1-p-bromophenyl-4,5-pyrazolinedione 4-(p-bromophenylhydrazone) (17b)

This compound has been prepared by the same method for **15a** . It was recrystallized from ethanol as orange needles, m.p. 160-161^{o}C (Found: C, 40.42; H, 2.40; N, 16.98, $C_{19}H_{13}Br_2N_7SO_2$ Calcd. for: C, 40.52; H, 2.33; N, 17.41%), ν_{max} 3149 (NH), 1698. ($NCOCH_3$), 1678 (OCN), 1593 cm^{-1} (C=N), NMR: δ (DMSO-d_6) 2.18 (s, 3H, C_2NCOCH_3), 6.62 (s, 1H, exchangeable C_2NH), 7.22-7.82 (m, 8H, aromatic-H), 11.99 (s, 1H, C_4, hydrazone NH).

Carboxaldehyde-1-phenyl-3-(S-benzyl hydrazinocarbodithiolate)-4,5-pyrazolinedione 4-(phenylhydrazone) (18)

A solution of **13** (1g; 3.42 mmol) in ethanol (30 ml) was treated wih S-benzylhydrazinocarbodithiolate (1g; 5.05 mmol) and the mixture was heated on a steam bath for 3h, and left to cool at room temperature. The solid obtained was filtered off, washed with ethanol and dried (0.6 g; 72%). It was recrystallized from ethanol as red needles, m.p. 230-231^{o}C, (Found: C, 61.37; H, 4.32; N, 17.38. $C_{24}H_{20}N_6S_2O$ Calcd for: C, 61.01; H, 4.27; N, 17.79%); ν_{max} 3100 (NH), 1660 (OCN), 1594 (C=N), 1148 cm^{-1} (C=S), λ_{max}^{EtOH} 230, 427 nm (log ε 4.57, 4.39), λ_{min} 369 nm (log ε 4.99).

3-(4-Acetyl-2-S-benzyl-Δ^2-1,3,4-thiadiazolin-5-yl)-1-phenyl-4,5-pyrazolinedione 4-(phenylhydrazone) 19

A solution of compound **18** (1g; 2.11 mmol) in pyridine (15 ml) was treated with Ac_2O (10 ml) and the mixture was kept overnight at room temperature. The mixture was poured onto crushed ice, and the solid was filtered off, washed with water and ethanol and dried (0.8g; 75%). It was recrystallized from ethanol as orange needles, m.p. 150-151^{o}C. (Found: C, 60.54; H, 4.55; N, 16.45. $C_{26}H_{22}N_6S_2O_2$ Calcd for: C, 60.68; H, 4.31; N, 16.33%), ν_{max} 1671 (OCN), 1594 cm^{-1} (C=N), NMR: δ (DMSO-d_6): 2.38 (s, 3H, N_4-$NCOCH_3$), 4.35 (s, 2H, CH_2), 7.22-7.48 (m, 15H, aromatic-H), 7.92 (s, 1H, C_5-H), 14.59 (s, 1H, hydrazone NH). MS *m/z* (%) 483 (M^+ + 1, 32.4), 482 (M^+, 16.3), 439 (22.6), 391 (18.5), 390 (6.4), 359 (76.4), 275 (36.4), 207 (6.7), 124 (16.8), 106 (100), 91 (5.2), 77 (10.2).

3-Carboxaldehyde-1-phenyl-4,5-pyrazolinedione-3-p-nitrobenzoylhydrazone 4-(phenylhydrazone) (20)

A solution of **13** (1 g; 3.42 mmol) in ethanol (30 ml) was treated with p-nitrobenzoylhydrazine (1.2 g; 6.6 mmol) and acetic acid (5 ml) and the mixture was heated under reflux for 3h. The mixture was concentrated and left to cool, and the solid was filtered off, washed with ethanol and dried (0.9 g; 95%). It was recrystallized from ethanol as red needles, m.p.260-261^{o}C, (Found: C, 59.21; H, 3.85; N, 21.36. $C_{23}H_{17}N_7O_4$. 0.5 H_2O Calcd. for: C, 59.48; H, 3.87; N, 21.12%), ν_{max} 1692 (CONH), 1676 cm^{-1} (OCN).

3-(3-Acetyl-5-p-nitrophenyl-2,3-dihydro-1,3,4-oxadiazol-2-yl)-1-phenyl-4,5-pyrazolinedione 4-(phenylhydrazone) (21)

A suspension of compound **20** (0.1 g; 0.22 mmol) in Ac_2O (10 ml) was heated under reflux for 1h, and the mixture was poured onto crushed ice. The solid was filtered off, washed with water and ethanol and dried (56 mg; 67%). It was recrystallized from chloroform-ethanol as orange needles, m.p. 180-181^{o}C. (Found: C, 60.52; H, 3.62; N, 19.58. $C_{25}H_{19}N_7O_5$ Calcd. for: C, 60.36; H, 3.85; N, 19.72%). ν_{max} 1673 (OCN), 1627 ($NCOCH_3$), 1595 cm^{-1} (C=N). NMR: δ (DMSO-d_6): 2.24 (s, 3H, N_4COCH_3), 7.22-7.64 (m, 10H, aromatic-H), 7.78 (d, 2H, J=7.6, aromatic-H), 7.98 (d, 2H, J=8.2, aromatic-H), 8.16 (s, 1H, oxadiazole-H), 13.24 (s, 1H, hydrazone NH).

Conclusion

The synthesized pyrazol-3-ylthiadiazole and thiadiazoline derivatives were characterized by various spectroscopic techniques. The data obtained from various spectroscopic studies and elemental analysis are in good agreement with proposed structures.

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