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REACTIONS OF 4-ALKYLIDENE (ARYLIDENE)-1-PHENYLPYRAZOLIDINE-3,5-DIONE

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Reactions of 4-alkylidene(arylidene)-1-phenylpyrazolidine-3,5-dione with oxidizing (chromium trioxide/acetic acid) as well as with reducing (sodium borohydride/methanol) agents were carried out. Phenylhydrazine reacted with 4-arylidene-1-phenylpyrazolidine-3,5-diones via fission of exo C=C bond to give 1-phenylpyrazolidine-3,5-dione and the corresponding aryl hydrazones.

Keywords: 4-alkylidene(arylidene)-1-phenylpyrazolidine-3,5-dione, oxidation, reduction.

Condensation of 1-phenyl-3,5-pyrazolidinedione (**1**) with carbonyl compounds readily give 4-alkylidene(arylidene)-1-phenyl-3,5-pyrazolidinediones **2** which were subjected to several investigations [1-4]. The purpose of this paper is to develop and study new products derived from **2** by oxidation, reduction, and reaction with phenylhydrazine.

The reactivity of the exocyclic double bond in 4-arylidene-1-phenyl-3,5-pyrazolidinedione **2** encouraged us to try its oxidation using chromium trioxide in glacial acetic acid aiming to obtain 1-phenyl-3,4,5-pyrazolidinetrione **3**, but no trione of the type **3** was obtained (Scheme 1). Elemental and mass spectrometric analysis of the oxidation product indicates that the starting arylidene derivative **2** loses a molecule of carbon monoxide. The IR absorption spectra indicate the presence of the amidic carbonyl group (1630-1670 cm^{-1}). ^1H NMR spectral analysis reveals the presence of an olefinic proton at a δ value of ~5.8 ppm. These analytical and spectral data led us to propose 5-aryl-1-phenyl-Δ^4-pyrazolin-3-ones **8** as the reaction products. The formation of **8** depends on oxidative cleavage of compound **2** to give the α,β-unsaturated carboxylic acid **4** which is easily decarboxylated to give the hydrazide **5** ⇆ hydrazone **6** tautomer. Aromatization of compound **5** *via* dehydrogenation with chromium trioxide yields **8** (Scheme 1).

Formation of compounds **8** is based on the cleavage of the $N_{(1)}$–$C_{(5)}$ bond in compounds **2** as it is the easier bond to be broken [5]. Cleavage of the $N_{(2)}$–$C_{(3)}$ bond to give **9** is not feasible due to the tautomeric form of **2** with the double bond between $N_{(2)}$–$C_{(3)}$.

The identity of derivative **8** was confirmed by comparison with an authentic sample obtained by a known method [6]. Compound **9** is known in the literature [7] and differs from derivative **8**. The aforementioned oxidation represents a general and convenient method for the synthesis of **8** from accessible chemicals as compared to the procedures mentioned in the literature [6].

