Synthesis and Reactions of 3-Aroyl Derivatives of 4-Hydroxy-2-quinolones and 4-Hydroxycoumarin

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Dedicated to the memory of Nicholas Alexandrou

3-Aroyl-4-hydroxy-2-quinolones **4** and **11** can be synthesized starting with **1** or **9** *via* Fries rearrangement of the corresponding esters **3** and **10**, catalyzed by potassium cyanide and 18-crown-6. A one pot procedure is presented in which the esters do not need to be isolated. Reduction of the aryl ketones **4** and **11** with zinc dust leads to the benzyl derivatives **5** and **12**. Reaction of the aryl ketones **4** and **11** with hydroxylamine and subsequent heating of the crude product leads *via* thermal Beckmann rearrangement and dehydration to oxazoloquinolones **7** and **14**. 2-Aroyloxypyrido[1,2-*a*]pyrimidin-4-ones **17** and **20** could not be converted to the corresponding ketones by Fries rearrangement.

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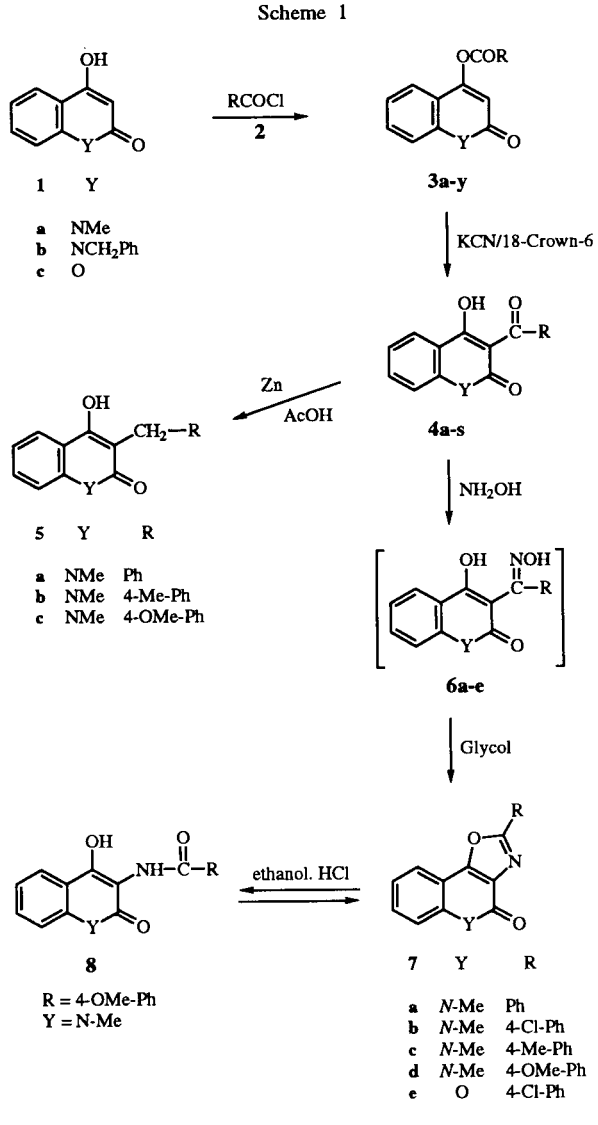
Cyclic tricarbonylmethane compounds, whether carbocyclic or heterocyclic, are an important class of natural products. Moreover, some of their synthetic derivatives play an important part in agrochemistry [1]. Thus oximated derivatives of aliphatic acyl cyclohexanediones (but *e.g.* also of 3-acyl-4-hydroxypyrones) show pronounced herbicidal activity. From this series of compounds some substances, such as "Alloxydim" ® and "Sethoxydim" ® were commercialized around 1980. More recently 2-benzoylcyclohexane-1,3-diones which are not oximated but have a characteristic substitution pattern at the aromatic nucleus have been shown to exhibit very potent herbicidal activity [1,2]. This has encouraged us to synthesize some 3-aroyl derivatives of 4-hydroxy-2(1*H*)quinolones and 4-hydroxycoumarins.

In recent years we have developed an easy entrance to the field of aliphatic 3-acyl derivatives in this series of heterocycles by ringopening of pyrono derivatives [3,4]. Also the well known Klosa-Ziegler acylation techniques (using the free acids and phosphoryl chloride) can be used for the synthesis of these types of compounds [5,6]. Unfortunately, 3-aroyl derivatives are not available by these methods. Therefore we have tried the Fries rearrangement of the corresponding 4-aroyloxy derivatives **3** and **10**, which in turn are easily obtained from 4-hydroxy-2(1*H*)quinolones **1a,b**, **9** and 4-hydroxycoumarin (**1c**), Schemes 1 and 2, see also Table 1 and 3. Two methods have been used for the preparations of esters **3** and **10**. Method A consists in reacting two equivalents of the acid chlorides **2** just in sodium carbonate solution. However, under these conditions some of the acid chlorides are also hydrolyzed back to the free acids. Since some of the acid chlorides **2** are quite expensive the preferred mode of synthesis uses only a small excess (20%) of **2** in dry toluene with one equivalent of triethylamine as base (Method B). This method is also advantageous since it allows a one pot reaction sequence to **4** and **11**, as shown in the next paragraph.

