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SYNTHESIS AND CRYSTAL STRUCTURE OF SOME 3,5-PYRAZOLIDINEDIONES

Saoud A. M. Metwally[1]*, Maisa I. Abdel Moneim[1], Yasser A. Elossely[1], Radwa I. Awad[2], Khaled Abou-Hadeed[3]

Syntheses of various derivatives of 3,5-pyrazolidenedione are reported. This includes 4-arylidene (alkylidene or aralkylidene)-3,5-pyrazolidinediones, which on epoxidation gave unreported oxiranes. The syntheses of these derivatives were based on either the Knoevenagel reaction of carbonyl derivatives with 3,4-pyrazolidinedione or cyclization of arylidene (alkylidene) malonic acid hydrazide with glacial acetic acid. 4-Arylazo-3,5-pyrazolidinedione derivatives were also prepared by coupling of aryldiazonium salts with 3,5-pyrazolidinedione or cyclization of arylazomalonic acid hydrazide. Reduction of 4-benzylidene derivatives gave the corresponding benzyl derivatives. The structure of the new products was confirmed by elemental and spectral analyses and X-ray crystallography.

Keywords: 3,5-pyrazolidinediones, X-ray crystallography.

Historically, dyes and pharmaceuticals derived from pyrazolinones were among the first successful commercial synthetic organic chemicals in which interest has continued actively until the present day. Research in this field has culminated in the discovery of the useful anti-inflammatory properties of 4-*n*-butyl-1,2-diphenyl-3,5-pyrazolidinedione (phenylbutazone) [1]. In spite of the problems encountered in the undesirable side reactions, principally agranulocytosis produced by these drugs [2-7], interest in them has never abated and one feels confident in predicting the discovery of additional useful and improved drugs in this class of compounds [8-10]. The development of new and improved dyes based on pyrazolinone structures has likewise led to modern developments of no inconsiderable magnitude. The use of tetrazine [11-14] as an approved color for foodstuffs is of significance. The synthesis of pyrazolinedione dyes for use as magenta couplers and sensitizers in color photography has been suggested [15, 16]. Metal chelate pyrazolidinone dye structures have caused a renewed interest in the use of these dyes in analytical procedures [17-19]. Recently 3,5-pyrazolidinediones have found extensive applications in veterinary medicine [20-34].

* To whom correspondence should be addressed, e-mail: Saoudmetwally@hotmail.com.

[1]Chemistry Department, Assiut University, Egypt.
[2]Forensic Medicine Laboratories, Assiut, Egypt.
[3]Institute of Organic Chemistry, University of Zurich, Switzerland.

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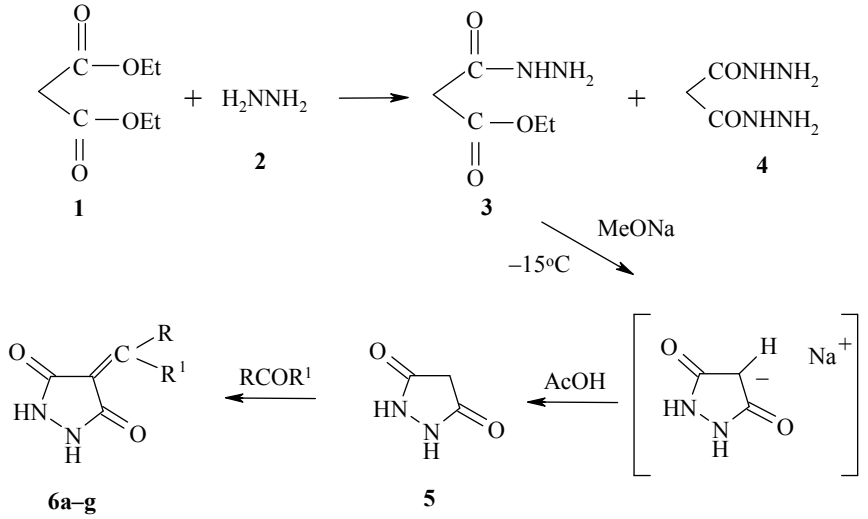
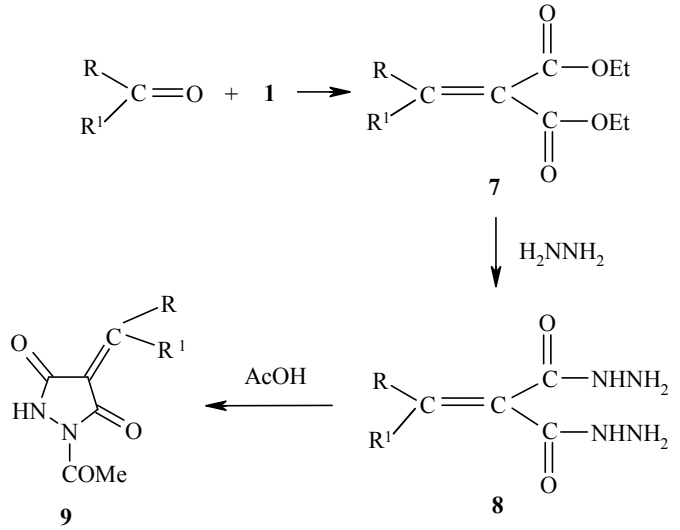
The aim of this work is the synthesis of 3,5-pyrazolidenedione derivatives **6** starting from the unsubstituted 3,5-pyrazolidinedione (**5**) or malonic acid hydrazide derivatives **8** and **15**. As an important starting material in this work, 3,5-pyrazolidinedione (**5**) was prepared according to [35] *via* cyclization of ethoxycarbonylacetohydrazide (**3**) [36] using sodium methoxide. Condensation of compound **5** with aliphatic or aromatic carbonyl derivatives gave the corresponding 4-alkylidene(arylidene)- or (aralkylidene)-3,5-pyrazolidinediones **6**.



1 **2** **3** **4** **5** **6a–g**

6 a R = R^1 = Me; **bf** R = H, **b** R^1 = *p*-BrC_6H_4, **c** R^1 = *p*-ClC_6H_4, **d** R^1 = *p*-OHC_6H_4,
e R^1 = *p*-$Me_2NC_6H_3$, **f** R^1 = *p*-MeC_6H_4, **g** R + R^1 = 4-(indoxyl-3-yl)

On the other hand, cyclization of alkylidene- or arylidenemalonic acid hydrazides **8** using glacial acetic acid yielded 1-acetyl-4-alkylidene(arylidene)-3,5-pyrazolidinediones **9**.