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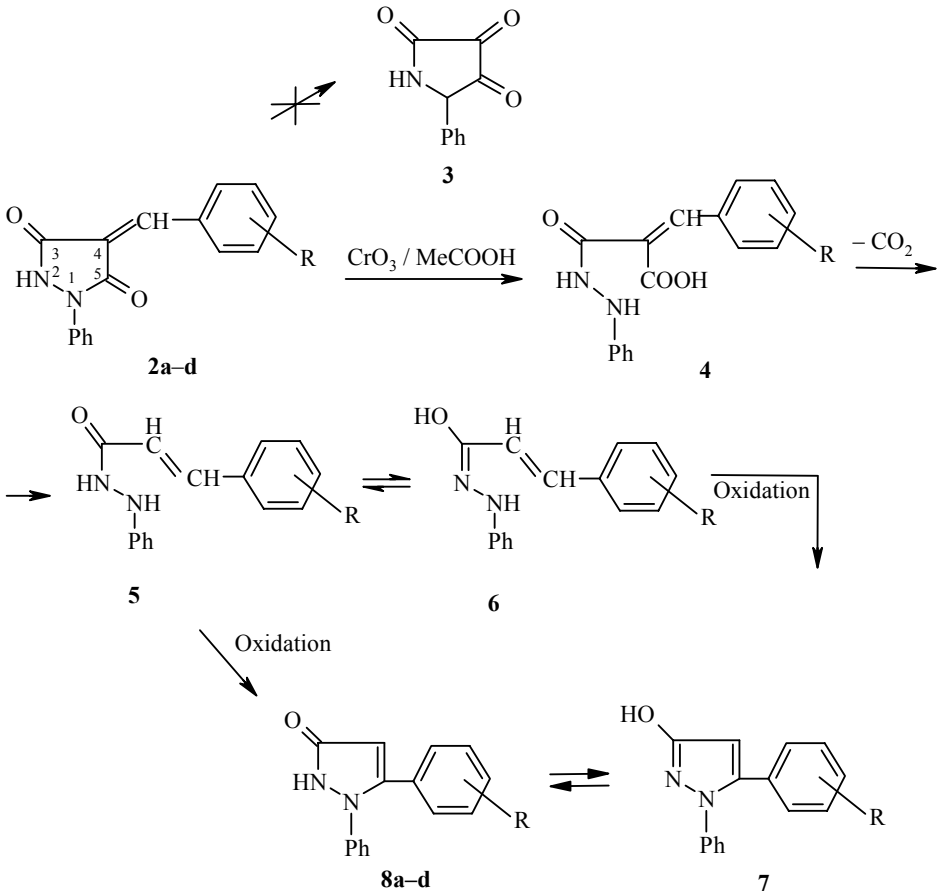
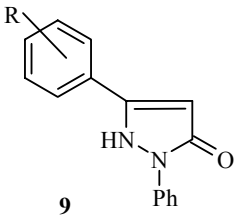
Scheme 1



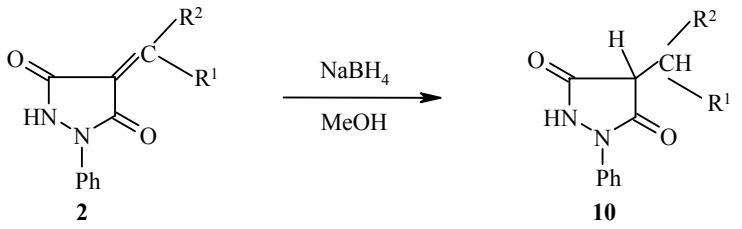
2, **8 a** R = H, **b** R = 4-Me, **c** R = 4-OMe, **d** R = 2-NO_2



9

Reduction of **2** was affected using sodium borohydride with or without palladium/charcoal catalyst. The reaction was aimed at the formation of 4-aryl-(alkyl)-3,5-pyrazolidinediones **10** with expected high biological activity. Sodium borohydride in methanol was found to be a selective reducing agent for the exocyclic double bond, yielding the required 4-aryl(alkyl)-3,5-pyrazolidinedione **10** in quantitative yield. The nitro group in arylidene derivative **2d** is not reduced under the above reaction conditions. Using sodium borohydride in methanol in the presence of palladium/charcoal catalyst affects the reduction of the nitro group in arylidene derivative **2d** to give the corresponding amino aryl compound **11**.

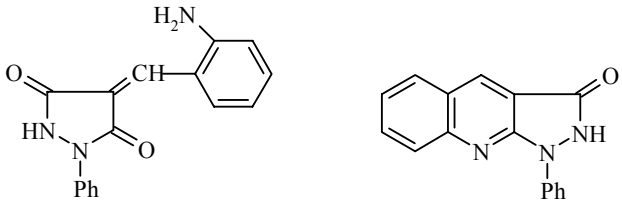
Attempted cyclization of **2d** using sodium borohydride/methanol and Pd/C or fusion of **11** to get pyrazolo[3,4-*b*]quinoline derivative **12** with expected interferon-eliciting activity [8–11] failed. This may be due to the spatial geometry of **11**.