The "classical" Fries rearrangement using aluminum trichloride (Method A) works well only with the unsubstituted benzoyloxy derivatives, see Tables 2 and 4.

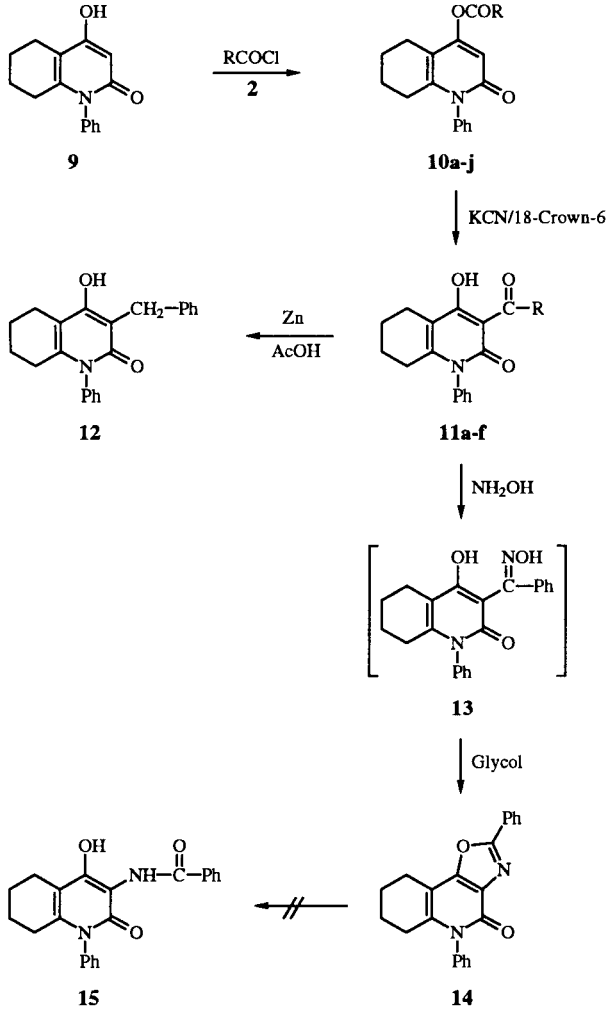
Scheme 1



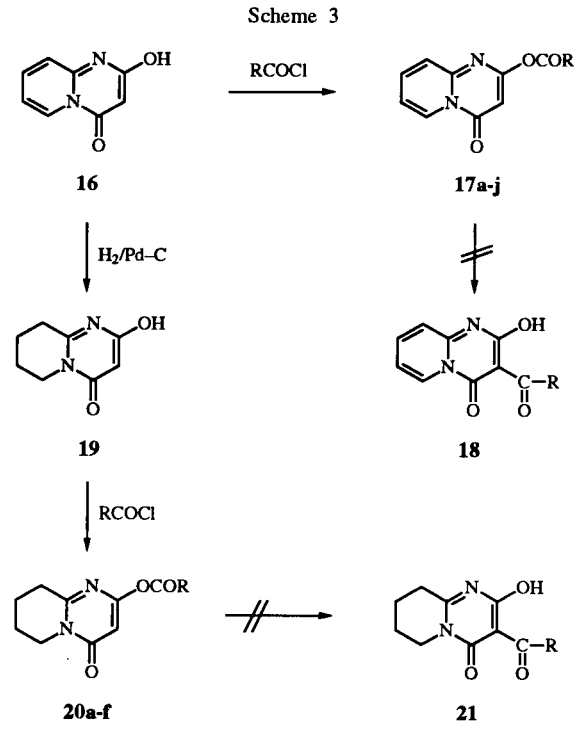
However, the use of potassium cyanide, (2 equivalents), triethylamine (1 equivalent), and a catalytic amount of 18-crown-6 in toluene as the solvent gave the rearranged compounds **4** and **11** in good yields (Method C, see Tables 2 and 4). As already mentioned, the mode of the ester preparation using **2** and triethylamine in toluene allows a one post preparation of the rearranged products **4** and **11** if after completion of the esterification potassium cyanide and 18-crown-6 catalyst is added (Method B). Inspection of Tables 2 and 4 reveals that most of the ketones have been prepared by this method.

The use of acetone cyanohydrine (as the source of cyanide anion) in the presence of triethylamine in acetonitrile has been used in the Fries rearrangement of *e.g.* 1-acyloxycyclohex-1-ene-3-ones [7]. This procedure did not work with our substrates. Potassium cyanide and 18-crown-6 had to be present and the use of acetonitrile as solvent led in our cases to a number of side products. The

Scheme 2



Scheme 3



mechanism of this reaction is still not resolved. It may be assumed that under the reaction conditions small amounts of aroylnitriles and the anion of the heterocycle are generated and that these two intermediates give the thermodynamically more stable *C*-acylated compounds [8,9].

