Substituted γ-Lactones [1]. Some Observations on the Synthesis and Reactivity of 4-Aroyl-3-hydroxy-2(5*H*)-furanones

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The reaction pathway towards formation of 4-aroyl-3-hydroxy-2(5*H*)-furanones **1** from the base catalyzed reaction between an acetophenone, diethyl oxalate and formaldehyde was investigated. If methoxide was used as base, a transesterification was found to occur in the first step, while a side reaction, namely the retro Claisen reaction, was in competition with the desired lactone formation in the second step. The nature of the solvent and the acidic character of **1** as well as the basicity of the aminoarylene were found to have a profound influence on the course of the reaction of **1** with aminoarylenes.

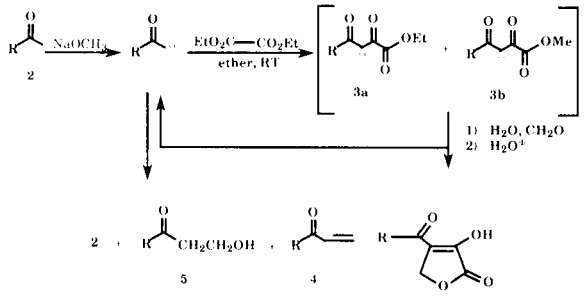
J. Heterocyclic Chem., **30**, 161 (1993).

In continuation of our interest in the chemical versatility of 4-aroyl-3-hydroxy-2(5*H*)-furanones **1**, we determined that they represent easily accessible building blocks for the synthesis of heterocyclic systems. In compounds **1** carbon atoms C-2, C-3, and C-6 represent electrophilic sites of different reactivity and could be used for the construction of condensed heterocyclic systems upon reaction with binucleophiles [4-6].

In this report, we would like to present our findings during the course of synthesizing the furanones **1**, as well as further investigations of their reactivity with nucleophiles.

The syntheses of **1** and analogues were basically the same as that originally reported by Nield [7] and developed by us [4] and others [8-10] (Scheme I).

Scheme I



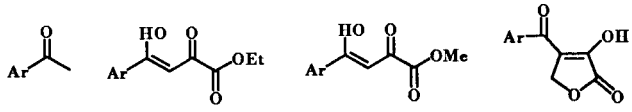
Though usually the reaction towards **1** and analogues normally results in crystalline products; many, however, gave gummy solids or viscous oils. The substituent seemed to effect the yields which are tabulated in Table I based on recrystallized compounds.

In an attempt to gain a better understanding of the mechanism of this reaction and to attempt to explain the overall low yields of **1** obtained, a small aliquot of the viscous reaction mixture of the reaction between the substituted acetophenone and diethyl oxalate was worked up (by acidifying and extracting with ether) prior to the addition of the water and formaldehyde. The organic phase then was analyzed by tlc and ^{1}H-nmr spectroscopy. This confirmed and clarified two pieces of information mentioned earlier [8].

The intermediate actually consisted of two anionic species (Scheme I); the anticipated condensation enolate

Table I

Yield Obtained of Reaction Intermediate and Product



2 **3a** **3b** **1**

#	Ar	ref	Yield %			
1a	Ph	4,7	[a]	29 [a]	71 [a]	57 [b]
1b	*p*-CH_3Ph	9	--	34	66	38
1c	*m*-CH_3Ph		--	37	63	42
1d	*p*-OCH_3 Ph	9	--	33	67	57
1e	*m*-OCH_3 Ph			43	57	46
1f	*o*-OCH_3 Ph		--	12	88	53
1g	*p*-BrPh		21	33	46	18
1h	*m*-BrPh		--	34	66	29
1i	*o*-BrPh		15	33	52	36
1j	*p*-ClPh	9	--	32	68	31
1k	*m*-ClPh		--	41	59	21
1l	*o*-ClPh		--	22	78	50
1m	*p*-OHPh [c]	9	59	29	12	11
1n	*m*-OHPh [c]		8	25	37	12
1o	*o*-OHPh [c]	10	--	33	67	30
1p	*p*-NO_2Ph	9	--	55	45	20
1q	*m*-NO_2Ph		--	56	44	19
1r	*o*-NO_2Ph		12	31	57	12
1s	*p*-CNPh		--	69	31	15
1t	*m*-CNPh		29	49	22	19

[a] Determination from the ^{1}H-nmr of each worked up reaction intermediate. [b] Best recrystallized yield obtained. [c] Two equivalents of base were used.

Table II

^{13}C-NMR Chemical Shifts of Compounds **1b-1l** and **1k-1t** [a] [b]

Compound No.	C'-2	C-3	C-4	C-5	C-6	C-1'	C-2'	C-3'	C-4'	C-5'	C-6'	CR
1b	169.74	144.08	121.97	68.03	189.01	134.52	128.90	129.09	143.65	129.09	128.90	21.23
1c	169.80	144.66	121.67	68.05	189.57	137.67	129.91	137.24	133.71	128.22	126.21	20.88
1d	170.04	143.70	122.60	68.38	187.88	129.84	131.71	113.81	163.61	113.81	131.71	55.70
1e	169.90	144.73	121.62	68.16	189.25	138.57	113.88	159.17	119.10	129.53	121.33	33.39
1f	169.99	145.99	122.70	67.65	189.24	122.70	157.37	111.81	132.60	120.29	128.75	55.86
1g	169.91	145.96	120.28	67.89	188.14	136.38	130.62	131.26	126.77	131.36	130.62	--
1h	169.95	145.44	120.73	67.83	187.90	139.28	131.39	121.45	135.40	130.47	127.65	--
1i	170.02	148.96	120.13	67.60	189.16	141.16	118.48	131.82	132.89	127.89	128.88	--
1k	169.65	145.38	120.78	67.86	188.06	139.09	130.29	133.08	132.57	128.56	127.33	--
1l	169.77	148.00	121.13	67.55	188.52	138.95	131.88	128.98	130.86	127.37	129.82	--
1m	170.05	143.57	122.94	68.45	187.77	128.50	132.13	115.38	162.79	115.38	132.31	--
1n	169.85	144.38	121.99	68.13	189.48	138.52	115.33	157.42	119.91	129.53	120.35	--
1o	169.62	144.80	122.44	67.77	191.49	123.74	158.43	116.92	134.69	118.95	130.82	--
1p	169.62	146.47	120.39	67.79	188.18	142.58	130.03	123.41	149.61	123.41	130.03	--
1q	169.65	146.02	120.56	67.90	187.38	138.50	123.58	147.62	127.15	130.10	135.03	--
1r	169.40	146.10	120.81	67.34	187.02	135.59	147.57	124.16	131.43	135.04	128.90	--
1s	169.76	146.18	120.62	67.94	188.55	141.03	129.45	132.39	118.37	132.39	129.45	114.91
1t	169.68	145.97	120.57	67.89	187.78	138.18	132.80	111.55	136.10	129.72	133.17	118.30

[a] ^{13}C-nmr spectral data for **1a** and **1j** were reported earlier [4]. [b] DMSO-d_6 used as solvent throughout.