2 **10**

a–d R^1 = H, **a** R^2 = Ph, **b** R^2 = 4-MeC_6H_4, **c** R^2 = 4-$O_2NC_6H_4$,

d R^2 = 2-$O_2NC_6H_4$, **e** R^1 = R^2 = Me



11 **12**

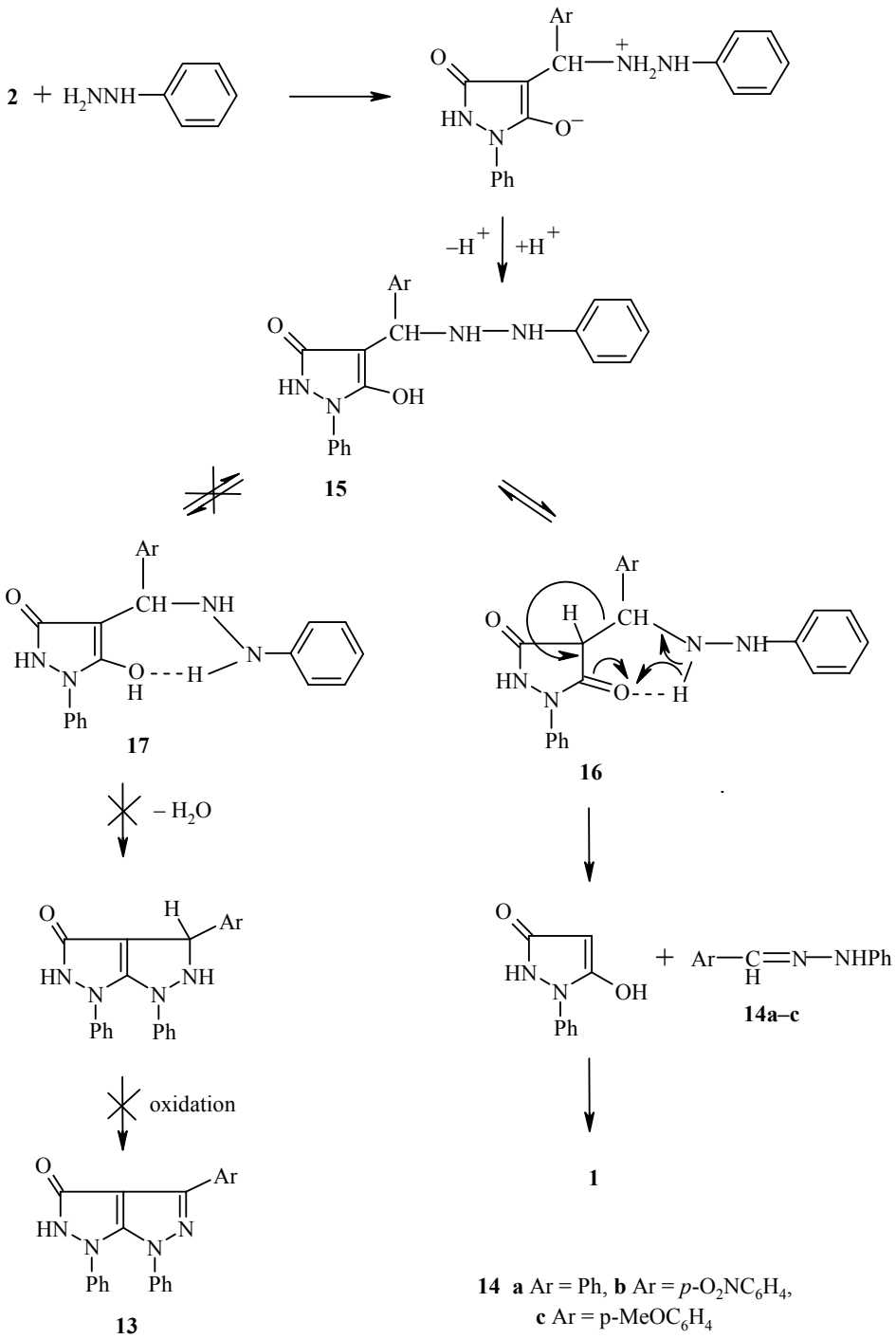
The reactivity of the exocyclic double bond in **2** encouraged us to try its reaction with phenylhydrazine with the aim to obtain the condensed pyrazolopyrazolone derivatives **13**. Reaction of 4-benzylidene derivative **2a** with phenylhydrazine took place *via* the cleavage of the *exo* methine bond and the arylidene group was trapped as the corresponding hydrazone **14 [**12] with the liberation of 1-phenyl-3,5-pyrazolidinedione (**1**). The formation of hydrazone derivative **14** could be explained by the nucleophilic addition of phenyl-hydrazine on the electropositive methine carbon as a first step in 1,4-addition reaction to give the enol intermediate **15** which is the tautomer of the keto form **16**. The transformation of **16** to the hydrazone **14** and pyrazolidinedione **1** occurred *via* the stable six-membered hydrogen-bonded intermediate (see arrows in **16**). Formation of pyrazolopyrazolidinone **13**, if it occurs, should go through the unstable seven-membered hydrogen-bonded intermediate **17** (Scheme 2).