7 **8** **9**

9 a R = H, R^1 = *o*-$O_2NC_6H_4$; **b** R = R^1 = isopropylidine;
ch R = H, **c** R^1 = *p*-MeC_6H_4, **d** R^1 = *p*-$Me_2NC_6H_3$, **e** R^1 = *p*-ClC_6H_4,
f R^1 = *p*-$O_2NC_6H_4$, **g** R^1 = *m*-$O_2NC_6H_4$, **h** R^1 = *p*-HOC_6H_4

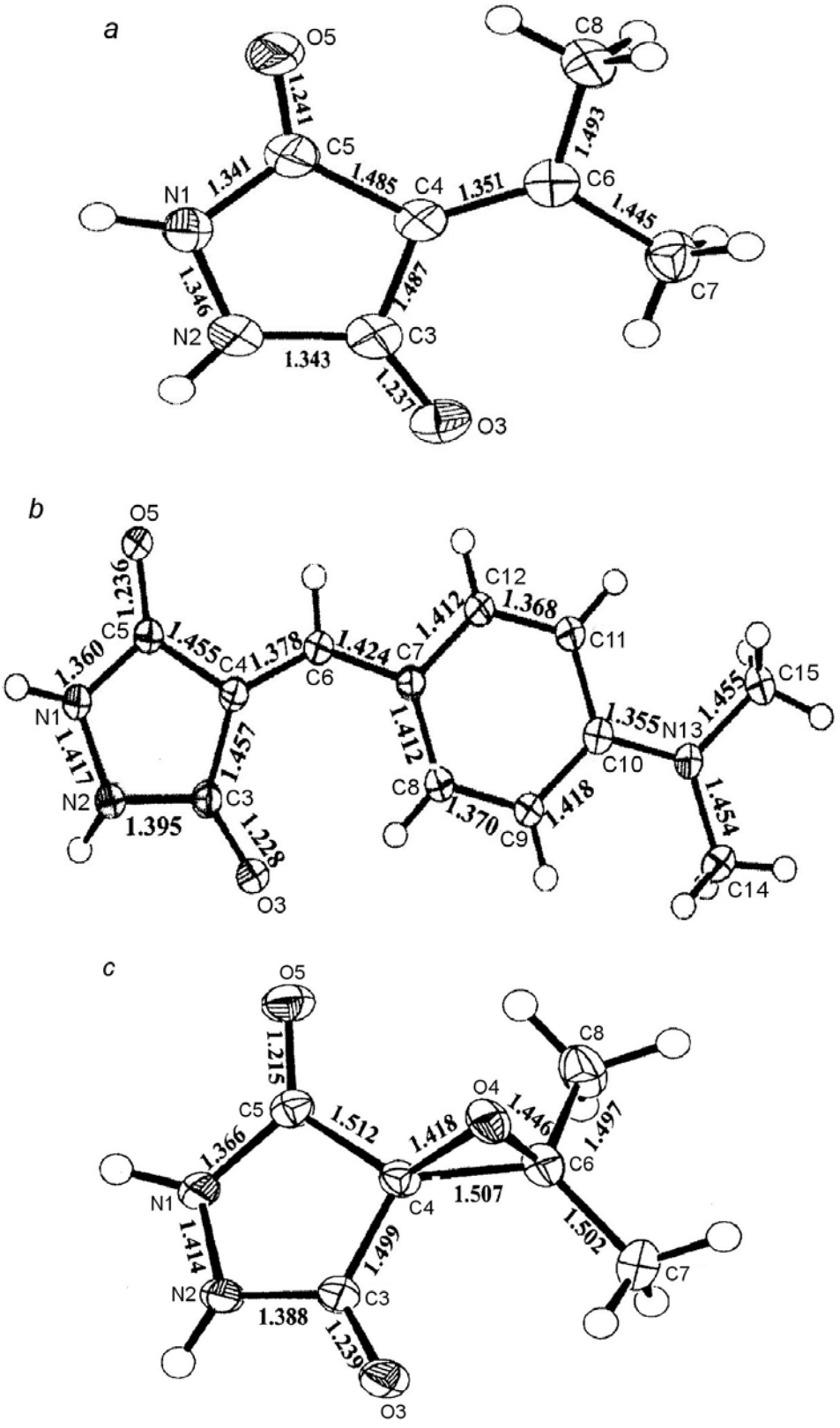
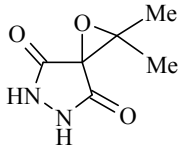


Fig. 1. The chemical structure of compounds **6a** (*a*), **6e** (*b*), and **10** (*c*)

The structure of 4-substituted 3,5-pyrazolidinediones **6** and 1-acetyl derivatives **9** [37] was determined using elemental analysis and spectroscopic methods.

Epoxidation of some 4-alkylidene or arylidene-3,5-pyrazolidinediones **6a,e** using alkaline hydrogen peroxide in ether [38] yielded the unreported oxirane derivatives **10** and **11**.



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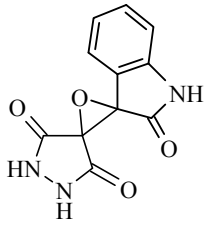

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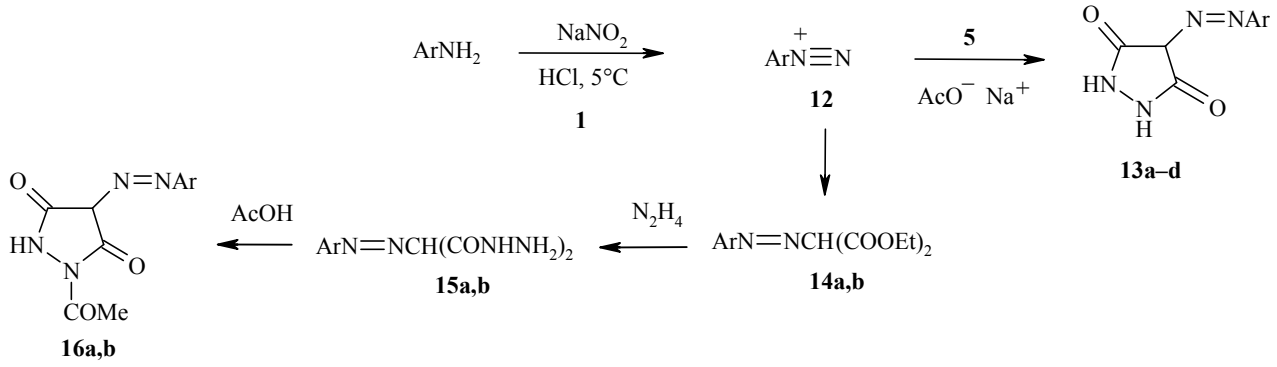
The chemical structure of compounds **6a,e** and **10** has been solved and refined successfully using X-ray crystallography (Fig. 1*a*–*c*). Both ring N-atoms showed a slight pyramidalization in compound **6a** and significant pyramidalization in compounds **6e** and **10** and particularly at N(2), rather than the usual planar arrangement common in amides. This is probably due to preferential delocalization of the C=O bonds with the C(4)=C(6) bond. The phenyl ring and C(10)−N(13) bonds showed a slight trend towards a quinoline type double bond localization, but the effect is very small. The X-ray structure of compound **6a** indicated that one amide group forms an intermolecular hydrogen bond with the O-atom of the same amide group of an adjacent molecule, thereby linking pairs of molecules into centrosymmetric dimers. The other amide group forms bifurcated intermolecular hydrogen bonds. The combination of these interactions creates a two-dimensional network. See Table 1 for full details.

