Synthesis and Reactions of 4-Hydroxy-2(1*H*)-pyridones with Thienyl and Pyridyl Substituents in Position 6 Starting with Azomethines and Malonates

Barbara Schnell

Institute of Organic Chemistry, Karl-Franzens University Graz, Heinrichstr. 28, A-8010 Graz, Austria

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The reaction of **4** with substituted diethyl malonates **5a**, or "magic malonates" (bis-2,4,6-trichlorophenylmalonates **5b**) leads to 4-hydroxy-2(1*H*)-pyridones **6**. The azomethines **4** are prepared *via* the *Strecker* compounds **3** starting with methyl ketones **1**, anilines, and potassium cyanide. Chlorination of pyridones **6** with sulfuryl chloride leads to compounds **7** while nitration gives **9**.

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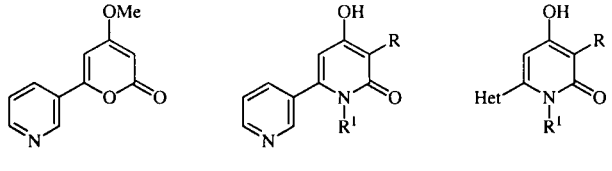
The 4-hydroxy-2(1*H*)-pyridone system represents an interesting class of pyridine derivatives. The basic structure can be found in many natural products, such as flavipucine [1], the long known and highly toxic ricinine [2,3], and the yellow pigments bassianin [4] and tellenin [5]. The latter two compounds have a 3-acyl-4-hydroxy-2-pyridone structure which is common for a large number of antibiotic substances, such as ilicolin H [6], funiculosin [7], harzianopyridon [8], sambutoxin [9], mocimycin [10], and aurodox [11], produced by a variety of *Streptomyces* species. Moreover, substances with this general structure belong to the large group of so-called "cyclic tricarbonyl compounds" which play an important role in agricultural chemistry [12,13,14]. 4-Hydroxy-2-pyridone itself (as "deazauracil") has also been used as base in the synthesis of nucleosides [15]. Exchange of the hydroxy group against the arylthio moiety leads to compounds with potent HIV-1 reverse transcriptase inhibitory properties [16].

The compounds mentioned above have alkyl, aryl or arylalkyl substituents in position 3,5, and 6, but no aromatic heterocycles. Anibin **I** [17,18] belongs to the so-called "tobacco alkaloids", in which the 3-pyridyl moiety is connected to the five-membered pyrrolidyl system (nicotine, nornicotine, myosmin) or to the six-membered piperidyl system (anabasin, anatabin, and their *N*-methyl derivatives) [19,20]. In view of our long experience in the preparation of 4-hydroxy-2(1*H*)-pyridones we have decided to prepare analogs of **I** for biological testing, but changing from the 4-hydroxy-2-pyrone moiety to the 2-pyridone system, as shown in formula **II**. At the same time it seemed desirable to have not only a 3-pyridyl substituent in position 6 of the 4-hydroxy-2-pyridone, but also the 2-pyridyl and the 4-pyridyl moiety as well as thienyl and furyl systems as depicted in the general formula **III** (Figure 1).



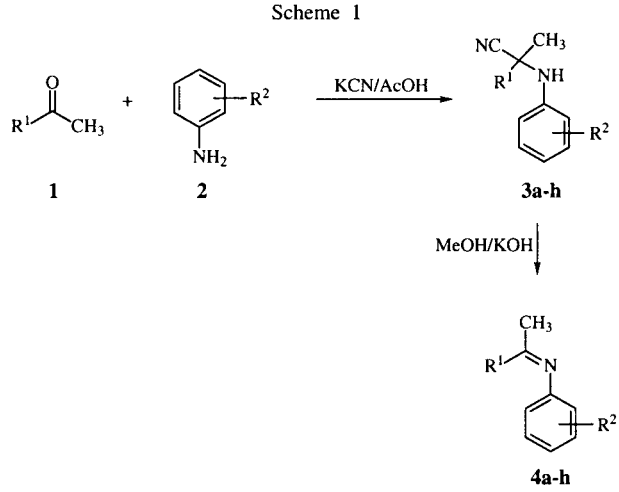
I **II** **III**

Het = 2,3,4-Pyridyl -Thienyl

Figure 1

The synthesis of 4-hydroxy-2(1*H*)-pyridones *via* condensation of enamines or azomethines with reactive malonic acid derivatives, such as carbon suboxide, chlorocarbonyl ketenes, and *bis*-2,4,6-trichlorophenyl malonates **5b** is well known, and literature surveys have been published [21,22]. As a general rule it has been assumed that only activated enamines - derived from β-ketoesters or 1,3-diketones with ammonia or primary amines - can be thermally condensed with substituted dialkyl malonates **5a**, and that non activated azomethines (*Schiff* bases) require "magic malonates", **5b** for a successful condensation to yield 4-hydroxy-2-pyridones. It was only recently that the condensation of non activated azomethines has been described [23,24,25].

Scheme 1



1 **2** **3a-h** **4a-h**

For the preparation of the required azomethines **4** we have used a recently described protocol [23] which so far has only briefly been reported in the literature [26-28], This new method is a two step synthesis *via* the *Strecker* type interme-

Table 1

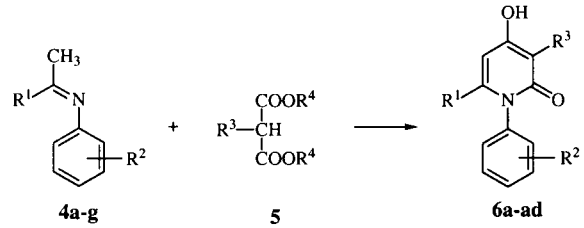
Experimental, Physical and Analytical Data for Compounds **3** and **4**