3a and the mixed ester enolate **3b** resulting from the transesterification of methoxide with one of the diethyl oxalate carbonyls and the starting ketone reacted completely with the diethyl oxalate to give 100% of intermediate **3** (Table I).

No obvious aryl substituent trend was observed to have an effect on the ratio of **3a** and **3b**. Further, the ratio did not seem to have an effect on the overall yield.

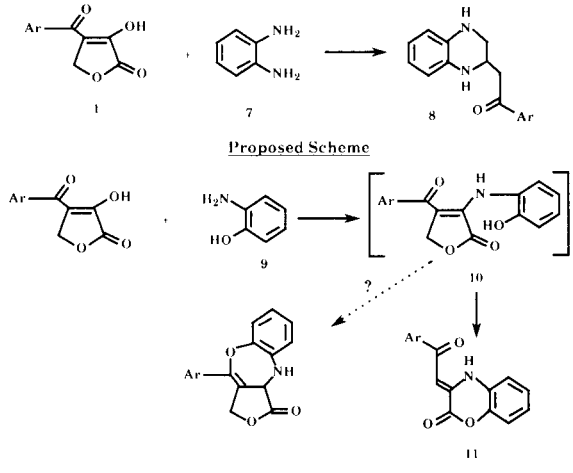
In an attempt to determine what was occurring in the second step of the reaction, the organic phase, remaining from the crude reaction mixture, was analyzed *via* gc-ms for each of the analogues synthesized. In all cases the α,β-unsaturated ketones **4** were observed and sometimes also its precursors **5**, along with some starting methyl ketone **2** (Scheme I). The availability of **2** after its condensation with diethyl oxalate can be explained by a retro Claisen condensation of **3a** and **3b**. This retro Claisen condensation apparently is in competition with the condensation of **3a** and **3b** with formaldehyde to give after acidification **1**. Such a scheme also would explain the low yields obtained for type **1** compounds.

In addition, the observed ^{13}C-nmr chemical shifts of type **1** compound are reported (Table II). They support the enolic structure of **1**.

Recently, we have demonstrated the reactivity of **1** with *o*-phenylenediamine **7** to afford 2(1*H*)-quinoxalinone ring system **8** (Scheme II) in which the binucleophilic attack of **7** occurred on C-3 followed by attack on C-2 of **1**, with opening of the lactone ring followed by a retro Aldo condensation.

To examine the validity of the furanones, **1** for the synthesis of 2*H*-1,4-benzoxazin-2-one ring system **11** *via* the same route mentioned above, a mixture of **1a** with *o*-aminophenol **9** was stirred at room temperature for several days. The orange solid that precipitated was recrystallized from methanol and analyzed.

Scheme II



The elemental analysis as well as the mass spectrum of the obtained solid agreed with the formula $C_{17}H_{13}NO_4$ indicating the elimination of a molecule of water from the sum of the reactant and at this point tentative Schiff base structures **10a** and **12a** were proposed for the reaction product. Based on its spectroscopic data and chemical behavior structure **12** was assigned to the reaction product. Its ^{13}C-nmr (62.9 MHz) (DMSO-d_6) exhibited fifteen peaks at δ 65.83, 105.95, 115.94, 118.77, 123.66, 124.76,

Table III

Structure Determination Summary for Compound **12a**

Crystal Data	
Formula	$C_{18}H_{17}NO_5$
Color and Habit	Red prisms
Size (mm)	0.35 x 0.38 x 0.38
Crystal System	Monoclinic
Space Group	P21/c (No. 14)
Unit Cell Dimensions	a 7.6157(9)
(a,b,c, Å)	b 29.550(3) β 103.793(9)
(angles°)	c 7.3637(9)
Volume (Å^3)	1609.4(3)
Z(formulae/cell)	4
Formula Weight	327.36
Density, Calcd. (g/cc)	1.35
Absorption Coeff. (cm^{-1})	0.93
F(000) (e-)	688
Data Collection	
Diffractometer	Siemens R3m/V
Radiation	Mo K_a (λ 0.71073 Å)
Monochromator	Highly oriented graphite crystal
Temperature (K)	294
2θ Range (°)	3.0-55.0
h,k,l Limits	$-9 \rightarrow 9, 0 \rightarrow 38, 0 \rightarrow 9$
Scan Type	2θ-θ
Scan Speed (° min^{-1})	Variable; 4.0 to 8.0
Scan Range (°)	0.8 on either side of K_{a12}
Background Measurement	Stationary crystal and counter at beginning and end of scan; total background time to scan time ratio of 0.5
Standard Reflections	3 measured every 37
Reflections Collected	4049 total; 3687 independent; R(int) 0.0207
Reflections Observed	1814: F>6σ (F)
Absorption Correction	N/A
Min./Max. Transmission	N/A
Solution and Refinement	
System Used	Siemens SHELXTL PLUS (Micro VAX II)
Solution	Direct Methods (XS:TREF)
Refinement Method	Full-Matrix Least-Squares (XLS)
Absolute Configureation	N/A
Extinction Correction	N/A
Final Residuals	R(F) 0.0487 wR(F) 0.0509
Goodness-of-fit	S 1.78
Max and Mean |Shift/ESD|	0.001 and 0.000
Number of Variables	229
Data-to-Parameter Ratio	7.9:1
Max./Min. Excursions	0.16 and -0.19 e- Å^{-3}