Identification of the hydrazone **14** as well as 1-phenyl-3,5-pyrazolidine-dione **1** was done using mp, mixed mp, IR, ^{1}H NMR, and mass spectrometric analysis and also comparing with authentic samples.

EXPERIMENTAL

Melting points were measured with an electronic melting point apparatus (Gallenkamp) and are not corrected. Elemental analyses were performed with an Elementar analysensysteme GmbH, verio EI. IR spectra were recorded with a Shimadzu 470 infrared spectrophotometer (KBr wafer technique). ^{1}H and ^{13}C NMR spectra were measured with a ^{1}H NMR LA 400 (Jeol) (400 and 100 MHz, respectively) with TMS as internal standard. Mass spectrometric analyses were recorded with JOEL-JMS 600.

Scheme 2



Reaction of 4-arylidene-1-phenyl-3,5-pyrazolidinediones (**2**) **with Chromium Trioxide (General Method)**. To a suspension of 4-arylidene-1-phenyl-3,5-pyrazolidinedione (**2**) (0.01 mol) in glacial acetic acid (30 ml), chromium trioxide (0.01 mol) dissolved in water (5 ml) was added. The reaction mixture was refluxed for 4 h. After filtration, the resulting filtrate was diluted with water to give a precipitate which was collected, crystallized from the proper solvent, and identified as 5-aryl-1-phenyl-4-pyrazolin-3-one **8** derivatives.

1,5-Diphenyl-4-pyrazolin-3-one (**8a**). Yellow amorphous solid from benzene, mp 250°C (authentic 251°C [6]); yield 76.87%. IR spectrum, ν, cm^{-1}: 3150 (NH), 3050 (CH aromatic), 1680 (C=O amidic), 1590 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 5.8 (1H, s, C<u>H</u>, pyrazolone proton), 9.94 (1H, s, NH), a multiplet extended at δ values: 7.12, 7.17, 7.10, 7.28, 7.24, and 7.15 (10H, aromatic protons). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 161.54 (C=O), 93.91 (=CH), 142.95 (C-5), 130.02, 127.84, 128.01, 127.79 (C_6H_s) 139.67, 124.07, 128.21, 124.77 (C_6H_5). Mass spectrum, *m/z* (I_{rel}, %): 236 $[M]^+$ (100), 235 (40.2), 208 (4.9), 218 (1.8), 207 (23.8), 193 (2), 180 (11.8), 130 (1.3), 134 (1.0), 133 (4.3), 119 (1.1), 108 (1.7), 107 (1.5), 77 (53.9). Found, %: C 76.10; H 5.07; N 11.78. $C_{12}H_{12}N_2O_5$ (236.27). Calculated, %: C 76.25; H 5.11; N 11.85.