No.	R^1	R^2	Yield (%)	Mp (°C)	Formula (F.W)		Analysis (%) Calcd./Found	
3a	2-Thienyl	H	55	140-142	$C_{13}H_{12}N_2S$	68.39	5.30	12.27
					(228.32)	68.32	5.31	12.27
3b	2-Thienyl	4-Cl	72	132-134	$C_{13}H_{11}ClN_2S$	59.42	4.19	10.67
					(262.52)	59.11	3.99	10.32
3c	3-Pyridyl	H	84	143-147	$C_{14}H_{13}N_3$	75.31	5.87	18.82
					(223.30)	75.17	5.79	18.74
3d	3-Pyridyl	4-Cl	82	157-158	$C_{14}H_{12}ClN_3$	65.26	4.66	16.31
					(257.45)	64.98	5.02	16.22
3e	4-Pyridyl	H	80	156-160	$C_{14}H_{13}N_3$	75.31	5.87	18.82
					(223.30)	74.91	5.80	18.68
3f	4-Pyridyl	4-Cl	73	160-161	$C_{14}H_{12}ClN_3$	65.26	4.66	16.31
					(257.45)	65.48	4.33	15.93
3g	2-Pyridyl	H	49	128-129	$C_{14}H_{13}N_3$	75.31	5.87	18.82
					(223.30)	75.11	5.84	18.83
3h	2-Furanyl	H	80	95-98	$C_{13}H_{12}N_2O$	73.58	5.66	13.21
					(212.00)	73.26	6.00	12.99
4a	2-Thienyl	H	92	70-71	$C_{12}H_{11}NS$	71.60	5.51	6.96
					(201.29)	71.62	5.59	6.95
4b	2-Thienyl	4-Cl	94	68-71	$C_{12}H_{10}ClNS$	61.14	4.24	5.94
					(235.52)	61.34	3.99	6.11
4c	3-Pyridyl	H	62	63-64	$C_{13}H_{12}N_2$	79.56	6.17	14.27
					(196.25)	79.19	6.26	14.40
4d	3-Pyridyl	4-Cl	86	71-73	$C_{13}H_{11}ClN_2$	67.68	4.81	12.14
					(230.71)	67.65	4.68	12.05
4e	4-Pyridyl	H	76	79-82	$C_{13}H_{12}N_2$	79.56	6.16	14.27
					(196.25)	79.29	6.21	14.32
4f	4-Pyridyl	4-Cl	90	156-158	$C_{13}H_{11}ClN_2$	67.68	4.81	12.14
					(230.71)	67.76	4.65	12.09
4g	2-Pyridyl	H	82	49-51	$C_{13}H_{12}N_2$	79.56	6.16	14.27
					(196.25)	79.46	6.30	14.20
4h	2-Furanyl	H	77	Oil	$C_{12}H_{11}NO$	77.83	5.95	7.57
					185.00	78.02	6.04	7.68

diate **3** (Scheme 1). Compounds **3** are obtained in good yields by the slow addition of solid potassium cyanide to a cooled mixture of **1** and **2** in glacial acetic acid (Table 1). Elimination of hydrogen cyanide from **3** to yield **4** can easily be accomplished with potassium hydroxide in refluxing methanol and leads to pure azomethines **4** which can be used for further reactions without distillation or recrystallization (Table 1) [23,27]. The mechanism of this elimination of hydrogen cyanide with sodium methoxide in methanol has recently been investigated in a kinetic study [28]. It has also been reported that compounds of type **3** undergo pyrolytic elimination of hydrogen cyanide at 210° to afford the azomethines **4** [29]. This fact prompted me to use *Strecker* compounds of type **3** directly for the condensation reactions with malonates. However, the yields of the resulting pyridones **6** were much lower than those obtained starting with **4**.

The results of the condensation reaction of **4** with diethyl malonates **5a** (Method A) and *bis*-2,4-6-trichlorophenyl malonates **5b**, (Methods B,C) are summarized in Table 6 (Scheme 2). Inspection of the table reveals that good results with **5a** are only obtained with the thienyl azomethines. In those cases where both methods have been employed it can

Scheme 2



4a-g **5** **6a-ad**

a, $R^4 = C_2H_5$
b, $R^4 = C_6H_2Cl_3$

be seen that Method B gives generally higher yields. What cannot be seen from the table is the fact that Method B affords also compounds of much higher purity, and therefore purification to colorless substances is much easier. This is especially the case with pyridyl substituents in position 6. Furthermore, 6-pyridyl derivatives could only be prepared in reasonable yield by Method A with diethyl *phenyl* malonate (**6t**, 72%; **6y**, 66%; **6ab**, 72%). The anil of 2-pyridylmethyl ketone presents a special case. Under normal reaction conditions of Method B only a 28% yield of **6ad** could be isolated. Performing the reaction in refluxing 1,2-dichlorobenzene