Table IV

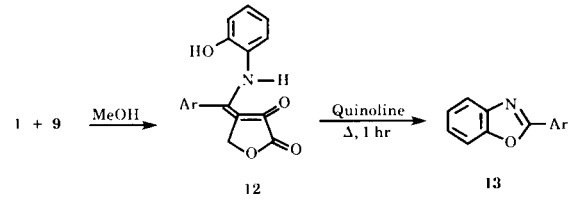
Atomic Coordinates (x 10^4) and Equivalent Isotropic Displacement Parameters (Å^2 x 10^3) for **12a**

Atom	X	Y	Z	U(eq)
O(1)	4500(3)	2766(1)	5595(3)	62(1)
C(2)	4926(5)	3133(1)	4701(5)	52(1)
O(2)	6018(3)	3117(1)	3764(4)	78(1)
C(3)	3863(4)	3531(1)	5114(4)	38(1)
O(3)	4030(3)	3920(1)	4511(3)	50(1)
C(4)	2766(4)	3373(1)	6242(4)	37(1)
C(5)	3159(5)	2880(1)	6633(5)	56(1)
C(6)	1597(3)	3646(1)	6972(4)	35(1)
C(7)	566(4)	3458(1)	8275(4)	35(1)
C(8)	-587(4)	3095(1)	7746(5)	49(1)
C(9)	-1515(5)	2916(1)	8994(6)	63(2)
C(10)	-1287(5)	3098(1)	10739(6)	67(2)
C(11)	-126(5)	3460(1)	11280(5)	60(1)
C(12)	799(4)	3638(1)	10050(4)	46(1)
C(1')	296(3)	4420(1)	6923(4)	35(1)
N(1')	1504(3)	4083(1)	6536(3)	37(1)
C(2')	1016(4)	4847(1)	7386(4)	37(1)
O(2')	2811(3)	4900(1)	7533(4)	53(1)
C(3')	-126(4)	5195(1)	7663(4)	46(1)
C(4')	-1944(4)	5111(1)	7461(5)	52(1)
C(5')	-2656(4)	4688(1)	6976(5)	54(1)
C(6')	-1539(4)	4339(1)	6073(4)	47(1)
C	4395(5)	5967(1)	9549(5)	70(2)
O	3747(3)	5775(1)	7772(4)	70(1)

127.09, 127.59, 129.19, 130.62, 130.83, 149.82, 159.66, 166.66 and 172.10 ppm. The latter two peaks are attributed to the carbonyl resonance of C-2 and C-3 and agreed with the assigned structure **12**.

On the other hand, heating **12** in quinoline for 1 hour afforded 2-phenylbenzoxazole **13a** in good yield (Scheme III). The definite structure proof of **12a** was secured by X-ray analysis (Tables III-VI). Perspective views of this compound are presented in Figures 1 and 2. The latter showed the internal and the external hydrogen bondings with the solvent molecules. Analogously, compounds **12b-c** were prepared by treatment of the corresponding **1** with **9**. These compounds also afforded the benzoxazole ring system upon pyrolysis in quinoline.

Scheme III



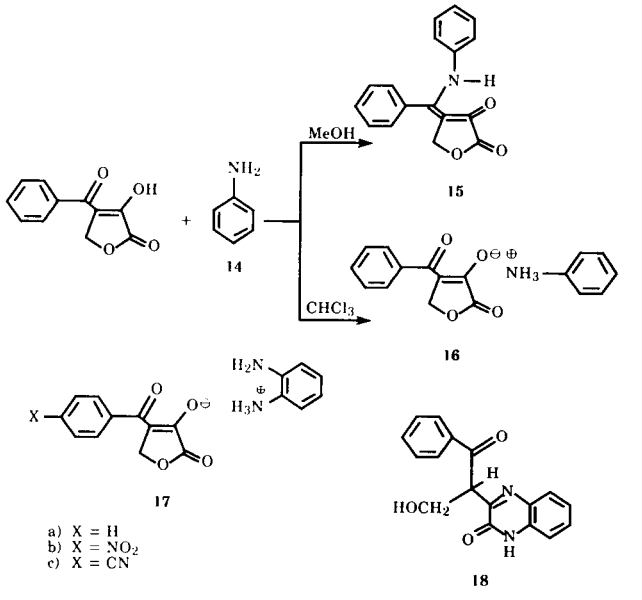
12 13

a) Ar = C_6H_5
b) Ar = p-ClC_6H_4
c) Ar = p-MeC_6H_4

Treatment of **1a** with aniline **14** under the condition employed for **9** (methanolic medium) afforded the Schiff base **15** as the only product. Again, its structure was confirmed by ^{13}C-nmr spectroscopy through the disappearance of the benzoyl carbonyl peak at δ 189 ppm and the shift of the C-3 carbonyl peak to δ 172 ppm. Changing the reaction solvent to chloroform led to the isolation of the acid-base adduct **16** instead of **15** (Scheme IV). Thus, it is reasonable to assume that more acidic analogues of **1** form acid-base adducts when reacted with *o*-phenylenediamine in chloroform. This hypothesis rationalizes the observation that **17b-17c** were the only products formed when **1p**

and **1s**, which contain stronger electron withdrawing aroyl groups, were allowed to react with **7** in chloroform.

Scheme IV



Finally, the reaction of **1a** with **7** in benzene was investigated. It was found that it proceeds *via* two different pathways; (1) by a nucleophilic attack on C-2 as previously observed, however, no retro aldol sequence took place to form **18**; (2) by an acid-base reaction to afford **17a**. The ^{1}H-nmr spectrum of the crude reaction solid showed clearly the presence of **18** as can be seen by a triplet and doublet at δ 5.45 and 4.14 (J = 6.4 Hz) respectively. These peaks are in its ^{1}H-nmr spectrum due to the CH-CH_2O (AM_2) structural element. On the other hand, the protonated diaminoaryl species of **17a** gave the corresponding