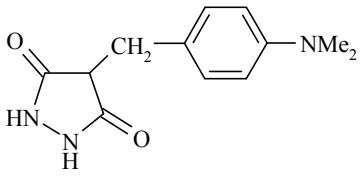
A series of 4-arylazo-3,5-pyrazolidinediones **13** was prepared either by coupling aryl diazonium salts **12** with compound **5** or cyclization of arylazomalonic acid hydrazide **15** using acetic acid to give 1-acetyl-4-arylazo-3,5-pyrazolidinedione derivatives **16**.



13 a Ar = Ph, **b** Ar = *p*-$MeOC_6H_4$; **13c**, **14a–16a** Ar = $O_2NC_6H_4$;
13d,**14b–16b** Ar = *o*-ClC_6H_4

The structure of 4-arylazo-3,5-pyrazolidinedione **13** or its 1-acetyl derivatives **16** was confirmed using elemental analysis and spectroscopic methods.

The exocyclic double bond at position 4 of compounds **6e** and **9f** was smoothly reduced to the corresponding single bond using sodium borohydride in methanol [39], yielding the corresponding 4-benzyl derivatives **17** and **18**, respectively.



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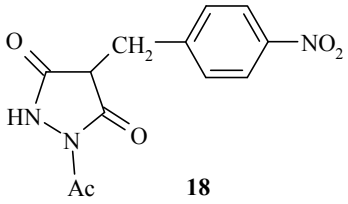

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TABLE 1. Crystallographic Data

	6a	**6e**	**10**
Crystallized from	MeOH	DMF/H_2O	MeOH
Empirical formula	$C_6H_8N_2O_2$	$C_{12}H_{13}N_3O_2$	$C_6H_8N_2O_3$
Formula weight, g·mol^{-1}	140.14	231.25	156.14
Crystal color, habit	Yellow, plate	Red, prism	Colorless, plate
Crystal dimensions, mm	0.07×0.20×0.25	0.12×0.20×0.20	0.07×0.22×0.25
Temperature, K	160(1)	160(1)	160(1)
Crystal system	Monoclinic	Triclinic	Orthorhombic
Space group	$P2_1/c$	$P\bar{1}$	*Pbca*
Z	4	2	8
Reflections for cell determination	1211	2923	2299
2θ range for cell determination, deg	4-50	4-60	4-60
Unit cell parameters			
a, Å	7.5852(3)	6.0986(4)	11.2797(3)
b, Å	6.8324(5)	7.9152(5)	8.5218(2)
c, Å	12.5924(7)	11.4088(6)	14.3066(3)
α, deg	90	100.815(4)	90
β, deg	104.773(4)	94.040(4)	90
γ, deg	90	102.145(3)	90
V, Å^3	631.03(6)	525.36(6)	1375.20(6)
F(000)	296	244	656
D_x, g·cm^{-3}	1.475	1.462	1.508
μ(MoKα), mm^{-1}	0.113	0.103	0.122
Scan type	ϕ and ω	ϕ and ω	ϕ and ω
$2\theta_{max}$, deg	50	60	60
Total reflections measured	9933	13 664	23 769
Symmetry-independent reflections	1111	3059	2002
R_{int}	0.063	0.047	0.056
Reflections with $I<2\sigma(I)$	932	2232	1613
Reflections used in refinement	1110	3059	2002
Parameters refined	101	164	111
$R(F)$ [$I<2\sigma(I)$ reflections]	0.0430	0.0549	0.0403
$wR(F^2)$ (all independent reflections)	0.1144	0.1547	0.1078
Weighting parameters [a;b]*	0.062; 0.164	0.0818; 0.1463	0.0505; 0.293
GOOF	1.067	1.028	1.064
Secondary extinction coefficient	—	—	0.015(3)
Final Δ_{max}/σ	0.001	0.001	0.001
Δρ (max, min), e Å^{-3}	0.16; -0.23	0.33; -0.33	0.29; -0.23

* $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, where $P = (F_o^2 + 2F_c^2)/3$.

EXPERIMENTAL

IR spectra were determined on a Shimadzu 480 IR spectrophotometer using the KBr pellet technique. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL LA 400 NMR spectrometer (400 and 100 MHz respectively),

solvent DMSO-d_6, internal standard TMS. The mass spectra were obtained on a JEOL route-600 H spectrometer using the direct inlet technique at 70 eV. All melting points were determined on an electric melting point apparatus (Gallenkamp) and are uncorrected. Elemental analyses were carried out by the microanalytical unit at Chemistry Department, Assiut University, using an Elementar Vario EI elemental analyzer.

Ethoxycarbonylacetohydrazide (**3**). The following is an improved preparation method [36]. Hydrazine hydrate (6.0 g, 0.187 mol) was added at room temperature to a solution of diethyl malonate (50 g, 0.312 mol) in ethanol (20 ml). The mixture was stored overnight, and malonohydrazide (**4**) (3.9 g) was separated by filtration, mp 151-153°C (154°C [40]). Evaporation of the filtrate left a partly crystalline residue, which was washed with ether to remove the unchanged ester. The solid ethoxycarbonylacetohydrazide was recrystallized twice from ethanol. Yield 7.5 g; mp 68-69°C (70°C [36]). The experiment was repeated twice with the recovered diethyl malonate; each time 0.3 mol of hydrazine hydrate was used. Total yield 15.5 g (34%) based on the original 50 g of diethyl malonate (8% [41]). IR spectrum, ν, cm^{-1}: 3300, 3040 (NH_2, NH), 1725, 1645 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.16 (3H, t, *J* = 7.1, CH_3); 3.13 (2H, s, CH_2); 4.05 (2H, q, *J* = 7.1, CH_2); 9.10 (1H, s, NH). ^{13}C NMR, δ, ppm: 14.05 (CH_3); 38.80 (CH_2); 164 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 146 $[M]^+$ (42), 115 (14), 101 (65), 100 (72), 87 (32), 69 (18), 60 (14), 59 (20), 58 (20), 32 (100). Found, %: C 41.18; H 6.84; N 19.21. $C_5H_{10}N_2O_3$. Calculated, %: C 41.09; H 6.90; N 19.17.

