SYNTHESIS OF 2-SUBSTITUTED-6,7-DIMETHOXY- AND 6,7,8-TRIMETHOXY-3-HYDROXYQUINOLIN-4(1*H*)-ONES

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Acetonyl and phenacyl esters of 4,5-dimethoxy- and 3,4,5-trimethoxyanthranilic acids **3** were prepared by reduction of corresponding nitro derivatives **2**. Acetonyl 4,5-dimethoxyanthranilate (**3a**) was prepared by reaction of 4,5-dimethoxyanthranilic acid and chloroacetone. Cyclization of these acetonyl and phenacyl esters in polyphosphoric acid provided the corresponding 2-substituted-6,7-dimethoxy- and 6,7,8-trimethoxy-3-hydroxyquinolin-4(1*H*)-ones **4**. A new method of the thermal cyclization is also described. The structure of the prepared compounds was confirmed by ^{1}H NMR spectroscopy.
Key words: Cyclization; Anthranilates; 3-Hydroxyquinolin-4(1*H*)-ones; Quinolinones.

2-Aryl-3-hydroxyquinolin-4(1*H*)-ones 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 Darzens reaction[1]. This method was used for the preparation of 3,6-dimethoxy-1-methyl-2-phenylquinolin-4(1*H*)-one, the plant alkaloid japonine[2]. Elbs peroxodisulfate oxidation of 2-substituted quinolin-4(1*H*)-ones to the corresponding 3-hydroxy derivatives[3] and a ring expansion of 1-acetyl-2-(aryl-methylene)indol-3(2*H*)-ones[4] have been described recently. We have recently described[5] a new method of preparation of 2-aryl-3-hydroxyquinolin-4(1*H*)-ones based on a rearrangement observed during cyclization of phenacyl anthranilates. The unexpected course of the

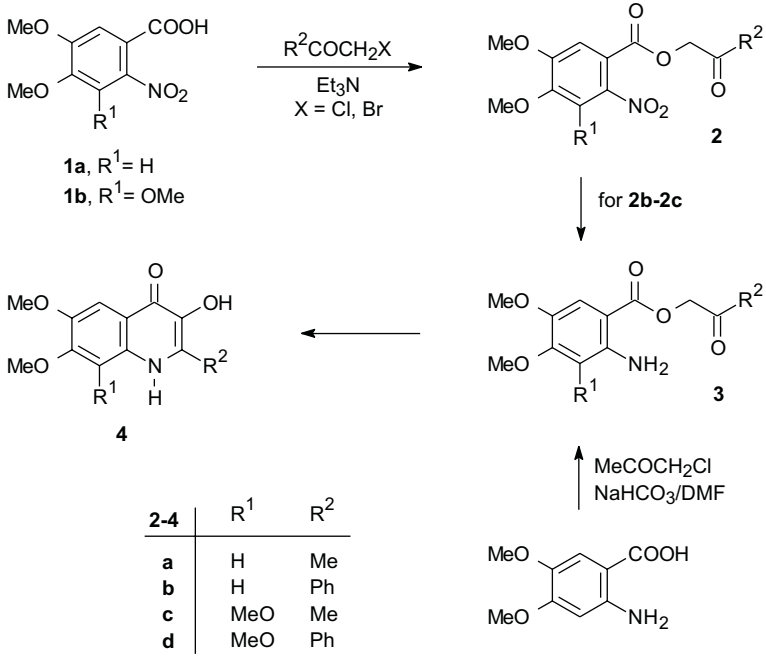
reaction was confirmed by ^{1}H NMR and ^{13}C NMR studies, and for several known compounds also by comparing their melting points with the published values.

2-Arylquinolin-4(1*H*)-ones are isosteric with flavones, naturally occurring compounds with a wide spectrum of biological activities. The flavone moiety is often substituted by hydroxy and/or methoxy groups at various positions, especially at position 3 and in the benzene part of the molecule. Some of these compounds are simple, for example 3,7-dihydroxy-2-phenylbenzopyran-4(1*H*)-one isolated from *Platymiscium praecox*[6] or 3,7-dihydroxy-8-methoxy-2-phenylbenzopyran-4(1*H*)-one (zuccagine) isolated from *Zuccagnia punctata*[7]. Others are polysubstituted, for example 3,5-dihydroxy-6,7,8-trimethoxy-2-phenylbenzopyran-4(1*H*)-one isolated from *Achyrocline bogotensis* or *Achillea nobilis*[8]. The best known compound of this class is 3,5,7-trihydroxy-2-(3,4-dihydroxyphenyl)benzopyran-4(1*H*)-one (quercetin) with effects on the cardiovascular system, circulation, as well as anticancer, analgesic, and anti-free radical activities[9]. 3-Hydroxy-6,7,8-trimethoxy-2-(4-methoxyphenyl)benzopyran-4(1*H*)-one, isolated from *Citrus aurantium*, shows immunosuppressant activity[10].

