Preparation of 1,2-Disubstituted-3-hydroxy-4(1*H*)-quinolinones and the Influence of Substitution on the Course of Cyclization

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Synthesis of 1,2-disubstituted-3-hydroxy-4(1*H*)-quinolinones by the cyclization of *N*-substituted phenacyl or acetonyl anthranilates is described. Two methods were employed for cyclization of anthranilates. Heating in polyphosphoric acid has a wide scope of applicability. The thermal cyclization in boiling *N*-methylpyrrolidone is limited by steric effect.

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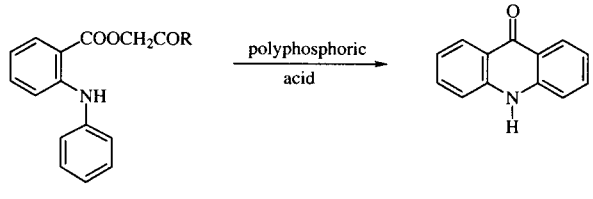
2-Aryl-3-hydroxy-4(1*H*)-quinolinones have not been extensively studied, but several methods of their preparation have been described. The oldest method, leading to the mentioned compounds in several steps from 2-nitrobenzaldehyde and phenacyl bromide, is based on a modification of the Darzen's reaction [1]. Elbs peroxodisulfate oxidation of 2-substituted-4(1*H*)-quinolinones to the corresponding 3-hydroxy derivatives [2] and a ring expansion of 1-acetyl-2-arylmethylene-3-indolinones [3] have been described recently. 3-Hydroxy-2-phenyl-4(1*H*)-quinolinone (**7b**) and 3-hydroxy-1-methyl-2-phenyl-4(1*H*)-quinolinone (**8b**) were synthesized *via* chalcone formation, epoxidation, ring closing and final oxidation [4]. We have recently described a new method of preparation of 2-aryl-3-hydroxy-4(1*H*)-quinolinones [5]. For the construction of this skeleton, thermal reaction of phenacyl anthranilates or reaction in polyphosphoric acid was employed [5]. The influence of substituents at the nitrogen atom as well as the influence of the ester's part in the course of reaction are of prime interest in this report.

Acetonyl and phenacyl derivatives were prepared by reaction of potassium salts of anthranilic acids **1-3** with haloketones (Scheme 1).

Slight modification of the original method was required for the *N*-substituted anthranilic acid and the reaction gave, in general, high yields. For cyclization anthranilates **4-6** were heated with polyphosphoric acid at 120° for 1 hour. The reaction mixture was diluted with water and neutralized to *p*H 7-8. The precipitate was collected to give quinolinones **7-9.** A slight difference in the course of the reaction was observed between *N*-nonsubstituted and *N*-substituted phenacyl esters. In the reaction of *N*-phenylanthranilic esters **6a** and **6b**, an intense bright spot was observed on tlc. This product was isolated and identified to be 9(10*H*)-acridone (**10**) (Scheme 2).

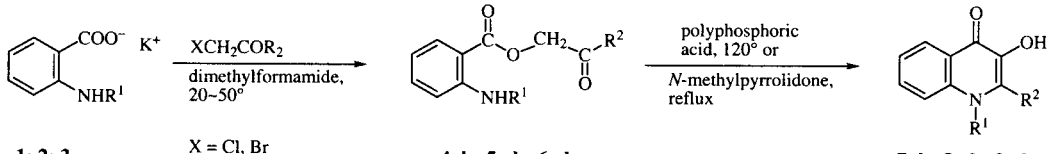
Scheme 2



6a,b **10**

a, R = methyl; **b**, R = phenyl

Scheme 1



1; 2; 3 **4ab; 5a,b; 6a,b** **7ab; 8a,b; 9a,b**

Compound No.	R^1	R^2
1	H	–
2	methyl	–
3	phenyl	–
4a; 7a	H	methyl
4b; 7b	H	phenyl
5a; 8a	methyl	methyl
5b; 8b	methyl	phenyl
6a; 9a	phenyl	methyl
6b; 9b	phenyl	phenyl