Malonohydrazide (4). Colorless flakes from ethanol. Yield 3.9 g (4.7%); mp 151-153°C (154°C [40]). IR spectrum, ν, cm^{-1}: 3295–3100 (NH_2, NH), 1640 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.41 (2H, s, CH_2); 9.06 (1H, s, NH); 10.32 (2H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 132 $[M]^+$ (35), 131 (25), 100 (84), 99 (74), 74 (18), 69 (58), 59 (72), 45 (17), 44 (94), 43 (88), 42 (70), 33 (68), 32 (100). Found, %: C 27.31; H 6.12; N 42.32. $C_3H_8N_4O_2$. Calculated, %: C 27.27; H 6.10; N 42.41.

3,5-Pyrazolidinedione (5). A solution of sodium methoxide (0.7 g sodium dissolved in 10 ml dry methanol) was added dropwise during 4-5 h to a cold solution of ethoxycarbonylacetohydrazide **3** (5 g dissolved in 35 ml dry methanol). The mixture was left in a refrigerator for 24 h, then filtered off, and the filtrate was cooled to -15°C and neutralized with glacial acetic acid (3.4 ml). The precipitated crystals were collected by filtration, washed with cold methanol, and dried. Colorless needles from methanol, 2.38 g, 70%; mp 290°C (decomp) (290°C [35]). IR spectrum, ν, cm^{-1}: 2995, 2720 (broad, NH, OH), 1655 (C=O). ^{1}H NMR spectrum, δ, ppm: 3.03 (2H, s, CH_2); 10.31 (2H, br. s, 2NH). ^{13}C NMR spectrum, δ, ppm: 40.05 (CH); 169.20 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 100 $[M]^+$ (100). Found, %: C 35.99; H 3.99; N 27.92. $C_3H_4N_2O_2$. Calculated, %: C 36.01; H 4.03; N 27.99.

Reaction of 3,5-Pyrazolidinedione (5) with Carbonyl Derivatives (General Method). A mixture of equimolar amounts of compound **5** and the selected carbonyl reagent (aldehyde or ketone) in pure methanol was refluxed for 30 min. After cooling, the precipitated product was collected and crystallized from the proper solvent and identified as a 4-alkylidene(arylidene)-3,5-pyrazolidinedione **6**.

4-Isopropylidene-3,5-pyrazolidinedione (6a). Yellow plates from methanol. Yield 76%; mp 238-239°C. IR spectrum, ν, cm^{-1}: 3290 (NH), 1650 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.41 (6H, s, CH_2); 7.82 (2H, br. s, 2NH). ^{13}C NMR spectrum, δ, ppm: 22.16 (CH_3), 23.19 (CH_3), 136.92 (C-6); 160.10 (C-4); 166.92 (C-3); 173.91 (C-5). Mass spectrum, *m/z* (I_{rel}, %): 140 $[M]^+$ (81), 125 (64), 123 (66), 109 (50), 97 (44), 83 (35), 82 (75), 72 (42), 67 (100). Found, %: C 51.36; H 5.81; N 19.87. $C_6H_8N_2O_2$. Calculated, %: C 51.42; H 5.75; N 19.99.

4-(4'-Bromobenzylidene)-3,5-pyrazolidenedione (6b). Dark-yellow flakes from ethanol. Yield 86%; mp 160°C. IR spectrum, ν, cm^{-1}: 3210 (NH), 1690 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.12-7.82 (4H, m, Ar); 8.61 (1H, s, =CH); 9.90 (2H, s, 2NH). ^{13}C NMR spectrum, δ, ppm: 115.1, 117.1, 119.3, 124.3, 172.2, 185.1. Mass spectrum, *m/z* (I_{rel}, %): 265 $[M]^+$ (58), 239 (42), 237 (38), 210 (90), 208 (100), 182 (32), 181 (36), 103 (55), 102 (52), 101 (28), 90 (31), 89 (63). Found, %: C 44.82; H 2.75; Br 29.63; N 10.43. $C_{10}H_7BrN_2O_2$. Calculated, %: C 44.97; H 2.64; Br 29.92; N 10.49.

4-(4'-Chlorobenzylidene)-3,5-pyrazolidinedione (6c). Colorless needles from ethanol. Yield 63%; mp 176-177°C. IR spectrum, ν, cm^{-1}: 3200 (NH); 1680 (C=O). ^{1}H NMR spectrum, δ, ppm: 7.53-8.20 (4H, m, Ar); 8.69 (1H, s, =CH); 11.83 (2H, br. s, 2NH). ^{13}C NMR spectrum, δ, ppm: 116, 118, 122.1, 126.3, 132.1, 136.2,

138.1, 162.1, 174.4. Mass spectrum, *m/z* (I_{rel}, %): 222 $[M]^+$ (93), 178 (14), 165 (100), 153 (60), 139 (66), 138 (80), 136 (80). Found, %: C 45.53; H 3.11; Cl 14.78; N 23.52. $C_9H_7ClN_4O_2$. Calculated, %: C 45.30; H 2.96; Cl 14.86; N 23.48.

4-(4'-Hydroxybenzylidene)-3,5-pyrazolidinedione (6d). Grayish needles from ethanol. Yield 80%; mp 260-261°C. IR spectrum, ν, cm^{-1}: 3100 (NH), 1650 (C=O). ^1H NMR spectrum, δ, ppm: 7.53–7.93 (4H, m, Ar); 8.69 (1H, s, =CH); 11.83 (2H, br. s, 2NH). ^{13}C NMR spectrum, δ, ppm: 116, 118, 119, 122.2, 126.1, 130.1, 132.2, 162.1, 174.3. Mass spectrum, *m/z* (I_{rel}, %): 204 $[M]^+$ (100), 203 (9), 146 (98), 136 (27.4), 120 (8), 119 (18), 118 (100). Found, %: C 58.66; H 4.11; N 13.69. $C_{10}H_8N_2O_3$. Calculated, %: C 58.82; H 3.95; N 13.72.