Recently [10], we have shown that aliphatic 3-acyl-4-hydroxy-2-quinolones, 2-pyridones [3,4], coumarins [5,6], and 2-pyrones can be easily reduced with zinc powder (particle size <45 μm) in acetic acid/hydrochloric acid to the corresponding 3-alkyl derivatives [10]. Thus the well known "dehydroacetic acid" (3-acetyl-4-hydroxy-6-methyl-2-pyrone) yields under these conditions 3-ethyl-4-hydroxy-6-methyl-2-pyrone. Using the same reaction conditions the 3-aroyl derivatives **4a,f,g** and **11a** give the 3-benzyl derivatives **5a-c** and **12**, respectively. This synthetic route to 3-benzyl-4-hydroxy-2-quinolones seems to be advantageous to the general method [11] when the corresponding diethyl benzylmalonates are not readily available.

The importance of oximated derivatives of cyclic tricarbonyl systems has been pointed out in the introduction. Most recently, we have prepared a number of oximes and their *O*-alkyl derivatives from 4-hydroxy-2-quinolones with an aliphatic acyl side chain in position **3** [12]. Here we describe the reaction of their aromatic counterparts **4** and **11** with hydroxylamine. However, the reaction products **6a-e** and **13** were mixtures of *E/Z* isomers which could not satisfactorily be separated. Therefore, we transformed this mixtures directly *via* thermal Beckmann rearrangement in boiling ethylene glycol to the oxazolo derivatives **7a-e** and **14**. It is interesting to note that the

Table 1

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

No	Y	R	Method/ Yield (%)	Mp (°C) (Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
3a	NMe	Ph	A/90 B/90	173-174 [a] (Ethanol)				
3b	NMe	4-Cl-Ph	A/91 B/88	166-169 (Ethanol)	$C_{17}H_{12}ClNO_3$	65.08 65.25	3.86 3.92	4.46 4.34
3c	NMe	2-Cl-Ph	A/68	137-138 (1-Butanol)	$C_{17}H_{12}ClNO_3$	65 08 64.90	3.86 3.96	4.46 4.26
3d	NMe	2-Br-Ph	A/59	112-113 (Toluene)	$C_{17}H_{12}BrNO_3$	57.00 56.63	3.38 3.59	3.91 3.88
3e	NMe	4-Cl-2-NO_2-Ph	A/61	177-178 (Toluene)	$C_{17}H_{11}ClN_2O_5$	56.91 56.72	3.07 3.22	7.81 7.70
3f	NMe	4-Me-Ph	B/60	182-183 (Ethanol)	$C_{18}H_{15}NO_3$	73.70 73.60	5.15 5.16	4.77 4.74
3g	NMe	4-OMe-Ph	B/76	169-174 (Ethanol)	$C_{18}H_{15}NO_4$	69.89 69.50	4.89 4.90	4.53 4.33
3h	NMe	2,4-Di-Cl-Ph	B/77	155-158 (Toluene)	$C_{17}H_{11}Cl_2NO_3$	58.64 58.69	3.19 3.33	4.02 4.12
3i	NMe	2,3-Di-Cl-4-SO_2Me-Ph	B/82	254-256 (DMF)	$C_{18}H_{13}Cl_2NO_5S$	50.71 50.66	3.07 3.16	3.29 3.24
3j	NMe	2-Me-Ph	B/51	133-135 (Ethanol)	$C_{18}H_{15}NO_3$	73.70 73.92	5.15 5.10	4.77 4.77
3k	NMe	2-Me-3-OMe-4-SO_2Me-Ph	A/50	190-195 (Ethanol)	$C_{20}H_{19}NO_6S$	59.84 58.59	4.77 4.81	3.49 3.21
3l	NMe	2-Thienyl	A/80 B/84	152-155 (Ethanol)	$C_{15}H_{11}NO_3S$	63.14 63.07	3.89 3.81	4.91 4.75
3m	NMe	3-Pyridyl	B/79	159-161 (Methanol)	$C_{16}H_{12}N_2O_3$	68.56 68.75	4.32 4.34	10.00 10.08
3n	NCH_2Ph	Ph	B/37	150-152 (Ethanol)	$C_{23}H_{17}NO_3$	77.73 77.81	4.82 4.88	3.94 3.87
3o	NCH_2Ph	4-Cl-Ph	B/31	176-180 (Ethanol)	$C_{23}H_{16}ClNO_3$	70.86 70.90	4.14 4.19	3.59 3.53
3p	NCH_2Ph	2-Cl-Ph	B/41	182-183 (Ethanol)	$C_{23}H_{16}ClNO_3$	70.86 70.81	4.14 4.38	3.59 3.51
3q	NCH_2Ph	2-Me-Ph	B/23	131-134 (Ethanol)	$C_{24}H_{19}NO_3$	78.03 78.27	5.18 5.15	3.80 3.75
3r	O	Ph	B/76	128-131 (Ethanol)	$C_{16}H_{10}O_4$	72.17 72.05	3.79 3.82	— —
3s	O	4-Cl-Ph	B/98	174-176 (Ethanol)	$C_{16}H_9ClO_4$	63.91 63.73	3.02 3.15	— —
3t	O	2-Cl-Ph	A/26 B/72	125-127 (Ethanol)	$C_{16}H_9ClO_4$	63.91 63.79	3.02 3.20	— —
3u	O	2-Br-Ph	A/40 B/72	145-146 (Ethanol)	$C_{16}H_9BrO_4$	55.67 55.28	2.63 2.70	— —
3v	O	4-Me-Ph	B/78	132-136 (Ethanol)	$C_{17}H_{12}O_4$	72.85 72.87	4.32 4.45	— —
3w	O	4-OMe-Ph	B/72	155-156 (Ethanol)	$C_{17}H_{12}O_5$	68.91 68.51	4.08 4.35	— —
3x	O	2,4-Di-Cl-Ph	B/88	135-137 (Ethanol)	$C_{16}H_8Cl_2O_4$	57.34 57.22	2.41 2.57	— —
3y	O	4-Cl-2-NO_2-Ph	A/58	153-154 (Ethanol)	$C_{16}H_8ClNO_6$	55.59 55.38	2.33 2.42	4.05 3.98