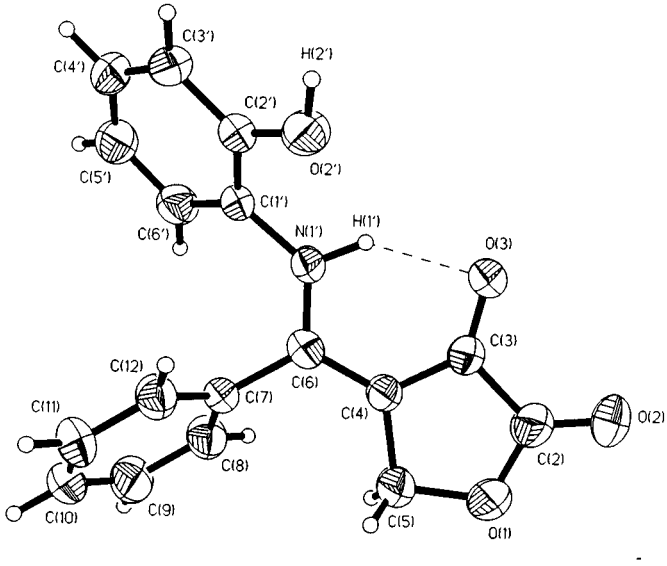


Figure 1

Table V
Bond Distances (Å) for **12a**

O(1)-C(2)	1.347	(4)
O(1)-C(5)	1.454	(5)
C(2)-O(2)	1.202	(5)
C(2)-C(3)	1.500	(5)
C(3)-O(3)	1.251	(4)
C(3)-C(4)	1.391	(4)
C(4)-C(5)	1.502	(4)
C(4)-C(6)	1.399	(4)
C(6)-C(7)	1.484	(4)
C(6)-N(1')	1.329	(4)
C(7)-C(8)	1.383	(4)
C(7)-C(12)	1.383	(4)
C(8)-C(9)	1.391	(6)
C(9)-C(10)	1.366	(6)
C(10)-C(11)	1.385	(5)
C(11)-C(12)	1.377	(5)
C(1')-N(1')	1.430	(4)
C(1')-C(2')	1.386	(4)
C(1')-C(6')	1.389	(4)
C(2')-O(2')	1.355	(4)
C(2')-C(3')	1.392	(4)
C(3')-C(4')	1.379	(4)
C(4')-C(5')	1.375	(5)
C(5')-C(6')	1.382	(5)
C-O	1.404	(5)
C(5)-H(5a)	0.960	
C(5)-H(5b)	0.960	
C(8)-H(8)	0.960	
C(9)-H(9)	0.960	
C(10)-H(10)	0.960	
C(11)-H(11)	0.960	
C(12)-H(12)	0.960	
N(1')-H(1')	0.946	(38)
O(2')-H(2')	0.851	(34)
C(3')-H(3')	0.960	
C(4')-H(4')	0.960	
C(5')-H(5')	0.960	
C(6')-H(6')	0.960	
C-H_a	0.960	
C-H_b	0.960	
C-H_c	0.960	
O-H	0.921	(39)

signals at δ 6.5 which is in a good agreement with the observed ^{1}H-nmr spectra for **17b** and **17c**. Finally, heating the crude reaction products in methanolic solution caused a retro aldo reaction and formation of the known quinoxalinone **8** (Ar = Ph).

EXPERIMENTAL

Melting points were determined on a Mel-Temp melting point apparatus and are uncorrected. Analytical tlc was performed using ascending technique with EM silica gel 60 F_{254} precoated on plastic sheets. The ir spectra were obtained on a Perkin-Elmer model 599 spectrometer, and were calibrated against the 1601 cm^{-1} band of polystyrene. The nmr spectra were recorded on Bruker AC-250 or Nicolet NT 300 MHz spectrometers. Chemical shifts are expressed in δ scale in parts per million downfield from

Table VI
Bond Angles (°) for **12a**

C(2)-O(1)-C(5)	110.6(2)	O(1)-C(5)-H(5a)	110.6(1)
O(1)-C(2)-O(2)	122.1(3)	C(4)-C(5)-H(5a)	110.6(2)
O(1)-C(2)-C(3)	109.1(3)	O(1)-C(5)-H(5b)	110.6(1)
C(2)-C(2)-C(3)	128.8(3)	C(4)-C(5)-H(5b)	110.6(2)
C(2)-C(3)-O(3)	123.0(3)	H(5a)-C(5)-H(5b)	109.5(1)
C(2)-C(3)-C(4)	106.8(3)	C(7)-C(8)-H(8)	120.1(2)
O(3)-C(3)-C(4)	130.3(3)	H(8)-C(8)-C(9)	120.1(2)
C(3)-C(4)-C(5)	108.6(3)	C(8)-C(9)-H(9)	119.9(2)
C(3)-C(4)-C(6)	124.3(3)	H(9)-C(9)-C(10)	119.9(2)
C(5)-C(4)-C(6)	126.9(3)	C(9)-C(10)-H(10)	119.9(2)
O(1)-C(5)-C(4)	104.9(3)	H(10)-C(10)-C(11)	119.9(2)
C(4)-C(6)-C(7)	121.1(2)	C(10)-C(11)-H(11)	120.2(2)
C(4)-C(6)-N(1')	118.0(3)	H(11)-C(11)-C(12)	120.1(2)
C(7)-C(6)-N(1')	120.9(3)	C(7)-C(12)-H(12)	119.8(2)
C(6)-C(7)-C(8)	120.4(3)	C(11)-C(12)-H(12)	119.8(2)
C(6)-C(7)-C(12)	119.9(2)	C(6)-N(1')-H(1')	113.9(20)
C(8)-C(7)-C(12)	119.6(3)	C(1')-N(1')-H(1')	117.1(20)
C(7)-C(8)-C(9)	119.8(3)	C(2')-O(2')-H(2')	113.4(24)
C(8)-C(9)-C(10)	120.1(3)	C(2')-C(3')-H(3')	120.1(2)
C(9)-C(10)-C(11)	120.3(4)	H(3')-C(3')-C(4')	120.1(2)
C(10)-C(11)-C(12)	119.8(3)	C(3')-C(4')-H(4')	119.5(2)
C(7)-C(12)-C(11)	120.3(3)	H(4')-C(4')-C(5')	119.5(2)
N(1')-C(1')-C(2')	116.6(2)	C(4')-C(5')-H(5')	120.2(2)
N(1')-C(1')-C(6')	122.3(3)	H(5')-C(5')-C(6')	120.1(2)
C(2')-C(1')-C(6')	120.9(3)	C(1')-C(6')-H(6')	120.3(2)
C(6)-N(1')-C(1')	129.0(3)	C(5')-C(6')-H(6')	120.3(2)
C(1')-C(2')-O(2')	117.2(3)	H_a-C-H_b	109.4
C(1')-C(2')-C(3')	118.9(3)	H_a-C-H_c	109.5
O(2')-C(2')-C(3')	123.8(3)	H_b-C-H_c	109.5
C(2')C(3')-C(4')	119.8(3)	H-a-C-O	111.0(2)
C(3')-C(4')-C(5')	121.1(3)	H_b-C-O	113.5(2)
C(4')-C(5')-C(6')	119.8(3)	H_c-C-O	103.7(2)
C(1')-C(6')-C(5')	119.5(3)	C-O-H	107.9(20)