Table 2

Spectroscopic Data for Compounds **3** and **4**

No.	IR (Potassium bromide cm^{-1})	^{1}H-NMR (δ, ppm)
3a	3340 s, 3100 m, 2210 w, 1600 s, 1510 s, 1490 m	2.00 (s, 3 H, CH_3), 6.60-6.78 (m, 3 H, 2 Aryl-H, Thiophene 4-H), 6.92 (s, 1 H, N-H), 7.02-7.18 (m, 3 H, Aryl-H), 7.22 (d, J = 4 Hz, Thiophene 3-H), 7.55 (d, J = 6 Hz, 1 H, Thiophene 5-H)
3c	3380 s, 306-3000 w, 2230 w, 1600 s, 1515s	1.93 (s, 3 H, CH_3), 6.49 (d, J = 8 Hz, 2 H, Aryl-H), 6.78 (t, J = 8 Hz, 1 H, Pyridine 5-H), 6.98 (s, 1H, NH), 7.00-7.12 (m, 2 H, Aryl-H), 7.40-7.50 (m, 1 H, Aryl-H), 7.88 (dd, J = 8 and 1.5 Hz, 1 H, Pyridine 4-H), 8.58 (m, 1 H, Pyridine 6-H), 8.70 (d, J = 1.5 Hz, 1 H, Pyridine 2-H)
3d	3285 s, 2190 w, 3100 w, 1600 s, 1590 m, 1575 m, 1525 m, 1495 s	1.95 (s, 3 H, CH_3), 6.52 (d, J = 8 Hz, 2 H, Aryl 2-H, 6-H), 7.16 (d, J = 8 Hz, 2 H, Aryl 3-H, 5-H), 7.20 (s, 1 H, NH), 7.44-7.57 (m, 1 H, Pyridine 5-H), 7.90 (dd, J = 8 and 1.5 Hz, 1 H, Pyridine 4-H), 8.60 (d, J = 6 Hz, 1 H, Pyridine 6-H), 8.74 (d, J = 1.5 Hz, 1 H, Pyridine 2-H)
3e	3300 s, 3040 m, 1950 w, 1600 s, 1560 w, 1525 m, 1500 s	1.90 (s, 3 H, CH_3), 6.50 (d, J = 8 Hz, 2 H, Aryl 2-H, 6-H), 6.70 (t, J = 7 Hz, 1 H, Aryl 4-H), 7.02-7.13 (m, 3 H, Aryl 3-H, 5-H, NH), 7.52 (d, J = 7 Hz, 2 H, Pyridine 3-H, 5-H), 8.68 (d, J = 7 Hz, Pyridine 2-H, 6-H)
3f	3380-3200 m, 3180 w, 3100 w, 3040 m, 1600 s, 1560 w, 1530 m, 1495 s	1.92 (s, 3 H, CH_3), 6.50 (d, J = 8 Hz, 2 H, Aryl 2-H, 6-H), 7.17 (d, J = 8 Hz, 2 H, Aryl 3-H, 5-H), 7.28 (s, 1 H, NH), 7.52 (d, J = 6 Hz, 2 H, Pyridine 3-H, 5-H), 8.68 (d, J = 6 Hz, Pyridine 2-H, 6-H)
3g	3392 s, 3080-3000 m, 2220 w, 1600 s, 1590 m, 1570 w, 1520 s	2.00 (s, 3 H, CH_3), 4.68 (s, 1 H, NH), 6.60 (d, J = 8 Hz, 2 H, Aryl H), 6.82 (t, J = 7 Hz, 1 H, Pyridine 4-H), 7.08-7.20 (m, 2 H, Aryl-H), 7.23-7.32 (m, 1 H, Aryl-H), 7.56 (dd,. J = 7 and 1.5 Hz, 1 H, Pyridine 3-H), 7.70 (t, J = 7 Hz, 1 H, Pyridine 5-H), 8.68 (dd, J = 6 and 1.5 Hz, 1 H, Pyridine 6-H)
3h	3340 s, 3120 w, 1605 s, 1515 w, 1490 s	1.95 (s, 3 H, CH_3), 6.40-6.50 (m, 2 H, Furan 4-H, NH), 6.60-6.72 (m, 4 H, Furan 3-H, Aryl-H), 7.10 (t, J = 8 Hz, 2 H, Aryl 3-H, 5-H), 7.70 (d, J = 1 Hz, Furan 5-H)
4a	3140-2920 w, 1610 s, 1590 s, 1480 m	2.21 (s, 3 H, CH_3), 6.82 (d, J = 7 Hz, 2 H, Aryl 2-H, 6-H), 7.06-7.20 (m, 2 H, Aryl 4-H, Thiophene 4-H), 7.38 (t, J = 7 Hz, 2 H, Aryl 3-H, 5-H), 7.68 (d, J = 4 Hz, 1 H, Thiophene 3-H), 7.74 (d, J = 6 Hz, 1 H, Thiophene 5-H)
4b	1620 s, 1480 s, 1425 m	2.24 (s, 3 H, CH_3), 6.78 (d, J = 8 Hz, 2 H, Aryl 2 H, 6-H), 7.10 (t, J = 5 Hz, 1 H, Thiophene 4-H), 7.31 (d, J = 8 Hz, 2 H, Aryl 3-H, 5-H), 7.45-7.52 (m, 2 H, Thiophene 3-H, 5-H)
4c	3100-2800 wb, 1625 s, 1595 s, 1570 m	2.28 (s, 3 H, CH_3), 6.80 (d, J = 7.5 Hz, 2 H, Aryl 2-H, 6-H), 7.10 (J = 7 Hz, 1 H, Pyridine 5-H), 7.32-7.42 (m, 3 H, ArH), 8.31 (dd, J = 7 and 1.5 Hz, 1 H, Pyridine 4-H), 8.68-8.73 (m, 1 H, Pyridine 6-H), 9.16 (d, J = 1.5 Hz, 1 H, Pyridine 2-H)
4d	1630 s, 1585 m, 1565 w, 1485 s	2.28 (s, 3 H, CH_3), 6.73 (d, J = 8 Hz, 2 H, Aryl 2-H, 6-H), 7.32 (d, J = 8 Hz, 2 H, Aryl 3-H, 5-H), 7.36-7.42 (m, 1H, Pyridine 5-H), 8.28 (dd, J = 7 and 1.5 Hz, 1 H, Pyridine 4-H), 8.70 (dd, J = 5 and 1 Hz, Pyridine 6-H), 9.12 (d, J = 1 Hz, 1 H, Pyridine 2-H)
4e	1625 s, 1600 s, 1540 m	2.21 (s, 3 H, CH_3), 6.68 (dd, J = 7 and 1.5 Hz, 2 H, Aryl 2-H, 6-H), 7.12 (t, J = 7 Hz, 1 H, Aryl 4-H), 7.35 (t, J = 7 Hz, 2 H, Aryl 3-H, 5-H), 7.80 (dd, J = 7 and 1.5 Hz, 2 H, Pyridine 3-H, 5-H), 8.22 (dd, J = 7 and 1.5 Hz, 2 H, Pyridine 2-H, 6-H)
4f	1630 s, 1590 s, 1550 m	2.23 (s, 3 H, CH_3), 6.72 (d, J = 8 Hz, 2 H, Aryl 2-H, 6-H), 7.32 (d, J = 8 Hz, 2 H, Aryl 3-H, 5-H), 7.80 (d, J = 6 Hz, 2 H, Pyridine 3-H, 5-H), 8.74 (d, J = 6 Hz, 2 H, Pyridine 2-H, 6-H)
4g		2.38 (s, 3 H, CH_3), 6.82 (d, J = 8 Hz, 2 H, Aryl 2-H, 6-H), 7.12 (t, J = 6 Hz, 1 H, ArH), 7.32-7.43 (m, 3 H, ArH), 7.72-7.84 (m, 1 H, ArH), 8.28 (d, J = 8 Hz, 1 H, ArH), 8.68 (d, J = 6 Hz, 1 H, ArH)
4h	3180-2820 wb, 1630 s, 1595 m, 1575 w, 1475 s	2.10 (s, 3 H, CH_3), 6.18 (t, J = 4 Hz, 1 H, Furan 4-H), 6.70 (d, J = 8 Hz, 2 H, Aryl 2-H, 6-H), 7.07 (t, J = 8 Hz, 1 H, Aryl 4-H), 7.17 (d, J = 4 Hz, 1 H, Furan 3-H), 7.35 (t, J = 8 Hz, 2 H, Aryl 3-H, 5-H), 7.87 (d, J = 1 Hz, Furan 5-H)