4-(4'-N,N-Dimethylaminobenzylidene)-3,5-pyrazolidinedione (6e). Red prisms from DMF–H_2O, 1:1. Yield 86%; mp 266-267°C. IR spectrum, ν, cm^{-1}: 3450 (OH or NH), 1690 (C=O). ^1H NMR spectrum, δ, ppm: 3.06 (6H, s, $2CH_3$); 6.74-8.10 (4H, m, Ar); 8.53 (1H, s, =CH); 9.22 (2H, br. s, 2NH). ^{13}C NMR spectrum, δ, ppm: 39.5 ($2CH_3$), 117.3, 119.2, 132.1, 140.3, 164.2, 171.2. Mass spectrum, *m/z* (I_{rel}, %): 231 $[M]^+$ (100), 230 (32), 202 (4), 163 (7.3), 147 (5.2), 146 (12), 145 (24), 173 (78). Found, %: C 62.46; H 5.73; N 18.24. $C_{12}H_{13}N_3O_2$. Calculated, %: C 62.33; H 5.67; N 18.17.

4-(4'-Methylbenzylidene)-3,5-pyrazolidinedione (6f). Colorless needles from ethanol. Yield 58%; mp 269-270°C. IR spectrum, ν, cm^{-1}: 3100 (NH), 1655 (C=O). ^1H NMR spectrum, δ, ppm: 2.52 (3H, s, CH_3); 7.41-7.65 (4H, m, Ar); 8.21 (1H, s, CH); 9.72 (2H, br. s, 2NH). ^{13}C NMR spectrum, δ, ppm: 40.0 (CH_3); 118.1, 121.1, 132.3, 135.0, 162.3, 174.2 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 202 $[M]^+$ (100), 187 (50), 174 (32), 146 (21), 113 (46). Found, %: C 65.42; H 5.02; N 13.76. $C_{11}H_{10}N_2O_2$. Calculated, %: C 65.34; H 4.98; N 13.85.

4-(Indoxyl-3-yl)-3,5-pyrazolidenedione (6g). Dark-grey needles from methanol. Yield 82%; mp 209-210°C. IR spectrum, ν, cm^{-1}: 3450, 3250 (OH, NH), 1680 (C=O). ^1H NMR spectrum, δ, ppm: multiplet, 7.35-7.62 (4H, m, Ar); 9.82 (2H, br. s, 3NH). ^{13}C NMR spectrum, δ, ppm: 118.1, 119.1, 121.3, 129.1, 142.2, 165.1, 172.1. Mass spectrum, *m/z* (I_{rel}, %): 229 $[M]^+$ (100). Found, %: C 57.72; H 3.21; N 18.45. $C_{11}H_7N_3O_3$. Calculated, %: C 57.65; H 3.08; N 18.33.

1-Acetyl-4-(2'-nitrobenzylidene)-3,5-pyrazolidinedione (9a). This derivative was prepared by fusion of equimolar amounts of *o*-nitrobenzaldehyde and compound **5** in the presence of a few drops of acetic anhydride for 5 min. The melt was cooled and triturated with ether. The solid was collected by filteration and crystallized from ethanol. Yield 86%; mp 181-182°C. IR spectrum, ν, cm^{-1}: 3200, 3100 (NH), 1640 (C=O). ^1H NMR spectrum, δ, ppm: 2.37 (3H, s, $COCH_3$), 7.92-8.31 (4H, m, Ar); 8.40 (1H, s, CH); 10.21 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 22.1 (CH_3); 123.4, 127.2, 176.1. Mass spectrum, *m/z* (I_{rel}, %): 233 $[M]^+$ (100), 203 (2), 149 (4), 148 (3), 147 (1). Found, %: C 52.85; H 3.42; N 15.32. $C_{12}H_9N_3O_5$. Calculated, %: C 52.37; H 3.30; N 15.27.

Synthesis of 1-Acetyl-4-alkylidene(arylidene)-3,5-pyrazolidenediones 9 from Malonohydrazide 4 and Carbonyl Derivatives 9 (General Method). A mixture of equimolar amounts of malonohydrazide **4** and the proper aldehyde or ketone dissolved in glacial acetic acid was refluxed for 30 min. The precipitated product on cooling was collected and crystallized from the proper solvent. All products were characterized as 1-acetyl-4-substituted 3,5-pyrazolidinediones **9** [37].

1-Acetyl-4-isopropylidene-3,5-pyrazolidinedione (9b). Yellow needles from methanol. Yield 75%; mp 252-253°C. IR spectrum, ν, cm^{-1}: 3200 (NH), 1710, 1680 (C=O). ^1H NMR spectrum, δ, ppm: 2.38 (6H, s, $2CH_3$); 2.52 (3H, s, $COCH_3$); 9.21 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 118.2, 165.2, 171.5. Mass spectrum, *m/z* (I_{rel}, %): 182 $[M]^+$ (42), 140 (100), 125 (40), 115 (7), 92 (11), 89 (14), 75 (13), 43 (99). Found, %: C 52.68; H 5.62; N 15.22. $C_8H_{10}N_2O_3$. Calculated, %: C 52.74; H 5.53; N 15.38.

1-Acetyl-4-(4'-methoxybenzylidene)-3,5-pyrazolidinedione (9c). Colorless needles from methanol. Yield 63%; mp 200-201°C. IR spectrum, ν, cm^{-1}: 3150 (NH), 1720, 1675 (C=O). ^1H NMR spectrum, δ, ppm: 2.45 (3H, s, $COCH_3$); 3.15 (3H, s, OCH_3); 7.41–7.63 (4H, m, Ar); 8.33 (1H, s, =CH); 9.50 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 24.1 (CH_3); 43.0 ($CO\underline{C}H_3$); 116.1, 118.3, 122.2, 126.1, 162.3, 174.4 (C=O). Mass spectrum, *m/z* (I_{rel}, %): 260 $[M]^+$ (100), 229 (45), 218 (31), 155 (21). Found, %: C 60.21; H 4.83; N 14.75. $C_{13}H_{12}N_2O_4$. Calculated, %: C 60; H 4.65; N 10.76.

1-Acetyl-4-(4'-N,N-dimethylaminobenzylidene)-3,5-pyrazolidinedione (9d). Red needles from DMF–H_2O, 1:1. Yield 63%; mp 266–267°C. IR spectrum, ν, cm^{-1}: 3190 (NH), 1715, 1670 (C=O). ^1H NMR spectrum, δ, ppm: 2.51 (3H, s, $COCH_3$); 3.15 (6H, s, NCH_3); 7.12 (4H, m, Ar); 7.75 (1H, s, =CH); 8.51 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 39.1, 42.0, 121.2, 122.3, 125.1, 172.0. Mass spectrum, *m/z* (I_{rel}, %): 273 $[M]^+$ (22), 258 (15), 231 (100), 229 (63), 155 (18). Found, %: C 61.72; H 5.72; N 15.42. $C_{14}H_{15}N_3O_3$. Calculated, %: C 61.53; H 5.53; N 15.38.