[a] Lit [21] mp 178-180°.

dehydration of this type of oximes does not lead to the corresponding isoxazoles. However, the corresponding isoxazoles can obtained by thermolysis of 3-acyl-4-azido derivatives, as has been shown recently by Stadlbauer [13]. It is also interesting to note that compounds **7a-d** (though having a rather complex structure) have been described in the literature [14], their synthesis started with the 3-amino derivative. The reaction sequence described here, using the thermal Beckmann rearrangement, represents another route to protected 3-amino-4-hydroxy-2-quinolones. This is a rather unstable class of compounds, however, their salts with inorganic acids and their acylated derivatives are stable compounds. Usually the aliphatic 3-acylamino derivatives are readily obtained by

Table 2

Experimental, Physical and Analytical Data of Compounds **4**

No	Y	R	Method/ Yield (%)	Mp (°C) (Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
4a	NMe	Ph	A/94	174-176 (Ethanol)	$C_{17}H_{13}NO_3$	73.12 73.11	4.66 4.71	5.02 5.00
4b	NMe	4-Cl-Ph	B/64 C/76	201-203 (Toluene)	$C_{17}H_{12}ClNO_3$	65.08 65.32	3.86 4.15	4.46 4.70
4c	NMe	2-Cl-Me	B/77 C/74	199 200 (Ethanol)	$C_{17}H_{12}ClNO_3$	65.08 65.16	3.86 3.99	4.46 4.38
4d	NMe	2-Br-Ph	B/66	183-184 (Ethanol)	$C_{17}H_{12}BrNO_3$	57.00 56.65	3.38 3.57	3.91 3.89
4e	NMe	4-Cl-2-NO_2-Ph	B/46	284-287 (Toluene)	$C_{17}H_{11}ClN_2O_5$	56.91 57.30	3.07 3.32	7.81 7.51
4f	NMe	4Me-Ph	B/83 C/85	175-177 (Ethanol)	$C_{18}H_{15}NO_3$	73.70 73.54	5.15 5.13	4.77 4.68
4g	NMe	4-OMe-Ph	B/80	196-197 (Ethanol)	$C_{18}H_{15}NO_4$	69.89 69.71	4.89 4.92	4.53 4.52
4h	NMe	2,4-Di-Cl-Ph	B/86	262-267 (Ethanol)	$C_{17}H_{11}Cl_2NO_3$	58.64 58.52	3.19 3.35	4.02 3.94
4i	NMe	2,3-Di-Cl-SO_2Me-Ph	B/83	217-219 (Toluene)	$C_{18}H_{13}Cl_2NO_5S$	50.71 50.67	3.07 3.58	3.29 3.19
4j	NMe	2-Me-Ph	B/43	192-195 (Methanol)	$C_{18}H_{15}NO_3$	73.70 73.90	5.15 5.21	4.77 4.66
4k	NMe	2-Me-3-OMe-4-SO_2Me-Ph	B/55	209-211 (Ethanol)	$C_{20}H_{19}NO_6S$	59.84 59 38	4.77 4.86	3.49 3.41
4l	NMe	2-Thienyl	B/77	167-169 (Ethanol)	$C_{15}H_{11}NO_3S$	63.14 63.08	3.89 4.07	4.91 4.93
4m	NCH_2Ph	Ph	C/66	133-135 (Ethanol)	$C_{23}H_{17}NO_3$	77.73 77.58	4.82 5.09	3.94 3.84
4n	NCH_2Ph	2-Cl-Ph	C/30	174-176 (Ethanol)	$C_{23}H_{16}ClNO_3$	70.86 70.46	4.14 4.37	3.59 3.63
4o	O	Ph	A/65	148-151 (Ethanol)	$C_{16}H_{10}O_4$	72.17 72.01	3.79 3.98	— —
4p	O	4-Cl-Ph	B/79	181-185 (Ethanol)	$C_{16}H_9ClO_4$	63.91 63.59	3.02 3.05	— —
4q	O	2-Cl-Ph	B/44	131-134 (Ethanol)	$C_{16}H_9ClO_4$	63.91 63.98	3.02 3.15	— —
4r	O	2-Br-Ph	B/37	208-211 (Ethanol)	$C_{16}H_9BrO_4$	55.67 55.41	2.63 2.80	— —
4s	O	4-Me-Ph	B/67 C/56	182-185 (Ethanol)	$C_{17}H_{12}O_4$	72.85 73.00	4.32 4.59	— —

hydrolysis of the 2-alkylisoxazoloquinolones [12]. In the aromatic series the hydrolysis can not be stopped as easily at the aroylamino stage. However, compound **8** was obtained in 54% yield by hydrolysis of **7d** with diluted hydrochloric acid. The reverse reaction, the cyclization of of **8** to **7d** by dehydration with hot polyphosphoric acid, has recently been described [14].