Table 3
Experimental, Physical and Analytical Data of Compounds **6**

No.	R^1	R^2	R^3	Reaction Temperature (°C)/ Time (hours)	Method Yield (%)	Mp (°C) (Solvent)	Formula	Analysis (%) Calcd./Found		
6a	2-Thienyl	H	CH_3	240/5.0	A/50	233-236*	$C_{16}H_{13}NO_2S$	67.82	4.60	4.94
				petroleum ether		methanol	(283.35)	67.50	4.51	4.87
6b	2-Thienyl	H	C_2H_5	230/2.0	A/30	267-269*	$C_{17}H_{15}NO_2S$	68.66	5.08	4.71
				ether		methanol	(297.38)	68.48	5.03	4.61
6c	2-Thienyl	H	n-C_3H_7	210/1.5	B/83	305-308*	$C_{18}H_{17}NOS$	69.43	5.50	4.50
				petroleum ether		methanol	(311.41)	69.39	5.48	4.44
6d	2-Thienyl	H	C_4H_9	245/2.0	A/38	288-290*	$C_{19}H_{19}NO_2S$	70.13	5.88	4.30
				ether		methanol	(325.43)	70.09	5.94	4.24
6e	2-Thienyl	H	C_6H_5	250/1.0	A/50	>350*	$C_{21}H_{15}NO_2S$	73.02	4.38	4.05
				ether		dimethylformamide	(345.42)	72.70	4.39	4.20
6f	2-Thienyl	H	CH_2-C_6H_5	250/6.0	A/44	293-295*	$C_{22}H_{17}NO_2S$	73.51	4.77	3.90
				ether		1-butanol	(359.45)	73.41	4.71	3.75
6h	2-Thienyl	4-Cl	n-C_4H_9	240/2.0	B/65	294-298	$C_{19}H_{18}ClNO_2S$	63.41	5.04	3.89
				ether		dimethylformamide/H_2O	(359.89)	63.47	4.82	3.74
6g	2-Thienyl	4-Cl	i-C_3H_7	240/2.0	B/87	>360*	$C_{18}H_{16}ClNO_2S$	62.51	4.66	4.05
				ether		ethanol	(345.85)	62.37	4.44	3.94
6i	2-Thienyl	4-Cl	C_6H_5	250/2.0	A/50	335-339*	$C_{21}H_{11}ClNO_2S$	66.40	3.71	3.69
				ether		1-butanol	(379.87)	66.32	3.59	3.62
6j	2-Thienyl	4-Cl	CH_2-C_6H_5	240/3.0	A/66	320*	$C_{22}H_{16}ClNO_2S$	67.09	4.07	3.56
				ether	B/93	1-butanol	(393.52)	66.43	4.24	3.30
6k	3-Pyridyl	H	C_2H_5	180/3.5	B/52	329-330*	$C_{18}H_{16}N_2O_2$	73.96	5.52	9.58
				ether		CH_3CN	(292.34)	73.94	5.55	9.65
6l	3-Pyridyl	H	n-C_3H_7	210/1.5	B/77	287-291*	$C_{19}H_{18}N_2O_2$	74.49	5.92	9.14
				petroleum ether		CH_3CN	(306.37)	74.04	5.85	9.13
6m	3-Pyridyl	H	i-C_3H_7	200/1.5	B/72	288-291*	$C_{19}H_{18}N_2O_2$	74.49	5.92	9.14
				ether		CH_3CN	(306.37)	74.18	5.79	9.09
6n	3-Pyridyl	H	n-C_4H_9	220/1.5	B/70	260-263*	$C_{20}H_{20}N_2O_2$	74.98	6.29	8.74
				ether		toluene	(320.4)	74.64	6.15	8.64
6o	3-Pyridyl	H	C_6H_5	240/2.0	B/92	>360	$C_{22}H_{16}N_2O_2$	77.63	4.74	8.23
				ether		ethanol	(340.0)	77.69	4.57	8.14
6p	3-Pyridyl	H	CH_2-C_6H_5	210/2.0	B/78	283-286*	$C_{23}H_{18}N_2O_2$	77.95	5.12	7.90
				ether		methanol	(354.41)	77.67	4.86	7.90
6q	3-Pyridyl	4-Cl	C_2H_5	230/2.0	B/92	315*	$C_{18}H_{15}ClN_2O_2$	66.16	4.63	8.57
				ether		ethanol	(326.79)	66.23	4.52	8.47
6r	3-Pyridyl	4-Cl	i-C_3H_7	245/2.5	B/91	>360	$C_{19}H_{17}ClN_2O_2$	66.96	5.03	8.22
				ether		1-butanol	(340.8)	66.71	4.98	8.18
6s	3-Pyridyl	4-Cl	n-C_4H_9	240/2.0	B/92	286-290*	$C_{20}H_{18}ClN_2O_2$	67.71	5.36	7.90
				ether		ethanol	(345.45)	67.68	5.37	7.85
6t	3-Pyridyl	4-Cl	Ph	240/2.0	A/72	328*	$C_{22}H_{15}ClN_2O_2$	70.50	4.03	7.47
				ether	B/98	ethanol	(374.45)	70.13	3.81	7.29
6u	3-Pyridyl	4-Cl	CH_2-Ph	240/2.0	B/87	274-278	$C_{23}H_{17}ClN_2O$	71.04	4.41	7.20
				ether		CH_3CN	(388.87)	70.64	4.21	7.16
6v	4-Pyridyl	H	C_2H_5	200/1.5	B/91	295-297*	$C_{18}H_{16}N_2O_2$	73.96	5.52	9.58
				ether		ethanol	(292.34)	73.87	5.40	9.65
6w	4-Pyridyl	H	i-C_3H_7	210/2.5	B/59	270*	$C_{19}H_{18}N_2O_2$	74.49	5.92	9.14
				ether		CH_3CN	(306.37)	74.18	5.79	9.09
6x	4-Pyridyl	H	n-C_4H_9	220/3.0	B/99	280-282	$C_{20}H_{20}N_2O_2$	74.98	6.29	8.74
				ether		CH_3CN	(320.39)	74.81	6.33	8.77
6y	4-Pyridyl	H	Ph	240/2.0	A/66	320*	$C_{22}H_{16}N_2O_2$	77.63	4.74	8.23
				ether	B/88	ethanol	(340.39)	77.74	4.75	8.15
6z	4-Pyridyl	4-Cl	i-C_3H_7	250/2.0	B/75	330*	$C_{19}H_{17}ClN_2O_2$	66.96	5.03	8.2
				ether		propanol	(340.81)	67.02	5.09	8.04
6aa	4-Pyridyl	4-Cl	n-C_4H_9	240/2.0	B/85	283-286	$C_{20}H_{19}ClN_2O_2$	67.70	5.40	7.89
				ether		CH_3CN	(354.86)	67.49	5.52	7.62
6ab	4-Pyridyl	4-Cl	Ph	240/2.0	A/78	350*	$C_{22}H_{15}ClN_2O_2$	70.50	4.03	7.47
				ether	B/94	ethanol	(374.45)	70.38	3.94	7.45
6ac	4-Pyridyl	4-Cl	CH_2-Ph	240/3.0	B/88	294-296*	$C_{23}H_{17}ClN_2O$	71.04	4.41	7.20
				ether		1-butanol	(388.87)	70.76	4.40	7.05
6ad	2-Pyridyl	H	n-C_4H_9	200/2.5	B/28	261-264	$C_{20}H_{20}N_2O_2$	74.98	6.29	8.74
				petroleum ether	C/56	ethanol	(320.39)	74.90	6.36	8.70

*Decomposition.