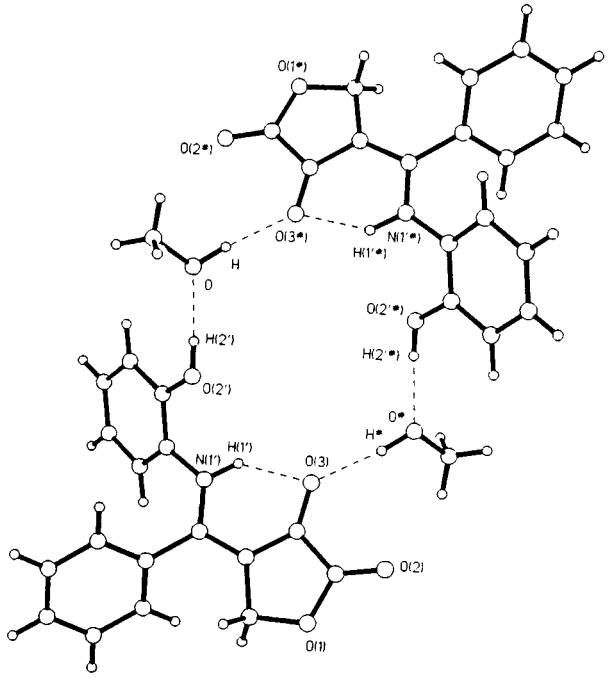


Figure 2

internal tetramethylsilane (Me_4Si) and apparent coupling constants (J) are given in Hertz (Hz). A Hewlett-Packard 5995 Gas Chromatograph/Mass Spectrometer was used to record ms data at 70 eV. The X-ray data were recorded on a Nicolet R3m diffractometer and analyzed on a Micro VAX II using the SHELXTL PLUS series of crystallographic programs. Elemental analyses were performed by M-H-W Laboratories, Phoenix, Arizona.

Preparation of 4-Aroyl-3-hydroxy-2(5*H*)-furanones **1** and Analysis of the Reaction Mixture Intermediates. General Procedure.

Fresh sodium methoxide was prepared before each reaction by slowly adding 2.56 g (0.11 g-atom) of freshly cut sodium metal to 100 ml of methanol in a 250 ml round-bottomed flask. (For the hydroxy substituted analogues 5.12 g of Na (0.22 g-atom) was used). The resulting white sodium methoxide was used crude. The reaction flask consisted of a 1 ℓ three-necked round-bottomed flask equipped with a mechanical stirrer and a 125 ml addition funnel. A reaction mixture was obtained by combining 0.11 mole of the methyl ketone in 100 ml of anhydrous diethyl ether, with 0.11 mole of the diethyl oxalate. This solution was added dropwise to the base with stirring. After stirring at room temperature for three hours it usually became very viscous. If it became too thick to stir, an additional 100 ml of anhydrous ether was added.

After the three hour stirring period, 100 ml of water was then added to the reaction mixture followed by a solution of 0.11 mole of 37% aqueous formaldehyde in 50 ml of water. The stirring was then continued until two clear layers formed (usually within half an hour). Sometimes, an additional 100 ml of water was added if the reaction was especially thick, or the solid appeared to react slowly. The clear, aqueous bottom layer was removed and the organic layer extracted three times with 100 ml of water. The combined aqueous extracts were cooled in the refrigerator followed by acidification with 7 ml of concentrated hydrochloric acid. At this point the furanone usually precipitated. The solution was then cooled overnight to ensure complete product formation. The resulting solid was collected, dried, and recrystallized from an appropriate solvent.

4-(3-Methylbenzoyl)-3-hydroxy-2(5*H*)-furanone (**1c**).

This compound was obtained in 42% yield (10.07 g), mp 135-136° (2-propanol); ^{1}H-nmr (300 MHz, 10% DMSO-d_6/deuteriochloroform): δ 2.45 (s, 3H), 5.30 (s, 2H), 7.45 (dd, J = 7.5 Hz, 7.2 Hz, 1H), 7.48 (d, J = 7.2 Hz, 1H), 7.55 (d, J = 7.5 Hz, 1H), 7.63 (s, 1H), 9.8 (br s, 1H, deuterium oxide exchangeable); ms: m/z 218 (M^+), 174, 146 (base peak), 131, 119, 103, 91, 77, 65; ir (potassium bromide): cm^{-1} 3500, 3400, 1760, 1640, 1600, 1650.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.16; H, 4.66.

4-(3-Methoxybenzoyl)-3-hydroxy-2(5*H*)-furanone (**1e**).

This compound was obtained in 46% yield (11.8 g), mp 150-151° (2-propanol); ^{1}H-nmr (300 MHz, 10% DMSO-d_6/deuteriochloroform): δ 3.84 (2, 3H), 5.09 (s, 2H), 7.11 (d, J = 8.1 Hz, 1H), 7.37 (m, 2H), 7.48 (d, J = 7.5 Hz, 1H), 8.8 (br s, 1H, deuterium oxide exchangeable); ms: m/z 234 (M^+, base peak), 190, 162, 147, 135, 119, 107, 92, 77, 64; ir (potassium bromide): cm^{-1} 3100, 1785, 1650, 1600, 1555.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.60; H, 4.48.

4-(2-Methoxybenzoyl)-3-hydroxy-2(5*H*)-furanone (**1f**).