"Malonyl-α-aminopyridin" **16**, first described by Chichibabin in 1924 [15], represents also a bicyclic malonyl heterocyclic system and is available on a large scale. Catalytic reduction of **16** by a method [16] recently described by us for zwitterionic derivatives leads in high yield to the tetrahydro derivative **19**. Also both compounds exist predominantly in their zwitterionic tautomer form [17], and can be alkylated under specific conditions at nitrogen to give the fixed zwitterionic derivatives [17,18], benzoylation under the conditions mentioned before occurs at the oxygen in postition 2 to yield the esters **17a-j** and **20a-j**, respectively, Scheme 3. This can be seen from their nmr spectra [19], thus the resonance signal of the proton in position 3 in **17** appear at 6.37-6.42 and those of **20** at 6.28-6.32 ppm. For a zwitterionic structure with its enolate structure this signal should be expected at about 4.5-5.0 ppm [16,20]. Unfortunately, none of the esters **17** and **20** could be rearranged to the desired *C*-aroyl derivatives **18** or **20**.

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 nmr was hexadeuteriodimethyl sulfoxide unless otherwise stated. Microanalyses were performed on a Carlo Erba 1106 Elemental

Table 3

Experimental, Physical and Analytical Data of Compounds **10**

No	R	Method/ Yield (%)	Mp (°C) (Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
10a	Ph	A/70	179-181	$C_{22}H_{19}NO_3$	76.50	5.54	4.06
		B/92	(Toluene)		76.54	5.57	3.94
10b	4-Cl-Ph	A/88	142-145	$C_{22}H_{18}ClNO_3$	69.56	4.76	3.69
		B/66	(Ethanol)		69.16	4.72	3.34
10c	2-Cl-Ph	A/82	160-165	$C_{22}H_{18}ClNO_3$	69.56	4.76	3.69
			(2-Propanol)		69.35	4.93	3.55
10d	2-Br-Ph	A/42	170-174	$C_{22}H_{18}BrNO_3$	62.27	4.27	3.30
		B/40	(Ethanol)		62.07	4.30	3.20
10e	4-Cl-2-NO_2-Ph	A/59	175-176	$C_{22}H_{17}ClN_2O_5$	62.20	4.00	6.60
		B/69	(Toluene)		62.10	4.10	6.45
10f	4-Me-Ph	B/48	174-178	$C_{23}H_{21}NO_3$	76.84	5.89	3.90
			(Ethanol)		76.76	5.89	3.95
10g	4-OMe-Ph	B/56	159-162	$C_{23}H_{21}NO_4$	73.58	5.64	3.73
			(Ethanol)		73.88	5.54	3.76
10h	2,3-Di-Cl-4-SO_2Me-Ph	B/66	262-264 (DMF)	$C_{23}H_{19}Cl_2NO_5S$	56.10	3.89	2.84
					55.78	4.01	2.84
10i	2-Me-3-OMe 4-SO_2Me-Ph	A/26	222-224	$C_{25}H_{25}NO_6S$	64.22	5.39	3.00
			(Toluene)		64.34	5.51	2.99
10j	2-Thienyl	A/53	189-192	$C_{20}H_{17}NO_3S$	68.35	4.88	3.99
			(Ethanol)		67.46	4.92	4.03

Table 4

Experimental, Physical and Analytical Data of Compounds **11**

No	R	Method/ Yield (%)	Mp (°C) (Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
11a	Ph	A/72	180-182	$C_{22}H_{15}NO_3$	76.50	5.54	4.06
			(Ligroin)		76.68	5.49	4.01
11b	4-ClPh	B/37	151-154	$C_{22}H_{18}ClNO_3$	69.56	4.76	3.69
		C/55	(Ethanol)		69.85	4.93	3.55
11c	2-Cl-Ph	B/63	187-190	$C_{22}H_{18}ClNO_3$	69.56	4.76	3.69
			(Ethanol)		69.80	4.94	3.70
11d	2-Br-Ph	B/40	194-197	$C_{22}H_{18}BrNO_3$	62.27	4.27	3.30
			(Ethanol)		62.05	4.47	3.34
11e	4-Cl-2-NO_2-Ph	B/50	188-190	$C_{22}H_{17}ClN_2O_5$	62.20	4.00	6.60
			(Toluene)		62.03	4.20	6.42
11f	2-Thienyl-	B/88	219-220	$C_{20}H_{17}NO_3S$	68.35	4.88	3.99
			(Ethanol)		68.32	4.91	3.92

analyzer. Infrared spectra were taken on a Perkin-Elmer 298 spectrophotometer in potassium bromide pellets. Common reagent-grade chemicals are either commercially available and were used without further purlfication 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 4-Benzoyloxy-2(1*H*)-quinolones **3a-q** and 4-Benzoyloxycoumarins **3r-y** and for 4-Benzoyloxy-1-phenyl-5,6,7,8-tetrahydro-2(1*H*)-quinolones **10a-j**.