Table 4

Spectroscopic data of Compounds **6**

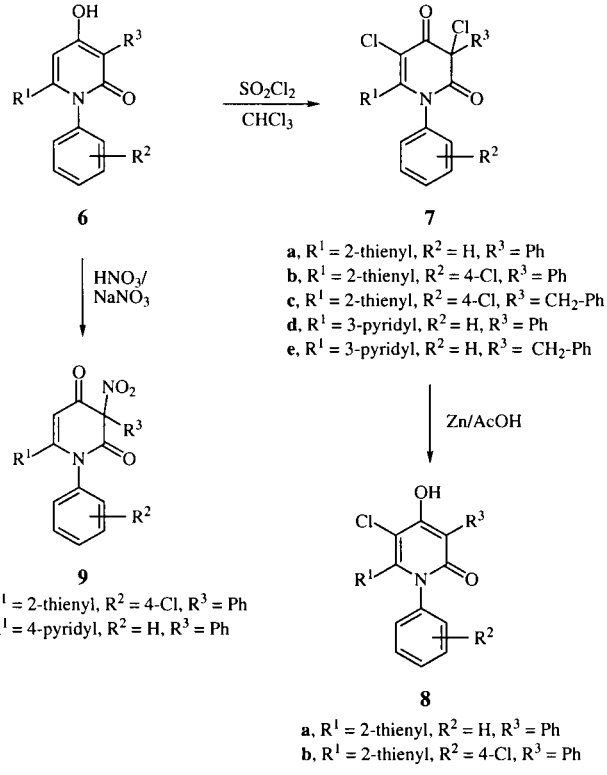
No.	IR (Potassium bromide cm^{-1})	^1H nmr (δ, ppm)
6a	2800-3200 wb 2650 w, 1630 s, 1585 s, 1535 s	1.92 (s, 3 H, CH_3), 6.30 (s, 1 H, 5-H), 6.76-6.78 (m, 1 H, Thiophene 3-H), 6.88-6.92 (m, 1 H, Thiophene 4-H) 7.15-7.22 (m, 2 H, ArH), 7.34-7.42 (m, 3 H, ArH), 7.54 (d, J = 6 Hz, 1 H, Thiophene 5-H), 10.52 (s, 1 H, OH)
6b	3280-2500 mb, 1630 s, 1585 s, 1535 s	1.04 (t, J = 8 Hz, 3 H, CH_3), 2.45 (q, 2 H, CH_2), 6.28 (s, 1 H, 5-H), 6.74-6.80 (m, 1 H, Thiophene 3-H), 6.82-6.92 (m, 1 H, Thiophene 4-H), 7.10-7.20 (m, 2 H, ArH), 7.30-7.42 (m, 2 H, ArH), 7.48 (d, J = 6 Hz, 1 H, Thiophene 5-H), 10.44 (s, 1 H, OH)
6c	3300-2300 mb, 1630 s, 1600 m, 1585 s, 1540 s	0.92 (t, J = 8 Hz, 3 H, CH_3), 1.38-1.57 (m, 2 H, CH_2), 2.40 (t, J = 8 Hz, 2H, CH_2), 6.28 (s, 1 H, 5-H), 6.78 (d, J = 4 Hz, 1 H, Thiophene 3-H), 6.89 (t, J = 6 Hz, 1 H, Thiophene 4-H), 7.09-7.20 (m, 2 H, ArH), 7.30-7.40 (m, 3 H, ArH), 7.50 (d, J = 6 Hz, 1 H, Thiophene 5-H), 10.50 (s, 1 H, OH)
6d	3200-2500 mb, 2130 w, 1630 s, 1600 m, 1585 s, 1550 s	0.92 (t, J = 7 Hz, 3 H, CH_2), 1.22-1.52 (m, 4 H, 2 CH_2), 2.38-2.50 (m, 2 H, CH_2), 6.25 (s, 1 H, H-5), 6.75 (d, J = 4 Hz, 1 H, Thiophene 3-H), 6.87 (t, J = 6 Hz, 1 H, Thiophene 4-H), 7.10-7.20 (m, 2 H, ArH), 7.30-7.42 (m, 3 H, ArH), 7.50 (d, J = 6 Hz, 1 H, Thiophene 5-H), 10.42 (s, 1 H, OH)
6e	3200-2500 mb, 1795 w, 1620 s, 1600 s, 1550 s	6.40 (s, 1 H, 5-H), 6.82-6.95 (m, 3 H, ArH, Thiophene 3-H, 4H), 7.17-7.50 (m, 9 H, ArH), 7.52 (d, J = 6 Hz, H, Thiophene 5-H), 10.75 (s, 1 H, OH)
6f	3240-2400 mb, 1625 s, 1600 m, 1585 s, 1540 s	3.80 (s, 2 H, CH_2), 6.32 (s, 1 H, 5-H), 6.80 (d, J = 4 Hz, 1 H, Thiophene 3-H), 6.90 (t, J = 6 Hz, 1 H, Thiophene 4-H), 7.12-7.42 (m, 10 H, ArH), 7.52 (d, J = 6 Hz, 1 H, Thiophene 5-H), 10.78 (s, 1 H, OH)
6g	3240-2500 mb, 1630 m, 1585 m, 1545 s	1.22 (d, J = 7 Hz, 6 H, 2 CH_3), 3.25-3.50 1 H, CH), 6.21 (s, 1 H, 5-H), 6.84 (d, J = 4 Hz, 1 H, Thiophene 3-H), 6.92 (t, J = 6 Hz, 1 H, Thiophene 4-H), 7.20 (d, J = 8 Hz, 2 H, Aryl 2-H, 6-H), 7.42 (d, J = 8 Hz, 2 H, Aryl 3-H, 5-H), 7.52 (d, J = 6 Hz, 1 H, Thiophene 5-H), 10.50 (s, 1 H, OH)
6h	3280-2500 mb, 1630 s, 1580 s, 1540 s	0.92 (t, J = 7 Hz, 3 H, CH_3), 1.25-1.50 (m, 4 H, 2 CH_2), 2.37-2.48 (m, 2 H, CH_2), 6.27 (s, 1 H, 5-H), 6.83-6.98 (m, 2 H, Thiophene 3-H, 4-H), 7.22 (d, J = 8 Hz, 2 H, Aryl 2-H, 6-H), 7.42 (d, J = 8 Hz, 2 H, Aryl 3-H, 5-H), 7.58 (m, 1 H, Thiophene 5-H), 10.56 (s, 1 H, OH)
6i	3240-2300 mb, 1625 s, 1600 w, 1550 s	6.40 (s, 1 H, 5-H), 6.90-7.00 (m, 2 H, Thiophene 3-H, 4-H), 7.20-7.50 (m, 9 H, ArH), 7.60 (d, J = 6 Hz, 1 H, Thiophene 5-H)
6k	3300-2400 mb, 1640 s, 1605 m, 1585 s, 1550 s	1.07 (t, J = 7 Hz, 3 H, CH_3), 2.40-2.58 (m, 2 H, CH_2), 6.06 (s, 1 H, 5-H), 7.09-7.32 (m, 6 H, ArH), 7.58 (d, J = 7 Hz, 1 H, ArH), 8.32-8.42 (m, 2 H,. ArH), 10.51 (s, 1 H, OH)
6n	3200-2500 mb, 1630 s, 1580 m, 1550 s	0.92 (t, J = 7 Hz, 3 H, CH_3), 1.24-1.54 (m, 4 H, 2 CH_2), 2.40-2.48 (m, 2 H, CH_2), 6.08 (s, 1 H, 5-H), 7.08-7.32 (m, 6 H, ArH), 7.58 (d, J = 7 Hz, 1 H, ArH), 8.32-8.46 (m, 2 H, ArH), 10.50 (s, 1 H, OH)
6o	3200-2400 mb, 1630 s, 1600 s, 1575 w, 1545 s	6.10 (s, 1 H, 5-H), 7.17-7.53 (m, 11 H, ArH), 7.63-7.70 m, 1 H, ArH), 8.40 (dd, J = 6 and 1.5 Hz, 1 H, Pyridine 6-H), 8.49 (d, J = 1.5 Hz, 1 H, Pyridine 2-H), 10.82 (s, 1 H, OH)
6p	3200-2500 mb, 1640 s, 1600 w, 1585 s, 1550 s	3.80 (s, 2 H, CH_3), 6.10 (s, 1 H, 5-H), 7.08-7.38 (m, H H, ArH), 7.58 (d, J = 8 Hz, 1 H, ArH), 8.32-8.42 (m, 2 H ArH)
6q	3300-2400 mb, 1635 s, 1590 s, 1545 s	1.08 (t, J = 8 Hz, 3 H, CH_3), 2.42-2.58 (m, 2 H, CH_2), 6.10 (s, 1 H, 5-H), 7.20 (d, J = 8 Hz, 2 H, Aryl 2-H, 6-H), 7.24-7.31 (m, 1 H, Pyridine 5-H), 7.35 (d, J = 8 Hz, 2 H, Aryl 3-H, 5-H), 7.62 (dd, J = 6 and 1.5 Hz, 1 H, Pyridine 4-H), 8.40-8.48 (m, 2 H, Pyridine 6-H, 2-H), 10.60 (s, 1 H, OH)