The cyclization of anthranilates **4a** and **4b** in polyphosphoric acid has appeared in literature [6]. The product from **4a** was incorrectly identified as 2-methyl-3*H*-benz[*e*][1,4]oxazepin-5-one [6]. The yield was not satisfac-

Table 1

Data for Acetonyl and Phenacylanthranilates

Compound	Yield (%)	mp (°C)	Formula MW	Elemental Analyses Calcd. (%)/(Found) C	H	N
4a	72	78-79 [a]	$C_{10}H_{11}NO_3$ 193.2	62.17 (62.30)	5.74 (5.99)	7.25 (6.78)
4b	78	124-128 [b]	$C_{15}H_{13}NO_3$ 255.3	[b]		
5a	77	76.5-78	$C_{11}H_{13}NO_3$ 207.2	63.76 (63.72)	6.32 (6.19)	6.76 (6.60)
5b	79	106-107	$C_{16}H_{15}NO_3$ 269.3	71.36 (71.35)	5.61 (5.26)	5.20 (5.00)
6a	91	60.5-61.5	$C_{16}H_{15}NO_3$ 269.3	71.36 (70.76)	5.61 (5.87)	5.20 (4.87)
6b	87	93-94.5	$C_{21}H_{17}NO_3$ 331.4	76.12 (75.86)	5.17 (5.28)	4.23 (4.20)

[a] The Compound **4a** has mp 76-78° in the literature [6]. [b] Compound **4b** was identified by comparing with a standard, mp 124.5-128° [5]; 122-124° [6].

Table 2

Data for 1,2-Disubstituted-3-hydroxy-4(1*H*)-quinolinones

Compound	Yield (%) method A/B	mp (°C) Reaction Time*	Formula MW	Elemental analyses Calcd. (%)/(Found) C	H	N
7a	30-58/72	298-306 [a] 10 minutes	$C_{10}H_9NO_2$ 175.2	68.56 (68.04)	5.18 (5.33)	7.99 (7.93)
7b	75/65	278-281 [b] 1.5 hours	$C_{15}H_{11}NO_2$ 237.3	[b]		
8a	57/73	251-255 6 hours	$C_{11}H_{11}NO_2$ 189.2	69.83 (69.46)	5.86 (5.92)	7.40 (7.17)
8b	65/8	275-279 [c] 15 hours	$C_{16}H_{13}NO_2$ 251.3	76.48 (76.19)	5.21 (5.27)	5.57 (5.60)
9a	51/27	257-259 6 hours	$C_{16}H_{13}NO_2$ 251.3	76.48 (76.09)	5.21 (5.31)	5.57 (5.46)
9b	43/0	303-308 15 hours	$C_{21}H_{15}NO_2$ 313.4	80.49 (79.98)	4.83 (5.43)	4.47 (4.44)

[a] The reported mp is 297° [1]; 275-280° [2]; 296-304° [6]. [b] The preparation of compound **7b** (method A) is reported in literature [5], mp 265-270° [1]; 272-273° [2]; 260-262° [4]; 278- 281° [5]. [c] The reported mp is 260-263° [4]. * Reaction time for the procedure B.

Table 3

^{1}H NMR Spectra (δ, ppm; J, Hz) for Acetonyl and Phenacylanthranilates [a]

Compound No.	1 CH_3	3 CH_2	5 Ar-H	6 Ar-H	7 Ar-H	8 Ar-H	N-H	9 N-CH_3	2' Ar-H	3' Ar-H	4' Ar-H	2" Ar-H	3" Ar-H	4"
4a	2.19 (s)	4.99 (s)	7.80 (dd, 8, 1)	6.60 (t, 8)	7.32 (td, 8, 1)	6.83 (d, 8)	6.69 (s)	–	–	–	–	–	–	–
5a	2.19 (s)	4.99 (s)	7.90 (dd, 8, 1)	6.65 (t, 8)	7.48 (td, 8, 1)	6.78 (d, 8)	7.51 (d, 5)	2.89 (d, 5)	–	–	–	–	–	–
5b	–	5.73 (s)	7.97 (dd, 8, 1)	6.69 (t, 8)	7.76 (t, 8)	6.79 (d, 8)	7.50-7.53* (m)	2.89 (d, 5)	8.06 (d, 8)	7.63 (t, 8)	7.50-7.53* (m)	–	–	–
6a	2.22 (s)	5.09 (s)	8.02 (dd, 8, 1)	6.88 (t, 8)	7.49 (td, 8, 1)	7.15 (t, 8)	9.26 (s)	–	–	–	–	7.29-7.32* (m)	7.41 (t, 8)	7.29-7.32* (m)
6b	–	5.83 (s)	8.07-8.10 [b] (m)	6.90 (t, 8)	7.39-7.76* (m)	7.14 (t, 8)	9.30 (s)	–		7.39-7.76* (m)		7.30-7.32 [c] (m)	8.07-8.10 [b] (m)	7.30-7.32 [c] (m)