Method A.

4-Hydroxy-2(1*H*)-quinolones **1a,b**, 4-hydroxycoumarin **1c**, or 4-hydroxy-1-phenyl-5,6,7,8-tetrahydro-2(1*H*)-quinolone **9** (0.01 mole), and the corresponding acid chloride **2** (0.02 mole) were stirred for 24 hours in aqueous sodium carbonate solution (16 g sodium carbonate decahydrate in 40 ml water). The product was filtered by suction, washed with water and dried.

Method B.

To a solution of 4-hydroxy-2(1*H*)-quinolones **1a,b**, 4-hydroxycoumarin (**1c**) or 4-hydroxy-1-phenyl-5,6,7,8-tetrahydro-2(1*H*)-quinolone (**9**) (0.01 mole) in dry toluene (50 ml) the corresponding acid chloride **2** (0.012 mole) and triethylamine (0.01 mole) were added. The solution was heated for 5 hours under reflux. After cooling to room temperature, 60-100 ml of methylenechloride was added and the mixture was washed several times with diluted hydrochloric acid in a separatory funnel. The organic phase was dried with sodium sulfate and the solvent removed by evaporation. For recrystallization of compounds **3n-o** treatment with activated carbon was necessary. For experimental, physical, and analytical data see Table 1 and 3.

General Procedure for the Synthesis of 3-Aroyl-4-hydroxy-2(1*H*)-quinolones **4a-n**, 3-Aroyl-4-hydroxycoumarins **4o-s** and for 3-Aroyl-4-hydroxy-1-phenyl-5,6,7,8-tetrahydro-2(1*H*)-quinolones **11a-f**.

Table 5

Physical and Analytical Data of Compounds **17**

No	R	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
17a	Ph	71	137-140 (Ethanol)	$C_{15}H_{10}N_2O_3$	67.66 67.85	3.79 3.89	10.52 10.48
17b	4-Cl-Ph	74	198-200 (Ethanol)	$C_{15}H_9ClN_2O_3$	59.91 59.95	3.02 3.11	9.32 9.25
17c	2-Cl-Ph	72	183-184 (Ethanol)	$C_{15}H_9ClN_2O_3$	59.91 59.74	3.02 3.19	9.32 9.27
17d	2-Br-Ph	54	174-177 (Ethanol)	$C_{15}H_9BrN_2O_3$	52.19 52.02	2.63 2.81	8.12 8.01
17e	4-Cl-2-NO_2-Ph	49	184-188 (Toluene)	$C_{15}H_8ClN_3O_5$	52.11 52.03	2.33 2.52	12.16 11.97
17f	4-Me-Ph	77	139-141 (Toluene)	$C_{16}H_{12}N_2O_3$	68.56 68.70	4.32 4.44	10.00 9.82
17g	4-OMe-Ph	53	160-162 (Ethanol)	$C_{16}H_{12}N_2O_4$	64.86 64.95	4.08 4.21	9.46 9.20
17h	2,4-Di-Cl-Ph	76	161-164 (Toluene)	$C_{15}H_8Cl_2N_2O_3$	53.75 53.61	2.41 2.53	8.36 8.08
17i	2-Me-Ph	80	139-141 (Toluene)	$C_{16}H_{12}N_2O_3$	68.56 68.65	4.32 4.42	10.00 9.95
17j	2-Thienyl	59	129-130 (Toluene)	$C_{13}H_8N_2O_3S$	57.34 57.17	2.96 3.04	10.30 10.09

Table 6

Physical and Analyticai Data of Compounds 20

No	R	Yield (%)	Mp (°C) (Solvent)	Formula	Analysis (%) Calcd./Found C	H	N
20a	2-Cl-Ph	69	138-141 (Ethanol)	$C_{15}H_{13}ClN_2O_3$	59.12 59.40	4.30 4.36	9.19 9.05
20b	2-Br-Ph	60	152-155 (Ethanol)	$C_{15}H_{13}BrN_2O_3$	51.59 51.59	3.75 3.91	8.02 7.94
20c	2,4-Di-Cl-Ph	56	98-101 (Petroleum ether)	$C_{15}H_{12}Cl_2N_2O_3$	53.11 53.31	3.56 3.92	8.26 8.12
20d	2-Me-3-OMe-4-SO_2Me-Ph	79	170-180 (2-Butanol)	$C_{18}H_{20}N_2O_3S$	55.09 55.31	5.14 5.00	7.14 7.32

Method A.

A mixture of 4-benzoyloxy-1-methyl-2(1*H*)-quinolone (**3a**), 4-benzoyloxycoumarin (**3r**) or 4-benzoyloxy-1-phenyl-5,6,7,8-tetrahydro-2(1*H*)-quinolone (**10a**) (0.01 mole) and aluminumchloride (0.02 mole) was heated for 1 hour to 130-140°. After cooling to 50° the melt is treated with diluted hydrochloric acid to obtain a precipitate, which is separated by suction, washed with water and dried.

Method B.