This compound was obtained in 53% yield (13.6 g), mp 109-110° (2-propanol); ^{1}H-nmr (300 MHz, deuteriochloroform): δ 3.90 (s, 3H), 5.03 (s, 2H), 6.99-7.11 (m, 2H), 7.45-7.58 (m, 2H), 9.1 (br s, 1H, deuterium oxide exchangeable); ms: m/z 234 (M^+), 190, 162, 147, 135 (base peak), 121, 105, 92, 77; ir (potassium bromide): cm^{-1} 3500, 3000, 1780, 1640, 1600, 1490.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.54; H, 4.30. Found: C, 61.31; H, 4.42.

4-(4-Bromobenzoyl)-3-hydroxy-2(5*H*)-furanone (**1g**).

This compound was obtained in 18% yield (5.6 g), mp 150-151° (2-propanol); ^{1}H-nmr (300 MHz, 10% DMSO-d_6/deuteriochloroform): δ 5.08 (s, 2H), 7.61 (d, J = 7.8 Hz, 2H), 7.72 (d, J = 7.8 Hz, 2H), 9.5 (br s, 1H, deuterium oxide exchangeable); ms: m/z 284, 282 (M^+ + 2, M^+), 240, 238, 212, 210 (base peak), 185, 183, 157, 155, 131, 103, 76; ir (potassium bromide): cm^{-1} 3280, 1795, 1750, 1660, 1630, 1590.

Anal. Calcd. for $C_{11}H_7BrO_4$: C, 46.67; H, 2.49; Br, 28.23. Found: C, 46.87; H, 2.60; Br, 28.41.

4-(3-Bromobenzoyl)-3-hydroxy-2(5*H*)-furanone (**1h**).

This compound was obtained in 29% yield (9.1 g), mp 151-152° (2-propanol); ^{1}H-nmr (300 MHz, 10% DMSO-d_6/deuteriochloroform): δ 5.06 (s, 2H), 7.37 (t, J = 7.8 Hz, 1H), 7.70 (dt, J = 7.8; 1.2 Hz, 1H), 7.82 (dt, J = 7.8; 1.2 Hz, 1H), 7.98 (t, J = 1.2, 1H), 10.00 (br s, 1H, deuterium oxide exchangeable); ms: m/z 284, 282 (M^+ + 2, M^+), 240, 238, 212, 210 (base peak), 185, 183, 157, 155, 131, 103; ir (potassium bromide): cm^{-1} 3090, 1785, 1650, 1585, 1560.

Anal. Calcd. for $C_{11}H_7BrO_4$: C, 46.67; H, 2.49; Br, 28.23. Found: C, 46.58; H, 2.56; Br, 28.06.

4-(2-Bromobenzoyl)-3-hydroxy-2(5*H*)-furanone (**1i**).

This compound was obtained in 36% yield (11.2 g) mp 126.127° (toluene); ^{1}H-nmr (300 MHz, 10% DMSO-d_6/deuteriochloroform): δ 5.03 (s, 2H), 7.29-7.42 (m, 3H), 7.58 (d, 1H, J = 8.1 Hz), 10.9 (br s, 1H, deuterium oxide exchangeable); ms: m/z 284, 282 (M^+ + 2, M^+), 239, 237, 212, 210, 203 (base peak), 185, 183, 159, 157, 155, 131, 103; ir (potassium bromide): cm^{-1} 3440, 1780, 1690, 1620, 1595.

Anal. Calcd. for $C_{11}H_7BrO_4$: C, 46.67; H, 2.49; Br, 28.23. Found: C, 46.75; H, 2.51; Br, 28.24.

4-(3-Chlorobenzoyl)-3-hydroxy-2(5*H*)-furanone (**1k**).

This compound was obtained in 21% yield (5.5 g), mp 165-166° (2-propanol); ^{1}H-nmr (300 MHz, 10% DMSO-d_6/deuteriochloroform): δ 5.07 (s, 2H), 7.41 (t, J = 8.1 Hz, 1H), 7.53 (dt, J = 8.1, 1.5 Hz, 1H), 7.79 (s, 1H), 7.82 (dt, J = 8.1, 1.5 Hz, 1H), 10.6 (br s, 1H, deuterium oxide exchangeable); ms: m/z 240, 238 (M^+ + 2, M^+), 194, 166 (base peak), 139, 103; ir (potassium bromide): cm^{-1} 3200, 1780, 1655, 1600, 1590, 1570.

Anal. Calcd. for $C_{11}H_7ClO_4$: C, 55.37; H, 2.95; Cl, 14.86. Found: C, 55.32; H, 3.01; Cl, 14.71.

4-(2-Chlorobenzoyl)-3-hydroxy-2(5*H*)-furanone (**1l**).

This compound was obtained in 50% yield (13.2 g), mp 137-138° (toluene); ^{1}H-nmr (300 MHz, 10% DMSO-d_6/deuteriochloroform): δ 5.02 (s, 2H), 7.29-7.40 (m, 4H), 11.3 (br s, 1H, deuterium oxide exchangeable); ms: m/z 240, 238 (M^+ + 2, M^+), 203, 166, 139 (base peak), 131, 111, 103; ir (potassium bromide): cm^{-1} 3240, 1780, 1690, 1620, 1600.

Anal. Calcd. for $C_{11}H_7ClO_4$: C, 55.37; H, 2.95; Cl, 14.86. Found: C, 55.26; H, 2.88; Cl, 14.69.

4-(3-Hydroxybenzoyl)-3-hydroxy-2(5*H*)-furanone (**1n**).

This compound was obtained in 12% yield (2.9 g), mp 166° (2-propanol); ^{1}H-nmr (300 MHz, DMSO-d_6): δ 5.04 (s, 2H), 7.03 (m, 1H), 7.21 (s, 1H), 7.27-7.35 (m, 2H), 9.7 (br s, 2H, deuterium oxide exchangeable); ir (potassium bromide): cm^{-1} 3300, 1750, 1650, 1600, 1580.

Anal. Calcd. for $C_{11}H_8O_5$: C, 60.01; H, 3.66. Found: C, 59.87; H, 3.69.

4-(3-Nitrobenzoyl)-3-hydroxy-2(5*H*)-furanone (**1q**).

