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NOVEL SYNTHESIS OF SOME ISATIN HYDRAZONES AND PYRIDAZINOPHTHALAZINES

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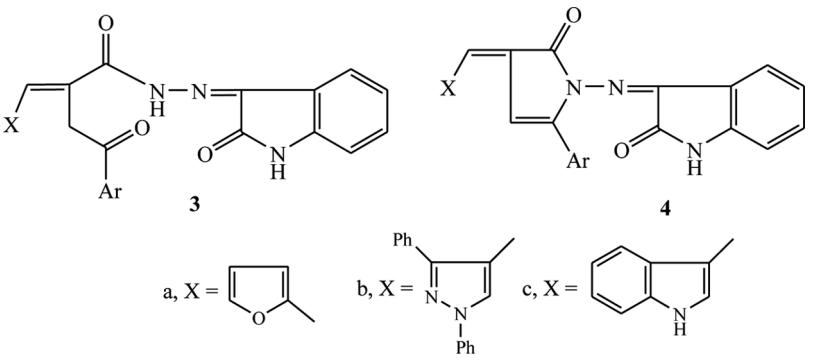
GRAPHICAL ABSTRACT



Abstract *The acid hydrazides bearing furyl, pyrazolyl, and indolyl rings* ***2*** *condense with isatin to give the corresponding hydrazones* ***3****. Ring closure of the latter in an HCl/AcOH mixture led to the construction of a new pyrrolinone ring* ***4****. The hydrazides* ***2*** *condensed also with phthalic anhydride to give the corresponding pyridazinophthalazines* ***5****.*

Keywords 2(3*H*)Furanones; isatinhydrazones; pyridazinophthalazines

INTRODUCTION

Nitrogen-containing heterocyclic compounds are widespread in nature, and their applications as biologically active pharmaceuticals and agrochemicals are becoming more important.[1] The development of new efficient methods to synthesize N-heterocycles with structural diversity is one major interest of modern synthetic organic chemists.[2] Among a large variety of nitrogen-containing heterocyclic compounds, heterocycles containing bridgehead azino group have received considerable attention because of their pharmacological properties and clinical applications.[3]

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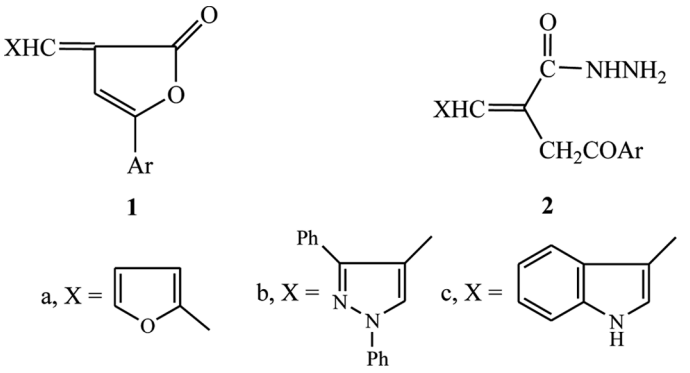


Scheme 1. (i) Ar = C_6H_5–; (ii) Ar = C_6H_4Cl(4-); and (iii) Ar = $C_6H_4OCH_3$(4-).

2(3*H*)-Furanones **1** are considered versatile starting materials for the construction of many heterocyclic systems of synthetic and biological importance.[4] Our research group was interested in the conversion of these furanones into pyrrolone,[5] pyrazole,[6] pyridazinone,[7,8] oxadiazole,[9] and triazole[10,11] derivatives. The key step in these conversions is the formation of the acid hydrazides **2**. These hydrazides are formed by the action of hydrazine hydrate on the furanones **1**, a reaction which occurs smoothly and mostly at room temperature (cf. Scheme 1).

Schiff and Mannich bases of isatin were reported to have a broad spectrum of biological activities such as antibacterial,[12,13] antifungal,[14,15] anti-HIV,[16] antiprotozoal,[17] and antihelminthic[18] activities.