To a solution of 4-hydroxy-2(1*H*)-quinolone **1a,b**, 4-hydroxycoumarin (**1c**), or 4-hydroxy-1-phenyl-5,6,7,8-tetrahydro-2(1*H*)-quinolone (**9**) (0.01 mole) in dry toluene (50 ml), the corresponding acid chloride **2** (0.012 mole) and triethylamine (0.01 mole) were added. The solution was heated for 5 hours under reflux. After cooling to room temperature potassium cyanide (0.02 mole, 1.3 g), triethylamine (0.01 mole, 1.4 ml) and catalytic amounts (0.4-0.5 g) of 18-crown-6 were added. The reaction mixture was stirred for 72 hours at room temperature. At the end of the reaction, 60 ml of methylenechloride were added and the mixture was washed several times with diluted hydrochloric acid in a separatory funnel. The organic phase was dried with sodium sulfate and the solvent removed by evaporation.

Method C.

A mixture of 4-benzoyloxy-1-methyl-2(*H*)-quinolone **3a-q**, 4-benzoyloxycoumarin **3r-y**, or 4-benzoyloxy-1-phenyl-5,6,7,8-tetrahydro-2(*H*)-quinolone **10a-j** (0.01 mole), triethylamine (0.01 mole, 1.4 ml), potassium cyanide (0.02 mole, 1.36 g) and catalytic amounts of 18-crown-6 (400-500 mg) in dry toluene (60 ml) was stirred for 48 hours at room temperature. After addition of 70 ml of methylene chloride the reaction mixture was washed several times with diluted hydrochloric acid in a separatory funnel. The organic phase was dried with sodium sulfate and the solvent removed by evaporation. For experimental, physical, and analytical data see Table 2 and 4.

3-Benzyl-4-hydroxy-1-methyl-2(1*H*)-quinolone (**5a**).

A solution of 3-benzoyl-4-hydroxy-1-methyl-2(1*H*)-quinolone (**4a**) (0.01 mole, 2.80 g) in ethanol/water (120 ml, 1:2) and 3 ml of concentrated hydrochloric acid was heated to boiling, and then added 13 g of Zn-powder (MERCK No. 1.08789) in small portions (about 1 g each time). The hot solution was filtered and the solvent was removed to 20 ml by evaporation. The solution was then poured into 30 ml of ice-water, to yield a precipitate (1.91 g, 72%), mp 214-216° (ethanol, lit [22] mp 219-220°).

4-Hydroxy-1-methyl-3-(4-methylbenzyl)-2(1*H*)-quinolone (**5b**).

This compound was obtained in a yield of 79%, mp 226-230° (from ethanol); ir: ν 3600-2720, 1645, 1600, 1550 cm^{-1}, ^1H nmr: δ 2.24 (s, 3H, CH_3), 3.60 (s, 3H, NCH_3), 3.98 (s, 2H, CH_2), 7.00-7.34 (m, 5H, ArH), 7.45-7.65 (m, 2H, ArH), 8.04 (dd, J = 1.5 + 7 Hz, 1H, 5-H), 10.38 (s, 1H, OH).

Anal. Calcd. for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.07; H, 6.20; N, 4.84.

4-Hydroxy-3-(4-methoxybenzyl)-1-methyl-2(1*H*)-quinolone (**5c**).

This compound was obtained in a yield of 76%, mp 185° (ethanol); ir: ν 3500-2600, 1640, 1610, 1570, 1515 cm^{-1}; ^1H nmr: δ 3.60 (s, 3H, NCH_3), 3.70 (s, 3H, OCH_3), 3.93 (s, 2H, CH_2), 6.82 (d, J = 9 Hz, 2H, ArH), 7.16-7.32 (m, 3H, ArH), 7.44-7.67 (m, 2H, ArH), 8.04 (dd, J = 1.5 + 7 Hz, 1H, 5-H), 10.40 (s, 1H, OH).

Anal. Calcd. for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.80; N, 4.74. Found: C, 72.83; H, 5.67; N, 4.66.

5-Methyl-2-phenyl-oxazolo[4,5-*c*]quinolin-4(5*H*)-one (**7a**).

A solution of 3-benzoyl-4-hydroxy-1-methyl-2(1*H*)-quinolone (**4a**) (0.01 mole, 2.80 g), hydroxylamine hydrochloride (0.02 mole, 1.39 g) and sodium hydrogencarbonate (0.02 mole, 1.68 g) in ethanol/water (160 ml, 3:1) was heated for 2 hours under reflux. The reaction mixture is then poured into ice-water and the precipitate filtered after standing for 2-3 hours. The crude product **6a** was dried overnight and then heated in ethyleneglycol (30 ml) for 2 hours under reflux. After cooling **7a** precipitated (1.31 g, 47%), mp 197-200° (ethanol, lit [14] mp 199°).

2-(4-Chlorophenyl)-5-methyloxazolo[4,5-*a*]quinolin-4(5*H*)-one (**7b**).

This compound was obtained in a yield of 45% from **4b**, mp 265-268° (toluene, lit [14] mp 274°).

5-Methyl-2-(4-methylphenyl)oxazolo[4,5-*c*]quinolin-4(5*H*)-one (**7c**).

This compound was obtained in a yield of 55% from **4f**, mp 234-235° (ethanol, lit [14] mp 245°).