[a] For the assignments of protons, see Figure 1. [*] Unresolved multiplets. [b] Unresolved multiplets. [c] Unresolved multiplets.

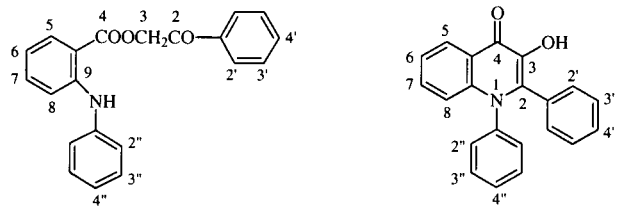


Figure 1.

tory and raising the temperature to 200° did not improve the yield. A better yield and purity of the product was obtained by the reaction conditions we applied. In polyphosphoric acid (procedure A) the yield of 2-methyl-3-hydroxy-4(1*H*)-quinolinone (**7a**) was moderate and was in the range of 30 to 58%, especially in larger scale experiments, probably due to the solubility problem of product **7a** in the solution. Thus we looked for different reaction conditions for the cyclization. When a solution of **4a** in *N*-methylpyrrolidone was refluxed (procedure B), compound **7a** was obtained in 72% yield in high purity. Product **7a** precipitated from the reaction mixture during the cooling operation. This method was used for the cyclization of other phenacyl and acetonyl anthranilates (Table 2).

The cyclization of acetonyl derivatives was found to be faster than that of the phenacyl compounds.

The reaction rate decreased with the increased volume of the substituent on the nitrogen atom. Thus *N*-methylanthranilate **5a** cyclized in a relatively short time in high yield, but *N*-phenyl derivative **6a** afforded a low yield after a long reaction time. In the phenacyl derivatives this trend was more valid and *N*-methyl derivative **8b** was isolated only in 8% yield after a reaction time of 15 hours. *N*-Phenyl derivative **6b** did not react under these reaction conditions.

In conclusion we have found that the increased volume of the substituent at positions 1 and 2 of the final 3-hydroxy-4(1*H*)-quinolinone causes the retardation of cyclization and a decrease in the yield. This substitution effect is remarkable especially in the thermal ring formation in *N*-methylpyrrolidone (procedure B). The thermal reaction of *N*-unsubstituted anthranilates gives 2-methyl or 3-hydroxy-2-phenyl-4(1*H*)-qinolinones in good yield, but its applicability is limited by steric effects. Heating in polyphosphoric acid (procedure A) has wide applicability.

EXPERIMENTAL

The ^{1}H nmr spectra were measured in hexadeuteriodimethyl. sulfoxide on a Brucker AMX-360 spectrometer (360 MHz); the chemical shifts reported are δ values in ppm with tetramethylsilane as the internal standard. Coupling constants J are expressed in Hz. Elemental analyses for CHN were performed using an EA 1108 Elemental Analyser (Fison Instrument). The tlc were observed on Polygram Sil G/UV$_{254}$ with uv light detection. Melting points were measured on the Koffler apparatus and are uncorrected. Characteristic data for the new compounds are presented in Tables 1 and 2. The ^{1}H-nmr spectra of compounds **4, 5,** and **6** are given in Table 3 and those of compounds **7, 8** and **9** in Table 4.