This compound was obtained in 19% yield (5.2 g), mp 172-173° (methanol); ^{1}H-nmr (300 MHz, 10% DMSO-d_6/deuteriochloroform): δ 5.09 (s, 2H), 7.70 (t, J = 7.8 Hz, 1H), 8.22 (dd, J = 7.8, 1.8 Hz, 1H), 8.39 (dd, J = 7.8, 1.8 Hz, 1H), 8.68 (s, 1H), 19.3 (br s, 1H, deuterium oxide exchangeable); ms: m/z 249 (M^+), 205, 177 (base peak), 150, 132, 104; ir (potassium bromide): cm^{-1} 3280, 1770, 1680, 1650, 1535.

Anal. Calcd. for $C_{11}H_7NO_6$: C, 53.02; H, 2.83; N, 5.62. Found: C, 52.92; H, 3.10; N, 5.54.

4-(2-Nitrobenzoyl)-3-hydroxy-2(5*H*)-furanone (**1r**).

This compound was obtained in 12% yield (3.3 g), mp 158-159° (ethanol); ^{1}H-nmr (300 MHz, DMSO-d_6: δ 5.08 (s, 2H), 7.62 (dd, J = 9.3, 1.05 Hz, 1H), 7.78 (t, J = 9.3 Hz, 1H), 7.91 (m, 1H), 8.24 (d, J = 8.1 Hz, 1H), 12.00 (br s, 1H deuterium oxide exchangeable): ms: m/z 249 (M^+), 162, 150, 143 (base peak), 121, 104; ir (potassium bromide): cm^{-1} 3270, 1770, 1695, 1660, 1530.

Anal. Calcd. for $C_{11}H_7NO_6$: C, 53.02; H, 2.83; N, 5.62. Found: C, 52.89; H, 3.00; N, 5.49.

4-(4-Cyanobenzoyl)-3-hydroxy-2(5*H*)-furanone (**1s**).

This compound was obtained in 15% yield (3.8 g), mp 108-109° (2-propanol); ^{1}H-nmr (300 MHz, 10% DMSO-d_6/deuteriochloroform): δ 5.07 (s, 2H), 5.89 (br s, 1H, deuterium oxide exchangeable), 7.79 (d, J = 8.1 Hz, 2H), 7.97 (d, J = 8.1 Hz, 2H); ms: m/z 229 (M^+), 185, 172, 157 (base peak), 130, 102; ir (potassium bromide): cm^{-1} 3200, 2240, 1780, 1680, 1625; hrms: m/z 229.0367 (M^+, Calcd. for $C_{12}H_7NO_4$ 229.0375).

4-(3-Cyanobenzoyl)-3-hydroxy-2(5*H*)-furanone (**1t**).

This compound was obtained in 19% yield (4.8 g), mp 163-164° (2-propanol); ^{1}H-nmr (300 MHz, 10% DMSO-d_6/deuteriochloroform): δ 5.08 (s, 2H), 7.63 (m, 1H), 7.77 (m, 1H), 8.12 (m, 1H), 8.18 (m, 1H), 9.10 (br s, 1H, deuterium oxide exchangeable); ms: m/z 229 (M^+), 185, 157 (base peak), 130, 102; ir (potassium bromide): cm^{-1} 3210, 3080, 2240, 1780, 1660, 1570.

Anal. Calcd. for $C_{12}H_7NO_4$: C, 62.89; H, 3.06; N, 6.11. Found: C, 62.76; H, 3.01; N, 5.94.

4-{1-[*N*-(2-Hydroxyphenyl)amino]substituted benzal}-2,3(5*H*)-furandione (**12**). General Procedure.

To a solution of **9** (1.96 g, 18 mmoles) in ethanol (100 ml) was added a hot ethanolic (60 ml) solution of the appropriately substituted furanone **1** (18 mmoles) and the mixture stirred at room temperature for 4 days. The solvent was evaporated and the gummy product was triturated with ether. The thus obtained solid

was filtered off and dried.

4-{1-[*N*-(2-Hydroxyphenyl)amino]benzal}-2,3(5*H*)-furandiones (**12a**).

This compound was obtained in 51% (2.71 g) as a bright red crystalline solid which turns to yellow powder upon drying, mp 202° (methanol); ^{1}H-nmr (250 MHz, DMSO-d_6): δ 4.88 (s, 2H), 6.46, 6.95, 7.49 (m, s, m, 9H), 10.52, 12.54 (2s, 2H, deuterium oxide exchangeable); ^{13}C-nmr (62.9 MHz, DMSO-d_6): δ 65.82, 105.95, 115.94, 118.77, 123.66, 124.76, 127.08, 127.59, 129.19, 130.62, 130.83, 149.82, 159.66, 166.66, 172.10; ms: m/z 295 (M^+), 277, 195 (base peak), 167, 115, 77; ir (potassium bromide): cm^{-1} 3428, 2134, 1769, 1617.

Anal. Calcd. for $C_{17}H_{13}NO_4$: C, 69.15; H, 4.44; N, 4.74. Found: C, 69.25; H, 4.51; N, 4.80.

4-{1-[*N*-(2-Hydroxyphenyl)amino]-4-chlorobenzal}-2,3(5*H*)-furandione (**12b**).

This compound was obtained in 53% (3.15 g), mp 217-218° (methanol); ^{1}H-nmr (250 MHz, DMSO-d_6): δ 4.90 (s, 2H), 6.55, 6.95, 7.46, 7.56 (m, m, d, d, 8H), 10.52, 12.43 (2s, 2H, deuterium oxide exchangeable); ^{13}C-nmr (62.9 MHz, DMSO-d_6): δ 65.73, 105.9, 115.99, 118.86, 124.04, 124.51, 127.30, 129.28, 129.40, 129.73, 135.54, 149.95, 158.60, 166.46, 172.25; ir (potassium bromide): cm^{-1} 3422, 3072, 1766, 1625.

Anal. Calcd. for $C_{17}H_{12}ClNO_4$: C, 61.92; H, 3.67. Found: C, 62.03; H, 3.56.

4-{1-[*N*-(2-Hydroxyphenyl)amino]-4-methylbenzal}-2,3(5*H*)-furandione (**12c**).