1-Acetyl-4-(4'-chlorobenzylidene)-3,5-pyrazolidinedione (9e). Colorless needles from methanol. Yield 61%; mp 160-161°C. IR spectrum, ν, cm^{-1}: 3120 (NH), 1710, 1680 (C=O). ^1H NMR spectrum, δ, ppm: 2.52 (3H, s, $COCH_3$); 7.31-7.52 (4H, m, Ar); 8.42 (1H, s, =CH); 9.42 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 21.1, 116.3, 123.1, 124.2, 162.1, 172.0. Mass spectrum, *m/z* (I_{rel}, %): 264 $[M]^+$ (100), 231 (24), 222 (52), 153 (14). Found, %: C 54.62; H 3.52; Cl 13.32; N 10.66. $C_{12}H_9ClN_2O_2$. Calculated, %: C 54.46; H 3.43; Cl 13.40; N 10.58.

1-Acetyl-4-(4'-nitrobenzylidene)-3,5-pyrazolidinedione (9f). Pale-yellow needles from methanol. Yield 62%; mp 210-211°C. IR spectrum, ν, cm^{-1}: 3210 (NH), 1705, 1670 (C=O), 1550 (NO_2). ^1H NMR spectrum, δ, ppm: 2.51 (3H, s, $COCH_3$); 7.42–7.81 (4H, m, Ar); 8.32 (1H, s, =CH); 9.22 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 21.2, 114.1, 115.2, 116.1, 123.1, 165.4, 172.3. Mass spectrum, *m/z* (I_{rel}, %): 275 $[M]^+$ (100), 259 (15), 233 (72), 229 (13). Found, %: C 52.44; H 3.25; N 15.18. $C_{12}H_9N_3O_5$. Calculated, %: C 52.37; H 3.30; N 15.27.

1-Acetyl-4-(3'-nitrobenzylidene)-3,5-pyrazolidinedione (9g). Brown needles from ethanol. Yield 68%; mp 206-207°C. IR spectrum, ν, cm^{-1}: 3120 (NH), 1710, 1680 (C=O), 1555 (NO_2). ^1H NMR spectrum, δ, ppm: 2.52 (3H, s, $COCH_3$); 7.32-7.61 (4H, m, Ar); 7.91 (1H, s, =CH); 9.15 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 22.3, 120.1, 126.2, 132.1, 165.1, 175.4. Found, %: C 52.47; H 3.44; N 15.33. $C_{12}H_9N_3O_5$. Calculated, %: C 52.37; H 3.30; N 15.27.

1-Acetyl-4-(4'-hydroxybenzylidene)-3,5-pyrazolidinedione (9h). Grayish needles from ethanol. Yield 86%; mp 250-251°C. IR spectrum, ν, cm^{-1}: 3600 (OH), 3250 (NH), 1705, 1660 (C=O). ^1H NMR spectrum, δ, ppm: 2.41 (3H, s, $COCH_3$); 6.92-7.77 (4H, m, Ar); 8.72 (1H, s, =CH); 10.63 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 25.1, 119.3, 124.0, 169.3, 170.2, 172.1. Mass spectrum, *m/z* (I_{rel}, %): 246 $[M]^+$ (100).

Epoxidation of 4-alkylidene(arylidene)-3,5-pyrazolidinedione (6) (General Method). A suspension of the compound **5** derivative (0.01 mol) in hydrogen peroxide (30 volume, 5 ml) and ether (10 ml) was stirred until the color disappeared. The solid was filtered, washed with cold methanol, and crystallized from the proper solvent.

2,2-Dimethyl-1-oxa-5,6-diazaspiro[2,4]heptane-4,7-dione (10). Colorless plates from methanol. Yield 54%; mp 207-208°C. IR spectrum, ν, cm^{-1}: 3199 (NH), 1680 (C=O). ^1H NMR spectrum, δ, ppm: 1.51 (6H, s, CH_3); 13.25 (2H, s, 2NH). ^{13}C NMR spectrum, δ, ppm: 18.1, 68.5, 58.6, 166.2. Mass spectrum, *m/z* (I_{rel}, %): 156 $[M]^+$ (30), 116 (75), 70 (11), 69 (25), 59 (16), 58 (13), 45 (100), 44 (34), 43 (82), 42 (43), 41 (58). Found, %: C 46.22; H 5.22; N 18.1. $C_6H_8N_2O_3$. Calculated, %: C 46.15; H 5.16; N 17.94.

2,3-Dihydro-1H-dispiro[indole-3,2'-oxirane-3',4''-pyrazolidine]-2,3'',5''-trione (11). Yellow needles from ethanol. Yield 56%; mp 268-270°C. IR spectrum, ν, cm^{-1}: 3450 (OH), 3250 (NH), 1690 (C=O). ^1H NMR spectrum, δ, ppm: 6.93-7.57 (4H, m, Ar); 10.22 (2H, s, 2NH). ^{13}C NMR spectrum, δ, ppm: 65.9, 90.3, 120.3, 124.3, 125.6, 128.2, 129.6, 137.7, 172.7, 174.8. Mass spectrum, *m/z* (I_{rel}, %): 245 $[M]^+$ (100). Found, %: C 53.72; H 2.72; N 17.26. $C_{11}H_7N_3O_4$. Calculated, %: C 53.88; H 2.88; N 17.14.

Synthesis of 4-Arylazo-3,5-pyrazolidinediones 13 (General Method). The primary aromatic amine derivative (0.01 mol) was diazotized by dissolving in hydrochloric acid (2.5 mol) and the resulting solution was cooled in an ice-salt bath to -5°C, then the equivalent amount of sodium nitrite (0.01 mol) dissolved in water (5 ml) was added. The resulting diazonium salt was coupled with compound **5** (0.01 mol) dissolved in methanol (10 ml) and the mixture was neutralized with sodium acetate. The precipitated azo dye was filtered off, washed thoroughly with water, dried, and crystallized from the proper solvent.

4-Phenylazo-3,5-pyrazolidinedione (13a). Red needles from methanol. Yield 70%; mp 278-279°C. IR spectrum, ν, cm^{-1}: 3290, 3215 (NH), 1655 (C=O). ^1H NMR spectrum, δ, ppm: 3.52 (1H, s, CH); 7.44 (5H, m, Ar); 7.97 (2H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 80.6, 122.3, 125.0, 129.1, 170.3. Mass spectrum, *m/z* (I_{rel}, %): 204 $[M]^+$ (100), 197 (2), 194 (1.5), 176 (2), 169 (3), 145 (5.3), 127 (37), 107 (4), 105 (9), 93 (34), 92 (35), 78 (11), 77 (67), 64 (18), 65 (46.6). Found, %: C 53.12; H 4.21; N 27.36. $C_9H_8N_4O_2$. Calculated, %: C 52.94; H 3.95; N 27.44.