5-(4'-Methylphenyl)-1-phenyl-4-pyrazolin-3-one (**8b**). Yellow amorphous solid from ethanol, mp 252-254°C; yield 77.86%. IR spectrum, ν, cm^{-1}: 3160 (NH), 3050 (CH aromatic), 2950 and 2850 (CH aliphatic), 1660 (C=O amidic), 1580 (C=N). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 5.88 (1H, s, C<u>H</u>, pyrazolone proton), 10.15 (1H, s, NH), 2.27 (3H, s, CH_3), a multiplet extended at δ values: 7.32, 7.09, 7.11, 7.23, and 7.14 (9H, aromatic protons). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 94.00 (C-4, =CH), 143.19 (C-5), 161.63 (C=O), 20.72 (CH_3), 139.96, 124.46, 128.16, 126.40 (C_6H_5), 129.06, 126.40, 128.78 and 137.74 (4-$CH_3C_6H_4$). Mass spectrum, *m/z* (I_{rel}, %): 250 $[M]^+$ (98.7), 249 (40.4), 221 (17.1), 144 (5.1), 135 (5.4), 133 (3.1), 119 (11.9), 108 (4.7), 107 (9.3), 106 (16.6), 103 (12.2), 92 (16.4), 91 (51.0), 77 (100). Found, %: C 6.77; H 5.242; N 10.91. $C_{16}H_{14}N_2O$ (250.29). Calculated, %: C 76.78; H 5.63; N 11.19.

5-(4'-Methoxyphenyl)-1-phenyl-4-pyrazolin-3-one (**8c**). Yellow amorphous solid from benzene, mp 225°C; yield 77.39%. IR spectrum; ν, cm^{-1}: 3220 (NH), 3050 (CH aromatic), 2900 and 2850 (CH aliphatic), 1680 (C=O amidic), 1600 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 5.88 (1H, s, C<u>H</u>, pyrazolone proton); 10.15 (1H, s, NH); 3.77 (3H, s, OCH_3); a multiplet extended at δ values: 6.10, 6.88, 7.16, 7.32, 7.23 (9H, aromatic protons). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 93.79 (C-4, CH); 143.08 (C-5); 161.67 (C=O); 55.13 (OCH_3); 122.73, 124.49, 113.98, 159.17 (4-$OCH_3C_6H_4$); 140.04, 129.59, 128.82, 126.36 (C_6H_5). Mass spectrum, *m/z* (I_{rel}, %): 266 $[M]^+$ (100), 265 (18.2), 248 (3.0), 210 (6.3), 135 (4.3), 133 (8.8), 119 (5.2), 92 (10.0), 105 (5.8), 77 (28.8). Found, %: C 71.85; H 4.78; N 10.35. $C_{16}H_{14}N_2O_2$ (266.29). Calculated, %: C 72.16; H 5.29; N 10.52.

5-(2'-Nitrophenyl)-1-phenyl-4-pyrazolin-3-one (**8d**). Brown amorphous solid from ethanol, mp 273-252°C; yield 71.82%. IR spectrum, ν, cm^{-1}: 3150 (NH), 3050 (CH aromatic), 2900 (CH aliphatic), 1680 (C=O amidic), 1590 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 5.88 (1H, s, =C<u>H</u>, pyrazolone proton); 12.16 (1H, s, NH); a multiplet extended at δ values 7.90, 7.49, 7.63, 7.57, 7.12, 7.33, and 7.27 (9H, aromatic protons). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 87.74 (C-4, =CH); 154.88 (C-5); 162.82 (C=O); 148.30, 130.71, 123.66, 128.86, 135.96, 129.03 (2-NO_2, C_6H_4); 143.03, 113.26, 130.71, 119.44 (C_6H_5). Found, %: C 64.21; H 3.89; N 14.65. $C_{12}H_{11}N_3O_3$ (281.26). Calculated, %: C 64.05; H 3.91; N 14.94.

Reduction of 4-arylidene(alkylidene)-1-phenyl-3,5-pyrazolidinedione (**2**) **with Sodium Borohydride (General Method)**. A slow stream of helium was bubbled through a solution of sodium borohydride (0.78 g, 0.02 mol) in water (15 ml), and compound **2** (0.01 mol) in methanol (20 ml) was added dropwise for 5 min. The mixture was left at room temperature for further 10 min, and the solution was acidified by using diluted HC1 to destroy the excess of sodium borohydride. The mixture was extracted with diethyl ether and dried over anhydrous sodium sulfate. The solvent was evaporated under reduced pressure, and the solid was collected and recrystallized from the proper solvent.