Hydralazine (1-hydrazinophthalazine) was introduced in the early 1950s as an antihypertensive agent. Recently, several phthalazine derivatives have been reported to act as modulators of angiogenesis and therefore emerged as powerful clinical tools in oncology and ophthalmology.[19]

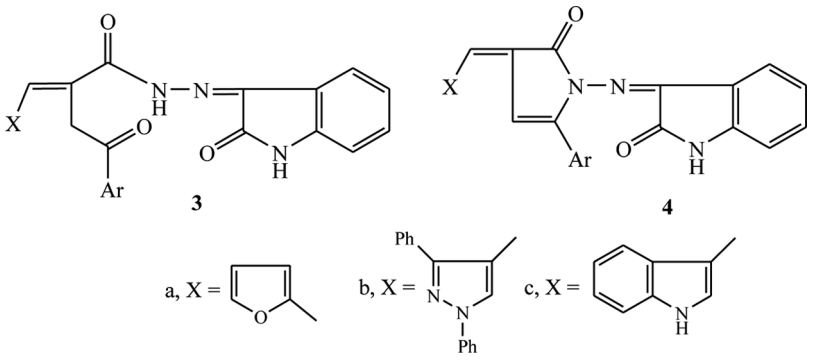
These diverse biological activities sparked our interest in utilizing the hydrazides **2** for the synthesis of some isatin hydrazone and pyridazinophthalazine derivatives.

RESULTS AND DISCUSSION

The hydrazides **2a** and **b** were previously prepared by ring opening of the furanones **1a** and **b** with hydrazine hydrate.[5,8] Using the same procedure, the hydrazides bearing the indolyl moiety **2c** were prepared and characterized.

The infrared (IR) spectra of these products showed the characteristic absorption bands for the amide $\nu_{C=O}$ at 1655 cm^{-1}, normal ketonic $\nu_{C=O}$ at 1685 cm^{-1}, and ν_{NH} at 3340 cm^{-1}. The ^1H NMR spectra of these products showed characteristic signals for the different protons (cf. Experimental). When the hydrazides **2** were refluxed with isatin in ethanol containing a few drops of acetic acid, the hydrazone derivatives **3** were obtained as the only isolable products.

Ring closure of the hydrazone derivatives in HCl/AcOH mixture led to the construction of a new pyrrolinone ring linked to the indolinone nucleus with the formation of **4** (cf. Scheme 2).



Scheme 2. (i) Ar = C_6H_5–; (ii) Ar = C_6H_4Cl(4-); and (iii) Ar = $C_6H_4OCH_3$(4-).

The same products **4** were also obtained by fusion of the hydrazides **2** in neat with isatin (cf. Experimental). The structures of the products **3** and **4** were confirmed by their analytical as well as spectral data (cf. Tables 1 and 2).

Condensation of the hydrazides **2** with phthalic anhydride in ethanol containing a few drops of acetic acid led to the formation of the corresponding pyridazinophthalazine derivatives, namely 2-heteryl methylene-4-arylpyridazino [1,2-b]phthalazine-1,6,11(2*H*)-triones **5** (cf. Scheme 3).

The structures of these derivatives were confirmed by their chemical analyses as well as their spectral properties (cf. Tables 1 and 2).

EXPERIMENTAL

Melting points were measured on an electrothermal melting-point apparatus. Elemental analyses were carried out at the Micro-Analytical Unit, Cairo University, Giza. IR spectra were measured on a Unicam SP-1200 spectrophotometer using the KBr wafer technique. ^{1}H NMR spectra were measured in dimethylsulfoxide (DMSO-d_6) on a Varian Plus instrument (300 MHz).

5-Aryl-3-heteryl Methylene-2(3*H*)-furanones (1)

These compounds were prepared according to the procedure described by a previous investigator.[20]

General Method for the Reaction of the 2(3*H*)-Furanones with Hydrazine Hydrates

Hydrazine hydrate (1.1 mmol) was added to a solution of the furanones (**1**) (1 mmol) in ethanol (20 ml). The reaction mixture was left at room temperature with occasional shaking. The product obtained was filtered off, washed with ethanol, and found to be the acid hydrazide (**2**).