Table 4 (continued)

Spectroscopic data of Compounds **6**

No.	IR (Potassium bromide cm^{-1})	^1H nmr (δ, ppm)
6r	3240-2400 mb, 1635 s, 1595 m, 1585 s, 1545 s	1.26 (d, J = 7 Hz, 6 H, 2 CH_3), 2.50-2.56 (m, 1 H, CH), 6.05 (s, 1 H, 5-H), 7.20 (d, J = 8 Hz, 2 H, Aryl 2-H, 6-H), 7.22-7.30 (m, 1 H, Pyridine 5-H), 7.32 (d, J = 8 Hz, Aryl 3-H, 5-H), 7.60 (dd, J = 6 and 1.5 Hz, 1 H, Pyridine 4-H), 8.38-8.44 (m, 2 H, Pyridine 6-H, 2-H), 10.55 (s, 1 H, OH)
6u	3100-2500 wb, 1630 s, 1595 s, 1580 m, 1540 w	3.78 (s, 2 H, CH_2), 6.10 (s, 1 H, 5-H), 7.12-7.37 (m, 10 H, ArH), 7.60 (d, J = 7 Hz, 1 H, ArH), 8.38-8.45 (m, 2 H, ArH), 10.83 (s, 1 H, OH)
6y	3200-2400 mb, 1630 s, 1600 m, 1580 m, 1550 s	6.20 (s, 1 H, 5-H), 7.18-7.50 (m, 12 H, ArH), 8.42 (d, J = 7 Hz, 2 H, Pyridine 2-H, 6-H), 10.89 (s, 1 H, OH)
6z	3200-2200 mb, 2000-1800 wb, 1650 s, 1610 w, 1595 w	1.28 (d, J = 7 Hz, 6 H, 2 CH_3), 2.50-2.56 (m, 1 H, CH), 6.06 (s, 1 H, 5-H), 7.18-7.28 (m, 4 H, Aryl 2-H, 6-H, Pyridine 3-H, 5-H), 7.35 (d, J = 8 Hz, 2 H, Aryl 3-H, 5-H), 8.46-8.49 (m, 2 H, Pyridine 6-H, 2-H), 10.60 (s, 1 H, OH)
6aa	3230-2500 mb, 1630 s, 1580 s, 1540 s	0.91 (t, J = 6 Hz, 3 H, CH_3), 1.22-1.50 (m, 4 H, 2 CH_2), 2.40-2.50 (m, 4 H, CH_2), 6.08 (s, 1 H, 5-H), 7.15-7.25 (m, 4 H, Aryl 2-K 6-H, Pyridine 3-H, 5-H), 7.35 (d, J = 8 Hz, 2 H, Aryl 3-H, 5-H), 8.45 (d, J = 6 Hz, 2 H, Pyridine 2-H, 6-H), 10.60 (s, 1 H, OH)
6ac	3200-2300 mb, 1630 s, 1580 m, 1545 s	3.78 (s, 2 H, CH_2), 6.12 (s, 1 H, 5-H), 7.15-7.40 (m, 11 H, ArH), 8.45 (d, J = 7 Hz, 2 H, Pyridine 2-H, 6-H), 10.94 (s, 1 H, OH)
6ad	3260-2500 mb, 1635 s, 1600 s, 1580 s, 1550 s	0.92 (t, J= 5 Hz, 3 H, CH_3), 1.23-1.57 (m, 4 H, 2 CH_2), 2.40-2.48 (m, 2 H, CH_2), 6.20 (s, 1 H, 5-H), 7.08 (d, J = 6 Hz, 2 H, ArH), 7.15-7.32 (m, 5 H, ArH), 7.62 (t, J = 5 Hz, 1 H, ArH), 8.20 (d, J = 2 Hz, 1 H, ArH), 10.48 (s, 1 H, OH)

Scheme 3



affords at least a 56% yield of **6ad**. The reaction of 2-furanylmethyl ketone anil (**4h**) with **5b** leads obviously to a 4-hydroxy-2-pyridone system, however, according to analytical and spectroscopic data the structure of the furyl substituent must have been affected in a so far unknown manner.