4-Isopropyl-1-phenyl-3,5-pyrazolidinedione (**10e**). Yellow amorphous solid from chloroform, mp 90-92°C; yield 85.5%. IR spectrum, ν, cm^{-1}: 3400 (NH), 3030 (CH aromatic), 2950, and 2850 (CH aliphatic), 1730 (C=O), 1670 (CO amidic). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz); 3.10 (6H, d, J = 4.5, $2CH_3$); 2.38 (1H, octet, J = 4.5, C<u>H</u>); 3.05 (1H, d, J = 7.5, CH) and a multiplet centered at δ 7.3 (6H, 5-C_6H_5 and 1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 218 $[M]^+$ (93.5), 203 $[M^+–CH_3]$ (100), 105 $[M^+–C_5H_9N_2O]$ (22.3), 176 $[M^+–C_3H_6]$ (28.3). Found, %: C 65.90; H 6.50; N 13.00. $C_{12}H_{14}N_2O_2$ (218). Calculated, %: C 66.05; H 6.42; N 12.84.

4-Benzyl-1-phenyl-3,5-pyrazolidinedione (**10a**). White amorphous solid from chloroform, mp 182°C; yield 61.53%. IR spectrum, ν, cm^{-1}: 3100 (NH), 2950 (CH aliphatic), 1710 (CO), 1660 (CO amidic). ^1H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.3 (2H, d, *J* = 6.0, CH_2), 3.55 (1H, t, *J* = 6, CH) and a multiplet centered at δ 7.3 (11H, 10 aromatic protons and 1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 266 $[M]^+$ (46.3), 248 (2.3), 92 (9.2), 175 (1.4), 91 (100). Found, %: C 71.47; H 5.45; N 11.05. $C_{16}H_{14}N_2O_2$ (266). Calculated, %: C 72.18; H 5.26; N 10.52.

4-(4'-Methylbenzyl)-1-phenyl-3,5-pyrazolidinedione (**10b**). White flakes from chloroform, mp 180-182°C; yield 59.57%. IR spectrum, ν, cm^{-1}: 3100 (NH), 2900 (CH aliphatic), 1730 (CO), 1670 (CO amidic). Mass spectrum, *m/z* (I_{rel}, %): 280 $[M]^+$ (25.7), 279 (1.9), 278 (4.7), 105 (100). Found, %: C 72.50; H 5.52; N 10.70. $C_{17}H_{16}N_2O_2$ (280). Calculated, %: C 72.85; H 5.71; N 10.00.

4-(4'-Nitrobenzyl)-1-phenyl-3,5-pyrazolidinedione (**10c**). Yellow amorphous solid from chloroform, mp 215–216°C; yield 99.35%. IR spectrum showed bands at, ν, cm^{-1}: 3030 (CH aromatic), 2850 (CH aliphatic), 1720 (CO), 1665 (CO amidic), 1500 (NO_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.25 (2H, d, *J* = 6, CH_2); 4.1 (1H, t, *J* = 6, CH) and a multiplet centered at δ 7.6 (10H, 9 aromatic protons; 1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 311 $[M]^+$ (17.72), 265 (1.51), 175 (6.71), 105 (17.3), 175 (16.1) 136 (14.08). Found, %: C 62.00; H 4.05; N 13.46. $C_{16}H_{13}N_3O_4$ (311). Calculated, %: C 61.73; H 4.18; N 13.50.

4-(2'-Nitrobenzyl)-1-phenyl-3,5-pyrazolidinedione (**10d**). Buff amorphous solid from chloroform, mp 193-194°C; yield 96.37%. IR spectrum, ν, cm^{-1}: 3300 (NH); 3030 (CH aromatic); 2900 and 2850 (CH aliphatic); 1725 (CO), 1680 (CO amidic). ^1H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.5 (2H, d, *J* = 7.5, CH_2); 4.0 (1H, t, *J* = 7.5, CH) and a multiplet centered at δ 7.65 (10H, 9 aromatic protons; 1H, NH). Mass spectrum, *m*/*z* (I_{rel}, %): 311 $[M]^+$ (13.1), 265 (3.05), 175 (5.31), 91 (32.26). Found, %: C 61.51; H 4.12; N 13.60. $C_{16}H_{13}N_3O_4$ (311). Calculated, %: C 61.74; H 4.18; N 13.50.