Table 1. Spectral data of compounds **3–5**

Compound	IR (ν_{max}) KBr (cm^{-1}) $\nu_{N\text{-}H}$	IR (ν_{max}) KBr (cm^{-1}) $\nu_{C=O}$	^{1}H NMR (DMSO-d_6)
3a$_{(i)}$	3237	1719 1645	δ = 3.36 (s, 2H, CH_2-CO), 6.63–8.01 (m, 12H, Ar-H), 8.34 (s, 1H, =CH), 10.72 (s, 1H, NH-CO, exchangeable), 12.06 (s, 1H, NH-CO, exchangeable)
3a$_{(ii)}$	3335 3141	1722 1660	δ = 3.37 (s, 2H, CH_2-CO), 6.79–8.11 (m, 11H, Ar-H), 8.32 (s, 1H, =CH), 10.90 (s, 1H, NH-CO, exchangeable), 12.01 (s, 1H, NH-CO, exchangeable)
3a$_{(iii)}$	3222	1715 1663	δ = 3.27 (s, 2H, CH_2-CO), 3.92 (s, 3H, OCH_3), 6.93–7.93 (m, 11H, Ar-H), 8.55 (s, 1H, =CH), 10.95 (s, 1H, NH-CO, exchangeable), 12.27 (s, 1H, NH-CO, exchangeable)
3b$_{(i)}$	3318 3132	1728 1673	δ = 3.28 (s, 2H, CH_2-CO), 6.58–8.07 (m, 20H, Ar-H), 8.37 (s, 1H, =CH), 9.31 (s, 1H, NH-CO, exchangeable), 11.01 (s, 1H, NH-CO, exchangeable)
3b$_{(ii)}$	3206	1729 1717 1673	δ = 3.32 (s, 2H, CH_2-CO), 6.72–8.13 (m, 19H, Ar-H), 8.29 (s, 1H, =CH), 9.85 (s, 1H, NH-CO, exchangeable), 11.69 (s, 1H, NH-CO, exchangeable)
3b$_{(iii)}$	3250	1712 1667	δ = 3.22 (s, 2H, CH_2-CO), 3.75 (s, 3H, OCH_3), 6.73–8.09 (m, 19H, Ar-H), 8.37 (s, 1H, =CH), 9.57 (s, 1H, NH-CO, exchangeable), 12.02 (s, 1H, NH-CO, exchangeable)
3c$_{(i)}$	3356 3254	1710 1685	δ = 3.91 (s, 2H, CH_2-CO), 6.23–7.84 (m, 15H, Ar-H + NH), 8.23 (s, 1H, =CH), 10.65 (s, 1H, NH-CO, exchangeable), 13.25 (s, 1H, NH-CO, exchangeable)
3c$_{(ii)}$	3320 3200	1715 1680	δ = 3.79 (s, 2H, CH_2-CO), 6.51–7.87 (m, 14H, Ar-H + NH), 8.07 (s, 1H, =CH), 10.30 (s, 1H, NH-CO, exchangeable), 12.83 (s, 1H, NH-CO, exchangeable)
3c$_{(iii)}$	3300 3234	1722 1686	δ = 3.72 (s, 2H, CH_2-CO), 3.95 (s, 3H, OCH_3), 6.90–7.76 (m, 14H, Ar-H + NH), 8.03 (s, 1H, =CH), 10.97 (s, 1H, NH-CO, exchangeable), 13.01 (s, 1H, NH-CO, exchangeable)
4a$_{(i)}$	3236	1650 1647	δ = 6.83–7.38 (m, 13H, Ar-H), 8.10 (s, 1H, =CH), 10.65 (s, 1H, NH-CO, exchangeable)
4a$_{(ii)}$	3235	1658 1650	δ = 6.71–7.81 (m, 12H, Ar-H), 8.22 (s, 1H, =CH), 10.39 (s, 1H, NH-CO, exchangeable)
4a$_{(iii)}$	3220	1656 1650	δ = 3.79 (s, 3H, OCH_3), 6.92–8.01 (m, 12H, Ar-H), 8.17 (s, 1H, =CH), 10.32 (s, 1H, NH-CO, exchangeable)
4b$_{(i)}$	3300	1650	δ = 6.61–7.98 (m, 21H, Ar-H), 8.21 (s, 1H, =CH), 10.20 (s, 1H, NH-CO, exchangeable)
4b$_{(ii)}$	3210	1658	δ = 6.97–7.92 (m, 20H, Ar-H), 8.12 (s, 1H, =CH), 11.03 (s, 1H, NH-CO, exchangeable)
4b$_{(iii)}$	3252	1662	δ = 3.91 (s, 3H, $-OCH_3$), 6.93–8.11 (m, 20H, Ar-H), 8.32 (s, 1H, =CH), 11.01 (s, 1H, NH-CO, exchangeable)
4c$_{(i)}$	2300 2217	1654 1650	δ = 6.59–8.03 (m, 16H, Ar-H + NH), 8.22 (s, 1H, =CH), 10.97 (s, 1H, NH-CO, exchangeable)
4c$_{(ii)}$	2290 2200	1657 2652	δ = 6.52–8.09 (m, 15H, Ar-H + NH), 8.09 (s, 1H, =CH), 11.73 (s, 1H, NH-CO, exchangeable)
4c$_{(iii)}$	2305 2220	1659 1651	δ = 3.92 (s, 3H, $-OCH_3$), 6.75–8.01 (m, 15H, Ar-H + NH), 8.30 (s, 1H, =CH), 12.01 (s, 1H, NH-CO, exchangeable)
5a$_{(i)}$	–	1716 1710	δ = 6.67–8.23 (m, 13H, Ar-H), 8.35 (s, 1H, =CH)
5a$_{(ii)}$	–	1715 1710	δ = 6.63–8.19 (m, 12H, Ar-H), 8.29 (s, 1H, =CH)
5a$_{(iii)}$	–	1717 1708	δ = 3.79 (s, 3H, OCH_3), 6.58–8.07 (m, 12H, Ar-H), 8.21 (s, 1H, =CH)