The chlorination of some selected 4-hydroxy-2(1*H*)-pyridones **6** with sulfuryl chloride in chloroform to the slightly yellow 3,5-dichloropyridine-2,4(1*H*,3*H*)-diones **7a-e**. This result is in agreement with previous observations on the chlorination on 3-substituted 4-hydroxy-2-pyridones [23], and of two 4-hydroxy-2-pyridones, unsubstituted in position 3, which resulted in the formation of 3,3-dichloropyridine-2,4-diones, and an additional introduction of a chloro atom in position 5 if this position was unsubstituted [30]. The reduction of the pyridinediones **7** to the aromatic pyridones **8** is easily accomplished with zinc powder in glacial acetic acid. The chloro atom at sp^3 carbon atom in position 5 remains uneffected. Nitration of **7** has been performed with two examples and leads to 3-nitro-2,4(1*H*,3*H*)-pyridinediones **9a,b**.

EXPERIMENTAL

Melting points were obtained on a Gallenkamp melting point apparatus, Model MFB-595 in open capillary tubes. The ^1H nmr

spectra (200 MHz) were obtained on a Varian Gemini 200 instrument. Chemical shifts are reported in ppm from internal tetramethylsilane standard and are given in δ-units. The solvent for ^{1}H nmr was hexadeuteriodimethyl. sulfoxide unless otherwise stated. Microanalyses were performed on a Carlo Erba 1106 Elemental analyzer. Infrared spectra were taken on a Perkin-Elmer 298 spectrophotometer in potassium bromide pellets. Common reagent-grade chemicals are either commerically available and were used without further purification or prepared by standard literature procedures. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel F-254 (Merck) plates using uv light (254 and 366 nm) for detection.

General Procedure for the Synthesis of 2-Substituted 2-Arylaminopropionitrile (**3**).

A stirred solution of ketone **1** (0.5 mole) and aniline **2** (0.6 mole) in 200 ml of glacial acetic acid was cooled in an ice bath. Solid potassium cyanide (0.6 mole = 39 g) was added slowly at such a rate that the temperature did not exceed 10°.

Caution: Some hydrogen cyanide gas is liberated. The reaction must be carried out in a good working hood, and the outlet of the reaction flask should be connected directly to the exhauster!

The reaction mixture was kept at this temperature for 4-5 hours and then overnight at room temperature. After dilution with ice water (400 ml), the product formed was filtered, washed several times with ice water (600 ml), and finally with petroleum ether (400 ml in small portions). Experimental data: Table 1; spectroscopic data: Table 2.

General Procedure for the Preparation of *N*-Alkylidenearylamines **4** from Nitriles **3**.

A solution of potassium hydroxide (0.5 mole = 28 g) in methanol (200 ml) was added to a boiling solution of **3** (0.2 mole) in methanol (240 ml). After refluxing for one hour and cooling to room temperature, the mixture was poured into ice water (500 ml) and the resulting crystalline precipitate was filtered with suction. If there was no precipitate formed, the solution was extracted with petrolether (400-500 ml), the extract was washed several times with water and after drying with sodium sulfate evaporated *in vacuo*. Experimental data: Table 1; spectroscopic data: Table 2.

General Procedure for the Preparation of 1,3,6-Trisubstituted 4-Hydroxy-2(1*H*)-pyridones (**6**).

Method A.

A mixture of the appropriate azomethine **4** (10 mmoles) and the substituted diethyl malonate **5a** (12 mmoles) was heated in an oil bath until no more alcohol was formed (in some cases diphenyl ether has been used as solvent). For reaction temperatures and reaction times, see Table 3. The resulting material was digested with diethyl ether or petroleum ether, filtered and crystallized from the appropriate solvent.

Method B.

A mixture of the appropriate azomethine **4** (10 mmoles) and *bis*-2,4,6-trichlorophenyl malonate **5b** (10 mmoles) was heated in an oil bath. For reaction temperatures and reaction times, see Table 3. The resulting material was digested with diethyl ether or petroleum ether, filtered and crystallized from the appropriate solvent.

Method C.

A mixture of the azomethine **4** (5 mmoles) and *bis*-2,4,6-trichlorphenyl malonate **5b** (5 mmoles) in 10 ml of 1,2-dichlorbenzene was heated for 2.5 hours under reflux. After cooling to room temperature the solution was treated with diethylether and after standing over night the precipitate formed was filtered by suction. Experimental data: Table 3; spectroscopic data: Table 4.

3,5-Dichloro-1,3-diphenyl-6-(2-thienyl)pyridine-2,4(1*H*,3*H*)-dione (**7a**).

To a stirred suspension of **6e** (5.17 g, 0.015 mole) in chloroform (25 ml), sulfuryl chloride (3.7 ml, 0.045 mole) was added in small portions. After stirring at room temperature for 10 minutes the solution was evaporated *in vacuo*, and the residue was trituated with methanol. The precipitate was filtered by suction. The yield was 3.45 g (55%), mp 156-158° (ethanol); ir: ν 1760 m, 1725 w, 1700 s, 1580 w, cm^{-1}; ^{1}H nmr: δ 6.90-7.08 (m, 2 H, Aryl H, Thiophene 3-H), 7.26-7.62 (m, 8 H, Aryl H, Thiophene 4-H), 7.65 (d, J = 6 Hz, 1 H, Thiophene 5-H), 7.78-7.90 (m, 2 H, Aryl H).

Anal. Calcd. for $C_{21}H_{13}Cl_2NO_2S$ (414.30): C, 60.88; H, 3.16; N, 3.28. Found: C, 60.74; H, 3.28; N, 3.01.

3,5-Dichloro-1-(4-chlorophenyl)-3-phenyl-6-(2-thienyl)pyridine-2,4(1*H*,3*H*)-dione (**7b**).

Compound **7b** was obtained from **6i** (3.03 g, 0.008 mole) according to the preparation of **7a**. The yield was 2.85 g (86%), mp 189-192° (ethanol).

Anal. Calcd. for $C_{21}H_{12}Cl_3NO_2S$ (448.76): C, 56.21; H, 2.70; N, 3.12. Found: C, 55.81; H, 2.97; N, 2.85.

3-Benzyl-1-(4-chlorophenyl)-3,5-dichloro-6-(2-thienyl)pyridine-2,4(1*H*,3*H*)-dione (**7c**).