4-(4'-Methoxyphenylazo)-3,5-pyrazolidinedione (13b). Dark-red needles from methanol. Yield 43%; mp 230-231°C. IR spectrum, ν, cm^{-1}: 3450 (OH), 3350 (NH), 1640 (C=O). ^1H NMR spectrum, δ, ppm: 3.42 (1H, s, CH); 3.73 (3H, s, CH_3O); 6.91 (4H, m, Ar); 9.85 (2H, br. s, 2NH). ^{13}C NMR spectrum, δ, ppm: 56.0, 80.6, 114.6, 123.3, 143.2, 159.4, 170.3. Mass spectrum, *m/z* (I_{rel}, %): 234 $[M]^+$ (75), 197 (2), 175 (3), 149 (2), 147 (3), 123 (21), 122 (100), 121 (14), 108 (14), 107 (9), 95 (13), 60 (44), 45 (68), 43 (79). Found, %: C 51.36; H 4.25; N 22.82. $C_{10}H_{10}N_4O_3$. Calculated, %: C 51.28; H 4.30; N 23.92.

4-(2'-Nitrophenylazo)-3,5-pyrazolidinedione (13c). Red needles from methanol. Yield 80%; mp 309-310°C. IR spectrum, ν, cm^{-1}: 3400 (OH), 3250 (NH), 1665 (C=O), 1550 (NO_2). ^1H NMR spectrum, δ, ppm: 3.41 (1H, s, CH); 6.60 (4H, m, Ar); 9.23 (2H, s, NH). ^{13}C NMR spectrum, δ, ppm: 80.6, 115.9, 120.1, 123.3, 123.7, 143.8, 170.3. Mass spectrum, *m/z* (I_{rel}, %): 249 $[M]^+$ (20), 248 (100), 163 (21), 150 (5), 138 (39), 136 (10), 127 (71), 122 (16), 90 (12), 43 (37). Found, %: C 43.42; H 2.95; N 28.23. $C_9H_7N_5O_4$. Calculated, %: C 43.38; H 2.83; N 28.11.

4-(2'-Chlorophenylazo)-3,5-pyrazolidinedione (13d). Dark-red needles from methanol. Yield 84%; mp 280-281°C. IR spectrum, ν, cm^{-1}: 3100 (NH), 1665 (C=O). ^1H NMR spectrum, δ, ppm: 3.41 (1H, s, CH); 7.22 (4H, m, Ar); 9.62 (2H, s, 2NH). ^{13}C NMR spectrum, δ, ppm: 82.4, 115.1, 122.3, 124.1, 125.1, 144.3, 170.4. Mass spectrum, *m/z* (I_{rel}, %): 238 $[M]^+$ (100). Found, %: 45.41; H 3.15; Cl 14.75; N 23.53. $C_9H_7ClN_4O_2$. Calculated, %: C 45.30; H 2.96; Cl 14.86; N 23.48.

Synthesis of Diethyl Arylazomalonate 14 (General Method). The aryl diazonium salts were prepared by diazotization of the corresponding primary aromatic amines using sodium nitrite and hydrochloric acid. It was coupled with the equivalent amount of diethyl malonate and the mixture was neutralized using sodium acetate to give the required azo derivative. The dye was filtered off, washed with water, and dried.

Diethyl 2-Nitrophenylazomalonate (14a). Pale-yellow needles from ethanol. Yield 75%; mp 79-80°C. IR spectrum, ν, cm^{-1}: 1715 (C=O), 1525 (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (6H, t, J = 6.7, $2CH_3$); 3.32 (1H, s, CH); 4.21 (4H, q, J = 6.7, $2CH_2$); 7.51 (4H, m, Ar). ^{13}C NMR spectrum, δ, ppm: 22.1, 38.3, 54.0, 119.4, 123.2, 128.1, 171.4. Mass spectrum, *m/z* (I_{rel}, %): 309 $[M]^+$ (100). Found, %: C 50.52; H 4.72; N 13.65. $C_{13}H_{15}N_3O_6$. Calculated, %: C 50.49; H 4.89; N 13.59.

Diethyl 2-Chlorophenylazomalonate (14b). Yellow needles from ethanol. Yield 73%; mp 60-61°C. IR spectrum, ν, cm^{-1}: 1710 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (6H, t, J = 6.4, $2CH_3$); 3.32 (1H, s, CH); 4.25 (4H, q, J = 6.4, $2CH_2$); 7.62 (4H, m, Ar). ^{13}C NMR spectrum, δ, ppm: 21.3, 38.1, 53.1, 122.0, 124.4, 130.2, 169.3. Mass spectrum, *m/z* (I_{rel}, %): 298 $[M]^+$ (43), 297 (69), 254 (11), 225 (35), 223 (79), 153 (18), 128 (21), 127 (61), 126 (60), 125 (100), 113 (15), 111 (38), 99 (56). Found, %: C 52.41; H 5.12; Cl 11.83; N 9.35. $C_{13}H_{15}ClN_2O_4$. Calculated, %: C 52.27; H 5.06; Cl 11.87; N 9.38.

Synthesis of Arylazomalonic Acid Hydrazides (15) (General Method). The arylazo diethyl malonate (0.01 mol) was dissolved in absolute ethanol (20 ml), the solution was treated with hydrazine hydrate (0.03 mol), and the mixture was stirred for 2 h. The precipitated product was filtered off, washed with water, and dried. It was crystallized from the proper solvent.

2-Nitrophenylazomalonic Acid Hydrazide (15a). Pale-yellow needles from methanol. Yield 98%; mp 258-259°C. IR spectrum, ν, cm^{-1}: 3450, 3200 (NH_2, NH), 1650 (C=O). ^1H NMR spectrum, δ, ppm: 2.51 (1H, s, CH); 7.93 (4H, m, Ar); 9.81 (4H, s, $2NH_2$); 13.76 (2H, br. s, 2NH). ^{13}C NMR spectrum, δ, ppm: 38.2, 122.1, 124.3, 136.1, 172.1. Mass spectrum, *m/z* (I_{rel}, %): 281 $[M]^+$ (100). Found, %: C 38.51; H 4.01; N 34.77. $C_9H_{11}N_7O_4$. Calculated, %: C 38.44; H 3.94; N 34.86.