(*Continued*)

Table 1. Continued

Compound	IR (ν_{max}) KBr (cm^{-1}) ν_{N-H}	IR (ν_{max}) KBr (cm^{-1}) $\nu_{C=O}$	^{1}H NMR (DMSO-d_6)
5b$_{(i)}$	–	1712 1700	δ = 6.13–8.19 (m, 21H, Ar-H), 8.37 (s, 1H, =CH)
5b$_{(ii)}$	–	1715 1700	δ = 6.27–7.91 (m, 20H, Ar-H), 8.19 (s, 1H, =CH)
5b$_{(iii)}$	–	1710 1702	δ = 3.81 (s, 3H, OCH_3), 6.15–7.83 (m, 20H, Ar-H), 8.23 (s, 1H, =CH)
5c$_{(i)}$	3200	1705 1700	δ = 6.19–8.01 (m, 16H, Ar-H + NH), 8.17 (s, 1H, =CH)
5c$_{(ii)}$	3210	1715 1705	δ = 6.17–8.07 (m, 15H, Ar-H + NH), 8.15 (s, 1H, =CH)
5c$_{(iii)}$	3200	1720 1712	δ = 3.91 (s, 3H, OCH_3), 6.25–7.97 (m, 15H, Ar-H + NH), 8.13 (s, 1H, =CH)

Data

2-((1*H*-Indol-3-yl)methylene)-4-oxo-4-phenylbutanhydrazide (2C$_i$). Yield 70%, colorless crystals, mp 213–215 °C. IR ν_{max} 3340, 3300, 3210 (NH), 1685, 1655 (C=O). ^{1}H NMR (DMSO-d_6) δ = 3.22 (s, 2H, CH_2-CO), 4.31 (s, 2H, NH_2, exchangeable), 6.40 (s, 1H, NH-CO, exchangeable), 6.91–8.02 (m, 11H, ArH + NH), 8.31 (s, 1H, =CH). Anal./calcd. for $C_{19}H_{17}N_3O_2$ (319): C, 71.46/71.89; H, 5.37/5.16; N, 13.16/13.30.

2-((1*H*-Indol-3-yl)methylene)-4-(4-chlorophenyl)-4-oxobutane hydrazide (2C$_{ii}$). Yield 55%, colorless crystals, mp 226–227 °C. IR ν_{max} 3320, 3215, 3200 (NH), 1682, 1660 (C=O). ^{1}H NMR(DMSO-d_6) δ = 3.30 (s, 2H, CH_2-CO), 4.30 (s, 2H, NH_2, exchangeable), 6.61 (s, 1H, NH-CO, exchangeable), 7.03–8.09 (m, 10H, ArH + NH), 8.27 (s, 1H, =CH). Anal./calcd for $C_{19}H_{16}ClN_3O_2$ (353.5): C, 64.50/65.02; H, 4.56/4.73; N, 11.88/11.69.

2-((1*H*-Indol-3-yl)methylene)-4-(4-methoxyphenyl)-4-oxobutan hydrazide (2C$_{iii}$). Yield 60%, colorless crystals, mp 218–219 °C. IR ν_{max} 3290, 3220, 3200 (NH), 1687, 1650 (C=O). ^{1}H NMR (DMSO-d_6) δ = 3.37 (s, 2H, CH_2-CO), 3.92 (s, 3H, OCH_3), 4.39 (s, 2H, NH_2, exchangeable), 6.35 (s, 1H, NH-CO, exchangeable), 6.92–7.99 (m, 10H, ArH + NH), 8.20 (s, 1H, =CH). Anal./calcd. for $C_{20}H_{19}N_3O_3$ (349): C, 68.75/68.37; H, 5.48/5.40; N, 12.03/12.35.