General Procedure for Preparation of Acetonyl and Phenacyl anthranilates **4, 5** and **6.**

Anthranilic acid **1**, **2** or **3** (60 mmoles) was dissolved in dimethylformamide (50 ml) and to the solution was added potassium carbonate (5.88 g, 43 mmoles). The reaction mixture was heated to 90° and stirred for 1 hour. Then the solution was cooled to 20° and either chloroacetone (4.62 g, 3.95 ml, 50 mmoles) or 2-bromoacetophenone (9.95 g, 50 mmoles) was added. The slightly exothermic reaction took place and the temperature increased to 25 to 32° during 5 minutes. After stirring for 30 minutes the reaction mixture was heated to 50° and kept at this temperature for 30 minutes. The content of the flask was then poured into a 500 g mixture of water and ice. The precipitated solid material was collected by filtration, washed with 100 ml of water and dried. The product was then recrystallized from ethanol. Yield and characteristic data are presented in Table 1.

General Procedure for Preparation of 1,2-Disubstituted-3-hydroxy-4(1*H*)-quinolinones **7, 8** and **9.**

Procedure A.

Table 4

^{1}H NMR Spectra (d, ppm; J, Hz) of 1,2-Disubstituted-3-hydroxy-4(1*H*)-quinolinones [a]

Compound No.	1 CH_3	2 CH_3	5 Ar-H	6 Ar-H	7 Ar-H	8 Ar-H	2' Ar-H	3' Ar-H	4' Ar-H	2" Ar-H	3" Ar-H	4" Ar-H
7a	–	2.43 (s)	8.15 (d)	7.26 (t, 8)	7.54-7.60 (m)		–	–	–	–	–	–
8a	3.84 (s)	2.57 (s)	8.27 (dd, 8, 1)	7.36 (t, 8)	7.70 (td, 8, 1)	7.82 (d, 8)	–	–	–	–	–	–
8b	3.57 (s)	–	8.35 (d, 8)	7.43 (t, 8)	7.75-7.83 (m)		7.50 (d, 8)	7.55-7.63 (m)		–	–	–
9a	–	2.09 (s)	8.31 (d, 7)	7.34 (t, 7)	7.69-7.76 [b] (m)	6.69 (d, 1)	–	–	–	7.48-7.51* (m)	7.69-7.76 [b] (m)	7.48-7.51* (m)
9b	–	–	8.39 (d, 7)	7.38-7.41* (m)	7.56 (t, 8)	6.81 (d, 7)	7.38-7.41* (m)			7.23-7.31 (m)		

[a] For the assignments of protons, see Figure 1. [*] Unresolved multiplets. [b] Unresolved multiplets.

Anthranilate **4**, **5** or **6** (5 mmoles) was added to polyphosphoric acid (10 g) which was pre-heated to 120° and the reaction mixture was stirred for 1 hour at this temperature. The reaction was continued until no starting material was detected on tlc. The reaction mixture was diluted with 100 ml of cold water and cooled to room temperature. The *p*H of the solution was adjusted between **7** and **8** by the addition of aqueous 10% sodium hydroxide solution and the precipitated crystalline material was collected, washed with 50 ml of water and dried at 60°. The crude product was recrystallized from dimethylformamide and acetone.

Procedure B.

A solution of anthranilate **4**, **5** or **6** (25 mmoles) in *N*-methylpyrrolidone (15 ml) was heated to reflux for the period mentioned in Table 2. When the reaction mixture was cooled to 60°, 60 ml of ethyl acetate was added and the suspension was cooled to 0-5° and stirred for 30 minutes. The precipitated product was collected by filtration, washed with 30 ml of distilled water and 10 ml of cooled ethanol, and dried at 100°.

9(10*H*)-Acridone (**10**).

The mother liquor after crystalization of **9a** was evaporated to dryness. Column chromatography on a silica gel (100 g) in a trichloromethane-acetone (10:3) mixture yielded **10** 0.082 g, (8%), mp 353-356° (literature [7] 356-358°). The structure of the compound was confirmed also by tlc comparing it with a standard sample obtained from Aldrich.

Anal. Calcd. for $C_{13}H_9NO$: C, 79.98; H, 4.65; N, 7.17. Found: C, 79.68; H, 4.82; N, 7.04.

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