Compound **7c** was obtained from **6j** (5.90 g, 0.015 mole) according to the preparation of **7a**. The yield was 4.95 g (71%), mp 180-182° (ethanol); ir: ν 1715 s, 1680 s, 1585 s, 1520 w cm^{-1}; ^{1}H nmr: δ 3.69 (s, 2 H, CH_2), 6.68-6.74 (m, 1 H, Aryl H), 6.89-6.98 (m, 2 H, Aryl H, Thiophene 3-H), 7.14-7.25 (m, 2 H, Aryl H, Thiophene 4-H), 7.34-7.50 (m, 6 H, Aryl H), 7.65 (d, J = 6 Hz, 1 H, Thiophene 5-H).

Anal. Calcd. for $C_{22}H_{14}C_{13}NO_2S$ (462.79): C, 57.10; H, 3.05; N, 3.03. Found: C, 57.11; H, 2.82; N, 2.92.

3,5-Dichloro-1,3-diphenyl-6-(3-pyridyl)pyridine-2,4(1*H*,3*H*)-dione (**7d**).

Compound **7d** was obtained from **6o** (2.72 g, 0.008 mole) according to the preparation of **7a**. The yield was 2.20 g (76%), mp 214-216° (ethanol); ir: ν 1730 s, 1680 s, 1600 m, 1575 m, cm^{-1}; ^{1}H nmr: δ 7.20-7.38 (m, 6 H, Aryl H), 7.53-7.65 (m, 6 H, Aryl H, Pyridine 4-H, 5-H), 8.37-8.45 (m, 2 H, Pyridine 2-H, 6-H).

Anal. Calcd. for $C_{22}H_{14}O_2N_2O_2$ (409.28): C, 64.56; H, 3.45; N, 6.84. Found: C, 64.92; H, 3.06; N, 6.78.

3-Benzyl-3,5-dichloro-1-phenyl-6-(3-pyridyl)pyridine-2,4(1*H*,3*H*)-dione (**7e**).

Compound **7e** was obtained from **6p** (5.31 g, 0.015 mole) according to the preparation of **7a**. The yield was 5.44 g (85%), mp 125-130° (ethanol); ir: ν 1720 s, 1680 s, 1630 w, 1590 m, cm^{-1}; ^{1}H nmr: δ 3.72 (s, 2 H, CH_2), 6.88-6.92 (d, J = 7 Hz, 1 H, Aryl H), 7.13-7.40 (m, 7 H, Aryl H), 7.40-7.50 (m, 3 H, Aryl H), 7.88 (m, 1 H, Aryl H), 8.38-8.50 (m, 2 H, Pyridine 2-H, 6-H).

Anal. Calcd. for $C_{23}H_{16}Cl_2N_2O_2$ (423.30): C, 65.26; H, 3.81; N, 6.62. Found: C, 64.92; H, 3.66; N, 6.42.

5-Chloro-1,3-diphenyl-4-hydroxy-6-(2-thienyl)-2(1*H*)-pyridone (**8a**).

To a solution of **7a** (3.32 g; 0.008 mole) in glacial acetic acid (20 ml), zinc powder (3.1 g) was added at 90° in small portions. An exothermic reaction took place that caused the reaction mixture to boil. After 2 minutes, the excess zinc was removed by filtration, the filtrate cooled, and diluted with water. The precipitate was filtered, washed with cold water and recrystallized. The yield was 1.50 g (50%), mp 278-280° (toluene); ^{1}H nmr: δ 6.88-6.98 (m, 1 H, Thiophene 4-H), 7.08 (d, J = 5 Hz, 1 H, Thiophene 3-H), 7.16-7.43 (m, 10 H, Aryl H), 7.58 (d, J = 6 Hz, 1 H, Thiophene 5-H).

Anal. Calcd. for $C_{21}H_{14}ClNO_2S$ (379.87): C, 66.40; H, 3.71; N, 3.69. Found: C, 66.21; H, 3.63; N, 3.48.

5-Chloro-1-(4-chlorophenyl)-4-hydroxy-3-phenyl-6-(2-thienyl)-2(1*H*)-pyridone (**8b**).

Compound **8b** was obtained from **7b** (1.25 g, 0.003 mole) according the preparation of **8a**. The yield was 1.00 g (86%), mp 249-251° (toluene); ir: ν 3600-2800 wb, 1630 s, 1600 w, 1550 m, 1510 w, cm^{-1}; ^{1}H nmr: δ 6.93-6.98 (m, 1 H, Thiophene 4-H), 7.09 (dd, J = 5 and 1 Hz, 1 H, Thiophene 3-H), 7.24-7.44 (m, 9 H, Aryl H), 7.62 (dd, J = 6 and 1.5 Hz, 1 H, Thiophene 5-H).

Anal. Calcd. for $C_{21}H_{13}Cl_2NO_2S$ (414.31): C, 60.88; H, 3.16; N, 3.38. Found: C, 60.78; H, 3.06; N, 3.21.

1-(4-Chlorophenyl)-3-nitro-3-phenyl-6-(2-thienyl)pyridine-2,4(1*H*,3*H*)-dione (**9a**).

To a suspension of **6i** (3.03 g, 0.008 mole) in acetic acid (30 ml) concentrated nitric acid (3 ml) and catalytic amounts of sodium nitrite was added. The solution was stirred for 30 minutes at room temperature and then poured into ice-water (250 ml). The precipitate filtered by suction and recrystallized. The yield was 3.20 g (98%), mp 137-139° (1-butanol); ir: ν 3120-3000 w, 1720 s, 1665 s, 1590 s, 1580 s, 1490 m, cm^{-1}; ^{1}H nmr: δ 6.50 (s, 1 H, 5-H), 7.02 (t, J = 6 Hz, 1 H, Thiophene 4-H), 7.30 (d, J = 5 Hz, 1 H, Thiophene 3-H), 7.43-7.75 (m, 9 H, Aryl H), 7.84 (d, J = 6 Hz, 1 H, Thiophene 5-H).

Anal. Calcd. for $C_{21}H_{13}ClN_2O_4S$ (424.87): C, 59.37; H, 3.08; N, 6.59. Found: C, 59.73; H, 3.16; N, 6.24.

1,3-Diphenyl-3-nitro-6-(4-pyridyl)pyridine-2,4(1*H*,3*H*)-dione (**9b**).

Compound **9b** was obtained from **6y** (1.70 g, 0.005 mole) according to the preparation of **9a**. The yield was 0.80 g (41%), mp, 130-132° (1-butanol); ir: ν 3160-2900 w, 1725 s, 1680 m, 1645 m, 1565 m, cm^{-1}; ^{1}H nmr: δ 6.35 (s, 1H, 5-H), 7.28-7.75 (m, 12 H, Aryl H), 8.50 (d, J = 7 Hz, 2 H, Pyridine 2H, 6-H).

Anal. Calcd. for $C_{22}H_{15}N_3O_4$ (385.00): C, 68.57; H, 3.89; N, 10.90. Found: C, 68.21; H, 3.80; N, 10.84.

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