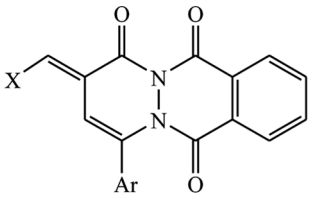
General Method for the Reaction of the Acid Hydrazides (2) with Isatin

Isatin (0.01 mol) in ethanol was added to a solution of the hydrazides (**2**) (0.01 mol) in ethanol (30 ml) containing a few drops of acetic acid. The reaction mixture was heated under reflux for 6 h. The solvent was distilled off under reduced pressure, and the solid obtained was washed thoroughly with ethanol, drained and recrystallized from the suitable solvent (cf. Table 2) to give 2-(furan-2-ylmethylene)-4-oxo-N-(2-oxoindolin-3-ylidene)-4-aryl butan hydrazide (**3a**), 2-((1,3-diphenyl-1*H*-pyrazol-4-yl)methylene)-4-oxo-N-(2-oxoindolin-3-ylidene)-4-aryl

Table 2. Physical and analytical of compounds **3–5**

Compound	Mp (°C) (color)	Yield (%)	Solvent for crystallization	Mol. formula (m.wt.)	Analysis (calcd./found) % C	H	N
3a$_{(i)}$	178–179 (yellow)	60	EtOH	$C_{23}H_{17}N_3O_4$ (399)	69.17/69.42	4.29/4.20	10.52/10.21
3a$_{(ii)}$	256–258 (orange)	50	EtOH	$C_{23}H_{16}ClN_3O_4$ (433.5)	63.67/64.02	3.72/3.91	9.69/9.92
3a$_{(iii)}$	230–232 (yellow)	52	Benzene/EtOH	$C_{24}H_{19}N_3O_4$ (429)	67.13/66.85	4.46/4.29	9.79/9.37
3b$_{(i)}$	242–243 (yellow)	32	Benzene/EtOH	$C_{34}H_{25}N_5O_3$ (551)	74.03/73.72	4.57/4.19	12.70/12.81
3b$_{(ii)}$	228–230 (yellow)	45	EtOH	$C_{34}H_{24}ClN_5O_3$ (585.5)	69.68/69.96	4.13/4.56	11.95/11.63
3b$_{(iii)}$	160–161 (orange)	50	Benzene/EtOH	$C_{35}H_{27}N_5O_4$ (581)	72.28/71.97	4.68/4.42	12.04/12.39
3c$_{(i)}$	172–173 (orange)	30	EtOH	$C_{27}H_{20}N_4O_3$ (448)	72.13/71.73	4.49/4.12	12.49/12.13
3c$_{(ii)}$	200–202 (yellow)	55	EtOH	$C_{27}H_{19}ClN_4O_3$ (482.5)	67.15/67.43	3.97/3.62	11.60/11.31
3c$_{(iii)}$	240–243 (yellow)	60	EtOH	$C_{28}H_{22}N_4O_4$ (478)	70.28/70.53	4.63/4.51	11.71/11.50
4a$_{(i)}$	152–153 (yellow)	30	EtOH	$C_{23}H_{15}N_3O_3$ (381)	72.43/72.11	3.96/3.47	11.02/11.34
4a$_{(ii)}$	218–220 (yellow)	49	EtOH	$C_{23}H_{14}ClN_3O_3$ (415.5)	66.43/66.20	3.39/3.01	10.11/10.41
4a$_{(iii)}$	212–213 (yellow)	60	Benzene/EtOH	$C_{24}H_{17}N_3O_4$ (411)	70.07/70.51	4.16/4.02	10.21/10.57
4b$_{(i)}$	230–153 (yellow)	76	Benzene/EtOH	$C_{34}H_{23}N_5O_2$ (533)	76.53/76.89	4.34/4.59	13.13/13.41