Preparation of 4-(2'-aminobenzylidene)-1-phenyl-3,5-pyrazolidinedione (**11**). A solution of sodium borohydride (1.0 g, 0.025 mol) in water (20 ml) was carefully added to a suspension of palladium/charcoal (0.1 g) in water (10 ml). To the resulting suspension a solution of 4-(2'-nitrobenzylidene)-1-phenyl-3,5-pyrazolidinedione (**2d**) (1.0 g, 6×10^{-3} mol), dissolved in methanol (50 ml), was added dropwise over a period of 30 min. Helium was bubbled through the reaction mixture during the addition of the nitro compound and for a further 15 min. The mixture was then filtered off and acidified with diluted HCl. The precipitated product was collected and crystallized from chloroform–petroleum ether, 1:1, mp 160°C, yield 72.22%. IR spectrum, ν, cm^{-1}: 3350 and 3250 (NH_2); 3030 (CH aromatic); 2900 (CH aliphatic); 1680 (C = O), 1590 (C=C). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 6.74 (1H, s, =CH), 8.50 (2H, s, NH_2) and a multiplet centered at δ values: 7.38, 7.26, 7.19, 7.02, 6.98, 7.36, and 6.82 (9H, aromatic protons). Mass spectrum, *m*/*z* (I_{rel}, %): 279 $[M]^+$ (5.9), 278 (8.9), 234 (1.5), 262 (1.0). Found, %: C 68.10; H 4.40; N 13.97. $C_{16}H_{13}N_3O_2$ (279.29). Calculated, %: C 68.80; H 4.69; N 15.04.

Reactions of 4-arylidene-1-phenyl-3,5-pyrazolidinedione (**2**) **with Phenylhydrazine.** A mixture of compound **2** (0.001 mol) and phenylhydrazine (0.001 mol) in absolute ethanol (10 ml) was heated under reflux for 2 h. The solvent was removed under reduced pressure and the precipitate formed was boiled in cyclohexane and filtered off, whereby the corresponding hydrazone was precipitated after concentration. The remained residue was recrystallized from ethanol to give the dione **1**. The results are summarized as follows.

1-Phenyl-3,5-pyrazolidinedione (**1**). Pale yellow plates from ethanol, mp 190-192°C; mp of authentic sample 190–192°C; yield 57.21%.

Benzaldehyde phenylhydrazone (**14a**)**.** Pale yellow needles from cyclohexane, mp 158-160°C, mp of an authentic sample 158-160°C; yield 66.44%. IR spectrum, ν, cm^{-1}: 3285 (NH), 3020 (CH aromatic); 1585 (C=N). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 7.20 apparently including all protons in the molecule. Found, %: C 78.50; H 5.80; N 14.28. $C_{13}H_{12}N_2$ (196). Calculated, %: C 79.59; H 6.12; N 14.28.

***p*-Nitrobenzaldehyde phenylhydrazone** (**14b**). Red flakes from diluted ethanol, mp 150-152°C, mp of authentic sample 150-152°C; yield 38.46%. IR spectrum, ν, cm^{-1}: 3300 (NH), 3030 (CH aromatic), 1590 (C=N), 1495 (C–NO_2). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.55 apparently including all protons. Mass spectrum, *m/z* (I_{rel}, %): 241 $[M]^+$ (85.5), 240 (13.7), 225 (2.2), 195 (5.0). Found, %: C 65.68; H 4.58; N 17.35. $C_{13}H_{11}N_3O_3$ (241). Calculated, %: C 64.73; H 4.56; N 17.42.

***p*-Methoxybenzaldehyde Phenylhydrazone** (**16c**). Yellow needles from *n*-hexane, mp 115°C, yield 39.02%. IR spectrum, ν, cm^{-1}: 3300 (NH), 3030 (CH aromatic), 2950, and 2900 (CH aliphatic), 1590 (C=N). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.9 (3H, s, OCH_3) and a multiplet centered at δ 7.3 (11H, 9 aromatic protons; 1H, –NH and 1H, =CH). Found, %: C 74.39; H 6.75; N 12.10. $C_{14}H_{14}N_2O$ (226). Calculated, %: C 74.33; H 6.19; N 12.38.

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