2-Chlorophenylazomalonic Acid Hydrazide (15b). Yellow needles from methanol. Yield 98%; mp 221-222°C. IR spectrum, ν, cm^{-1}: 3300, 3200 (NH_2, NH), 1660 (C=O). ^1H NMR spectrum, δ, ppm: 3.12 (1H, s, CH); 6.91-7.35 (4H, m, Ar); 9.43 (4H, s, $2NH_2$); 10.62 (2H, s, NH). ^{13}C NMR spectrum, δ, ppm: 39.2, 118.1, 123.0, 130.2, 175.2. Mass spectrum, *m/z* (I_{rel}, %): 270 $[M]^+$ (74), 238 (40), 152 (9), 139 (18), 129 (17), 128 (27), 127 (58), 126 (64), 125 (13), 111 (35), 40 (13), 32 (100). Found, %: C 40.12; H 4.15; Cl 13.22; N 31.16. $C_9H_{11}ClN_6O_2$. Calculated, %: C 39.94; H 4.10; Cl 13.10; N 31.05.

Synthesis of 1-Acetyl-4-arylazo-3,5-pyrazolidinediones 16 (General Method). Arylazo malonic acid hydrazide **15** (0.1 mol) was refluxed in glacial acetic acid for 2 h. The reaction mixture was poured on ice-water and the resulting product was filtered off, washed with water, and dried. The pyrazolidenedione derivative was crystallized from the proper solvent and the results are summarized as follows:

1-Acetyl-4-(2'-nitrophenylazo)-3,5-pyrazolidinedione (16a). Yellow needles from methanol. Yield 75%; mp 309-310°C. IR spectrum, ν, cm^{-1}: 1690 (C=O), 1550 (NO_2). ^1H NMR spectrum, δ, ppm: 2.52 (3H, s, $COCH_3$); 3.12 (1H, s, CH); 7.54-8.22 (4H, m, Ar); 9.42 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 22.1, 112.0, 114.3, 118.2, 122.1, 162.4, 170.1. Mass spectrum, *m/z* (I_{rel}, %): 291 $[M]^+$ (2), 249 (100), 190 (5), 189 (6), 173 (20), 163 (13), 138 (21), 127 (47), 122 (11). Found, %: C 45.42; H 3.12; N 14.14. $C_{11}H_9N_5O_5$. Calculated, %: C 45.37; H 3.11; N 14.05.

1-Acetyl-4-(2'-chlorophenylazo)-3,5-pyrazolidinedione (16b). Yellow needles from methanol. Yield 75%; 280-281°C. IR spectrum, ν, cm^{-1}: 3200 (NH), 1690 (C=O). ^1H NMR spectrum, δ, ppm: 2.51 (3H, s, $COCH_3$); 3.21 (1H, s, CH); 7.22-7.80 (4H, m, Ar); 9.32 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 22.0, 39.2, 118.2, 122.4, 126.1, 164.2, 175.4. Mass spectrum, *m/z* (I_{rel}, %): 238 $[M]^+$ (90), 237 (12), 202 (29), 153 (13), 151 (38), 139 (12), 128 (26), 127 (100), 126 (65), 125 (32), 111 (39), 101 (18), 99 (50), 69 (23). Found, %: C 47.22; H 3.35; Cl 12.58; N 20.14. $C_{11}H_9ClN_4O_3$. Calculated, %: C 47.07; H 3.23; Cl 12.63; N 19.96.

Reduction of 4-Arylidene-3,5-pyrazolidinediones. Synthesis of 4-Benzyl-3,5-pyrazolidinediones (General Method). A suspension of the 3,5-pyrazolidenedione derivative **6** (0.01 mol) in methanol (10 ml) was refluxed with an aqueous solution of sodium borohydride (0.02 mol in 10 ml water) for 2 h. The reaction mixture was cooled to room temperature and neutralized with diluted hydrochloric acid. The precipitated solid was collected, washed thoroughly with water, and dried. It was crystallized from the proper solvent.

4-(4'-N,N-Dimethylaminobenzyl)-3,5-pyrazolidinedione (17). Grayish needles from dioxane. Yield 30%; mp 220-221°C. IR spectrum, ν, cm^{-1}: 3410 (broad, OH, NH), 1655 (C=O). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.85 (6H, s, $2CH_3$); 2.91 (2H, d, $J = 6.3$, CH_2); 3.21 (1H, t, $J = 6.3$, CH); 6.72–7.53 (4H, m, Ar); 7.62 (2H, br. s, 2NH). ^{13}C NMR spectrum, δ, ppm: 28.7, 43.6, 66.1, 113.3, 128.8, 129.7, 141.7, 172.1. Mass spectrum, *m/z* (I_{rel}, %): 233 $[M]^+$ (100). Found, %: C 61.78; H 6.51; N 18.14. $C_{12}H_{15}N_3O_2$. Calculated, %: C 61.79; H 6.48; N 18.01.

1-Acetyl-4-(4'-nitrobenzyl)-3,5-pyrazolidinedione (18). Pale-brown needles from dioxane. Yield 31%; mp 238-239°C. IR spectrum, ν, cm^{-1}: 3200 (NH), 1680 (C=O), 1520 (NO_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 2.41 (3H, s, CH_3); 3.07 (2H, d, $J = 6.4$, CH_2); 3.76 (1H, t, $J = 6.4$, CH); 7.62–8.33 (4H, m, Ar); 8.91 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 21.1, 43.3, 58.2, 116.1, 122.0, 124.3, 126.1, 175.2. Found, %: C 52.12; H 3.92; N 15.23. $C_{12}H_{11}N_3O_5$. Calculated, %: C 51.99; H 4.00; N 15.16.

X-ray Analysis. X-ray crystal-structure determinations for compounds **6a,e** and **10** (Table 1 and Fig. 1*a*,*c*). All measurements were conducted on a Nonius KappaCCD area detector diffractometer [41] using graphite-monochromated MoKα radiation (λ 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. Data reduction was performed with HKLDENZO and SCALEPACK [42]. The intensities were corrected for Lorentz and polarization effects, but not for absorption, and equivalent reflections were merged. Each structure was solved by direct methods using either SHELXL97 [43] or SIR92 [44], which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms of each structure were refined anisotropically. The amide H-atoms were placed in the positions indicated by a difference electron density map and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in

geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom (1.5 U_{eq} for methyl groups). The structures were refined on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2–F_c^2)^2$. A correction for secondary extinction was applied in the case of compound **6e**. For compound **10** one low-angle reflection were omitted from the final refinement because the observed intensities of this reflection was much lower than the calculated value as a result of being partially obscured by the beam slope. Neutral atom scattering factors for non-hydrogen atoms were taken from [45], and the scattering factors for H-atoms were taken from [46]. The values of the mass attenuation coefficients were those of [47]. All calculations were performed using SHELXL97 [43]. The crystallographic diagrams were drawn using ORTEPII [48]. CCDC-750291-750293, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge crystallographic data centre *via* www.ccdc.cam.ac.uk/data-request/cif.

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