This compound was obtained in 30% (1.67 g), mp 230-231° (methanol); ^{1}H-nmr (250 MHz, DMSO-d_6): δ 2.35 (2, 3H), 4.90 (s, 2H), 6.47, 6.95, 7.30 (m, s, s, 8H), 10.50, 12.53 (2s, 2H, deuterium oxide exchangeable); ^{13}C-nmr (62.9 MHz, DMSO-d_6): δ 20.93, 65.86, 106.00, 115.93, 118.78, 123.75, 124.81, 127.03, 127.59, 129.74, 140.80, 149.84, 159.92, 166.76, 171.86; ms: m/z 309 (M^+), 210, 209 (base peak), 208; ir (potassium bromide): cm^{-1} 3422, 3072, 1766, 1625.

Anal. Calcd. for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89. Found: 69.73; H, 5.01.

Pyrolysis of **12**. General Procedure.

A mixture of **12** (0.1 g) in quinoline (1 ml) was heated under reflux for 3 hours. The reaction mixture was chromatographed through a silica gel Ptlc using chloroform as eluent and the corresponding 2-substituted benzoxazole **13** was obtained. Its structure was confirmed by gc-ms and comparison of its melting point with the reported one in the literature [11,12].

4-[1-(*N*-Phenylamino)benzal]-2,3(5*H*)-furandione (**15**).

To a methanolic solution (100 ml) of **1a** (2.04 g, 10 mmoles) was added dropwise aniline (0.93 g, 10 mmoles) and refluxed overnight. After evaporating to half its volume it was chilled and the solid was filtered and dried, 51% yield (1.43 g), mp 215-218° (methanol); ^{1}H-nmr (300 MHz, DMSO-d_6): δ 4.91 (s, 2H), 6.9-7.5 (m, 10H), 10.1 (br s, 1H, deuterium oxide exchangeable); ^{13}C-nmr (75.5 MHz, DMSO-d_6): δ 65.98 (t), 105.97 (s), 119.19 (d), 124.04 (s), 126.25 (d), 128.17 (d), 129.12 (d), 130.32 (s), 130.93 (d), 137.21 (s), 160.19 (s), 166.47 (s), 172.51 (s); ms: m/z 279 (M^+), 206 (base peak), 180, 130, 77; ir (potassium bromide): cm^{-1} 3433, 1774, 1636, 1566.

Anal. Calcd. for $C_{17}H_{13}NO_3$: C, 73.12; H, 4.66; N, 5.02. Found: C, 72.90; H, 4.80; N, 5.26.

Phenylammonium 4-benzoyl-2(5*H*)-furanone 3-Oxide (**16**).

To a solution of **1** (1.02 g, 5 mmoles) in chloroform (75 ml) was added aniline (0.47 g, 5 mmoles) and the reaction mixture stirred at room temperature. After standing overnight, a solid was collected and dried, 45% yield (0.67 g), mp 122-123°; ^{1}H-nmr (300 MHz, DMSO-d_6): δ 5.04 (s, 2H), 6.55 (m, 3H); 6.98 (m, 2H), 7.21 (br s, 3H), 7.45 (m, 3H), 7.78 (d, J = 7.2 Hz, 2H); ^{13}C-nmr (75.5 MHz, DMSO-d_6): δ 68.13 (t), 115.44 (d), 117.69 (d), 119.37 (s), 128.16 (d), 128.89 (d), 132.66 (d), 137.67 (s), 146.04 (s), 147.18 (s), 170.64 (s), 189.00 (s); ir (potassium bromide): cm^{-1} 3000, 2550, 1760, 1635, 1600, 1580.

Anal. Calcd. for $C_{17}H_{15}NO_4$: C, 68.69; H, 5.05; N, 4.71. Found: C, 68.68; H, 5.15; N, 4.50.

(2-Aminophenyl)ammonium 4-(4-nitrobenzoyl)-2(5*H*)-furan 3-Oxide (**17b**).

To a solution of **1p** (0.5 g, 2 mmoles) in chloroform (30 ml) was added dropwise a solution of **7** (0.22 g, 2 mmoles) in chloroform (10 ml) and stirred at room temperature. After standing overnight, a solid was collected and dried, 56% yield (0.4 g), mp 127-132° dec; ^{1}H-nmr (250 MHz, DMSO-d_6): δ 4.98 (s, 2H), 6.10 (br s, 5H), 6.72 (2m, 2H), 6.84 (m, 2H), 8.07 (d, J = 8.53 Hz, 2H), 8.23 (d, J = 8.53 Hz, 2H); ^{13}C-nmr (62.9 MHz, DMSO-d_6): δ 67.84, 111.60, 118.58, 121.13, 122.66, 129.62, 130.92, 144.76, 148.36, 156.41, 172.4, 184.72.

Anal. Calcd. for $C_{17}H_{15}N_3O_6$: C, 57.14; H, 4.23. Found: C, 56.97; H, 4.25.

(2-Aminophenyl)ammonium 4-(4-cyanobenzoyl)-2(5*H*)-furan 3-Oxide (**17c**).

The procedure was the same as above using **1t** instead of **1p**, 63% yield (0.4 g), mp 142-145° dec; ^{1}H-nmr (250 MHz, DMSO-d_6): δ 4.96 (s, 2H), 5.61 (br s, 5H), 6.70 (m, 2H), 6.82 (m, 2H), 7.87 (d, J = 8.33 Hz, 2H), 8.03 (d, J = 8.33 Hz, 2H); ^{13}C-nmr (62.9 MHz, DMSO-d_6): δ 67.93, 112.00, 112.95, 118.64, 121.18, 192.11, 131.00, 131.55, 142.95, 155.79, 172.48, 185.30.

Anal. Calcd. for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48. Found: C, 63.89; H, 4.65.

REFERENCES AND NOTES

[1] This is part **39** of the series Substituted γ-Butyrolactones; for Part **38** of this series see: reference 6.

[2] Ph.D. Thesis, University of Cincinnati, 1989.

[3] Taken as Part **8** of Synthetic Reactions and Structural Studies of Heterocycles Containing Nitrogen, for Part **7** of this series see: A. Amer and D. Ho, *Z. Naturforsch.*, **47b**, 000 (1992).

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