2-(4-Methoxyphenyl)-5-methyloxazolo[4,5-*c*]quinolin-4(5*H*)-one (**7d**).

This compound was obtained in a yield of 49% from **4g**, mp 234-236° (ethanol, lit [14] mp 224°).

2-(4-Chlorophenyl)oxazolo[4,5-*c*]coumarin (**7e**).

A solution of **4p** (0.01 mole, 3.0 g), hydroxylamine hydrochloride (0.02 mole, 1.39 g) and sodium hydrogencarbonate (0.02 mole, 1.68 g) in ethanol/water (150 ml, 2:1) was heated for 1 hour under reflux. The solvent was removed and the residue was solved in 30 ml of water and extracted with ethyl acetate. The organic phase was dried with sodium sulfate and the solvent removed by evaporation. The crude **6e** was heated in ethylene glycol (30 ml) for 2 hours under reflux. Ethanol was added to the cold reaction mixture and after standing for 5 days 0.70 g (23%) of **7e** precipitated, mp 187-191° (ethanol).

Anal. Calcd. for $C_{16}H_8ClNO_3$: C, 61.21; H, 4.04; N, 10.20. Found: C, 61.33; H, 4.19; N, 10.30.

4-Hydroxy-1-methyl-3-(4-methyoxybenzoyl)amino-2(1*H*)-quinolone (**8**).

A solution of **7d** (0.003 mole, 0.93 g) in 30 ml of ethanol and 20 ml of 6 *N* hydrochloric acid was heated for 1 hour under reflux. After cooling 0.53 g (54%) of **8** is precipitated, mp 192-195° (dimethylformamide); ir: ν 3650-3350, 3300, 3000-2850, 1640, 1607, 1594, 1565, 1535 cm^{-1}; ^1H nmr: δ 3.68 (s, 3H, NCH_3), 3.86 (s, 3H, OCH_3), 7.10 (d, J = 9 Hz, 2H, ArH), 7.35 (dd, J = 7 Hz, 1 Hz, ArH), 7.52-7.72 (m, 2H, ArH), 8.02 (d, J = 9 Hz, 3H, ArH), 9.58 (s, 1H, NH), 11.95 (s, 1H, OH).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.92; H, 4.52; N, 8.67.

3-Benzyl-4-hydroxy-1-phenyl-5,6,7,8-tetrahydro-2(1*H*)-quinolone (**12**).

As described for the synthesis of **5a** compound **11a** (0.005 mole, 1.70 g) yields 1.20 g (74%) of **12**, mp 256-258° (ethanol, lit [23] mp 259°).

2,5-Diphenyl-6,7,8,9-tetrahydrooxazolo[4,5-*c*]quinoline-4(5*H*)-one (**14**).

As described for the synthesis of **7a** compound **11a** (0.01 mole, 3.45 g) gives 2.0 g (58%) of **14**, mp 270-275° (ethanol); ir: ν 3500, 2940, 1690 s, 1610 m, 1555 cm^{-1}; ^1H nmr: δ 1.72 (s, 4H, H-7, H-8), 2.12 (s, 2H, H-6), 2.68 (s, 2H, H-9), 7.27-7.32 (m, 2H, ArH), 7.50-7.68 (m, 6H, ArH), 8.10-8.20 (m, 2H, ArH).

Anal. Calcd. for $C_{22}H_{18}N_2O_2$: C, 77.17; H, 5.30; N, 8.18. Found: C, 76.79; H, 5.38; N, 8.06.

General Procedure for the Synthesis of 2-Benzoyloxypyrido-[1,2-*a*]pyrimidin-4-ones **17a-j** and for the Synthesis of 2-Benzoyloxy-6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidin-4-ones **20a-d**.

To a solution of **16** or **19** (0.01 mole) in dry toluene (50 ml) the corresponding acid chloride **2** (0.012 mole) and triethylamine (0.01 mole) were added. The solution was heated for 5 hours under reflux. After cooling to room temperature 70 ml of methylene chloride was added and the organic phase was washed several times with diluted hydrochloric acid in a separatory funnel. The organic phase was dried with sodium sulfate and the solvent removed by evaporation. For physical and and analytical data see Tables 5 and 6.

2-Hydroxy-6,7,8,9-tetrahydropyrido[1,2-*a*]pyrimidin-4-one (**19**).

To a solution of 2-hydroxypyrido[1,2-*a*]pyrimidin-4-one (**16**) (0.05 mole, 8.10 g) in DMF (150 ml) was added 1.50 g of 10% palladium on charcoal catalyst. The mixture was hydrogenated for 72 hours at 80° and at pressure of about 5 bar. At the end of the reaction the mixture was heated for boiling, and while still hot filtered twice to remove the catalyst. After cooling **19** precipitated (5.00 g, 60%), mp 257-258° (dimethylformamide); ir: ν 3260-2400, 1700, 1665, 1585 cm^{-1}; ^1H nmr: δ 1.69-1.92 (m, 4H, H-7, H-8), 2.75 (t, J = 7 Hz, 2H, H-9), 3.70 (t, J = 7 Hz, 2H, H-6), 5.02 (s, 1H, H-3), 11.44 (s, 1H, OH) [24].

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.63; H, 6.22; N, 17.01.

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