4b$_{(ii)}$	210–211 (yellow)	55	EtOH	$C_{34}H_{22}ClN_5O_2$ (567.5)	71.89/71.57	3.90/4.25	12.33/12.65
4b$_{(iii)}$	150–153 (yellow)	50	EtOH	$C_{35}H_{25}N_5O_3$ (563)	74.59/74.83	4.47/4/10	12.43/12.09
4c$_{(i)}$	185–186 (yellow)	50	EtOH	$C_{27}H_{18}N_4O_2$ (430)	75.34/75.82	4.21/3.90	13.02/13.30
4c$_{(ii)}$	190–191 (yellow)	35	Benzene/EtOH	$C_{27}H_{17}ClN_4O_2$ (464.5)	69.75/69.29	3.69/3.38	12.05/12.30
4c$_{(iii)}$	225–227 (yellow)	45	EtOH	$C_{28}H_{20}N_4O_3$ (460)	73.03/73.41	4.38/4.01	12.17/12.59
5a$_{(i)}$	243–244 (yellow)	53	EtOH	$C_{23}H_{14}N_2O_4$ (382)	72.25/72.73	3.69/3.91	7.33/6.98
5a$_{(ii)}$	269–271 (yellow)	59	EtOH	$C_{23}H_{13}ClN_2O_4$ (416.5)	66.28/66.68	3.14/3.01	6.72/6.49
5a$_{(iii)}$	252–255 (yellow)	70	EtOH	$C_{24}H_{16}N_2O_5$ (412)	69.90/69.97	3.91/3.60	6.79/6.34
5b$_{(i)}$	290–291 (yellow)	30	EtOH	$C_{34}H_{22}N_4O_3$ (534)	76.39/75.99	4.15/4.49	10.48/10.11
5b$_{(ii)}$	278–279 (yellow)	35	EtOH	$C_{34}H_{21}ClN_4O_3$ (568.5)	71.77/71.39	3.72/3.25	9.85/9.73
5b$_{(iii)}$	220–223 (yellow)	35	EtOH	$C_{35}H_{24}N_4O_4$ (564)	74.46/74.61	4.28/4.01	9.92/9.60
5c$_{(i)}$	281–284 (yellow)	45	Benzene	$C_{27}H_{17}N_3O_3$ (431)	75.16/75.43	3.97/3.70	9.74/9.40
5c$_{(ii)}$	219–221 (yellow)	60	EtOH	$C_{27}H_{16}ClN_3O_3$ (465.5)	69.61/70.02	3.46/3.17	9.02/9.25
5c$_{(iii)}$	267–268 (yellow)	60	EtOH	$C_{28}H_{19}N_3O_4$ (461)	72.88/73.03	4.15/4.07	9.11/9.32



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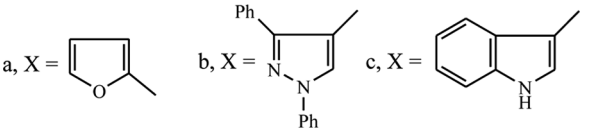

Scheme 3. (i) Ar = C_6H_5–; (ii) Ar = C_6H_4Cl(4-); and (iii) Ar = $C_6H_4OCH_3$(4-).

butanhydrazide (**3b**), and 2-((1*H*-indol-3-yl)methylene-4-oxo-N-(2-oxoindolin-3-ylidene)-4-aryl butanhydrazide (**3c**).

General Method for the Ring Closure of the Butanhydrazide (3) Using HCl/AcOH Mixture

A solution of (**3**) (1 g) in a mixture of HCl (34%)/AcOH(glacial) 1:1 (30 ml) was heated under reflux for 1 h and then left to cool. The solid obtained was filtered off, washed with water, and recrystallized from the suitable solvent (cf. Table 2) to give 3-(furan-2-ylmethylene)-2-oxo-5-aryl-2,3-dihydropyrrol-1-ylimino) indolin-2-one (**4a**), 2-((1,3-diphenyl-1*H*-pyrazole-4-yl)methylene)-2-oxo-5-aryl-2,3-dihydropyrrol-1-ylimino) indolin-2-one (**4b**) and 3-((1*H*-indol-3-yl)methylene)-2-oxo-5-aryl-2,3-dihydropyrrol-1-ylimino) indol-2-one (**4c**).

General Method for the Reaction of the Acid Hydrazides (2) with Phthalic Anhydride

Phthalic anhydride (0.01 mol) in ethanol was added to a solution of the hydrazides (**2**) (0.01 mol) in ethanol (30 ml) containing a few drops of acetic acid. The reaction mixture was heated under reflux for 2 h. The solvent was distilled off under reduced pressure, and the solid obtained was drained and recrystallized from the suitable solvent (cf. Table 2) to give 2-(furan-2-ylmethylene)-4-arylpyridazino[1,2-b]phthalazin-1,6,11-(2*H*)-trione (**5a**), 2-((1,3-diphenyl-1H-pyrazol-4-yl)methylene)-4-arylpyridazino[1,2-b] phthalazin-1,6,11-(2*H*)-trione (**5b**), and 2-((1*H*-indol-3-yl) methylene)-4-arylpyridazino[1,2-b]phthalazine-1,6,11(2H)-trione (**5c**).

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