The above-mentioned activities of 3-hydroxyflavones inspired us to prove the applicability of our method of synthesis of 2-aryl-3-hydroxyquinolin-4(1*H*)-ones to the preparation of these compounds bearing substituents typical of flavones. In our previous paper[5], we have shown that the reaction is compatible with a wide range of substituents on the 2-phenyl group. In order to show applicability of our method to the preparation of polymethoxyquinoline flavone isosteres, the present paper describes the synthesis of 2-substituted-3-hydroxyquinolin-4(1*H*)-ones with two or three methoxy groups in the quinoline part of the molecule. Cyclization of similar acetonyl esters under the described conditions as well as thermal cyclization of these compounds are also studied.

Starting 4,5-dimethoxy- (**1a**) and 3,4,5-trimethoxy-2-nitrobenzoic (**1b**) acids were prepared by described methods[11,12]. These acid treated with chloroacetone and phenacyl bromide provided their respective acetonyl and phenacyl esters **2**. Simple reduction of these intermediates then yielded corresponding amino derivatives **3** (Scheme 1). However, some unexplained differences were observed in the reduction. Though compound **2b** was reduced under conditions previously used for reduction of phenacyl esters of unsubstituted 2-nitrobenzoic acid[13], this method did not work for other derivatives. A very similar compound **2d** did not react with iron under the described conditions, zinc dust and acetic acid must be used in this case. Acetonyl esters were more sensitive to hydrolysis than phenacyl esters

and starting acids were formed in the mixture during washing and therefore only limited washing and rapid work up is essential. Acetonyl derivative **2c** was reduced in the same way as **2d**. However, we failed to prepare **3a** using this way and therefore we started from 4,5-dimethoxyanthranilic acid and the same procedure described for unsubstituted anthranilic acid was used[5]. The higher stability of compound **2c** in comparison with **2a** could be caused by a steric effect of the 3-methoxy group. The lower reactivity of **2d** compared with **2b** could have the same reason.



2-4	R^1	R^2
a	H	Me
b	H	Ph
c	MeO	Me
d	MeO	Ph

SCHEME 1

Cyclization of these substituted phenacyl anthranilates occurred in polyphosphoric acid, except with compound **3a**. In this case, compound **4a** was present in the reaction mixture (TLC) but we failed to isolate it and therefore an alternative procedure was applied. Thermal cyclization of **3** in *N*-methylpyrrolidone yielded the required product. 3,4,5-Trimethoxyanthranilates could also be successfully cyclized by this method but a longer reaction time was necessary, probably for steric reasons. Generally, the thermal cyclization method is simple and affords very pure products.

Since natural flavones often possess hydroxy groups, we tried to prepare hydroxy substituted quinolones by demethylation of the corresponding

methoxy compounds. We failed to demethylate compounds **4b** and **4d** under various conditions known to be used in the literature for demethylation of similar compounds. The used agents included pyridinium hydrochloride[14], aluminium trichloride[15], as well as hydrobromic acid[16]. No reaction was observed under mild conditions and when higher temperature was applied, complex mixtures were obtained. Similar results were obtained with boron tribromide[17]. If the reaction was performed at room temperature and the excess of boron tribromide was lower than 3 equivaletns, the starting compound was isolated after the workup with sodium hydroxide. When either higher excess of the agent was used or the reaction was performed in boiling chloroform solutions, nonseparable complex mixtures were obtained from which no compound was successfully isolated and identified.

EXPERIMENTAL

The melting points were measured on a Koffler block and are uncorrected. The ^{1}H NMR spectra were measured in hexadeuteriodimethyl sulfoxide solutions on an AMX-360 Bruker spectrometer (360 MHz) with tetramethylsilane as an internal standard. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. Elemental analyses were performed using an EA 1108 Elemental Analyser (Fison Instrument). TLC was performed on a Polygram Sil G/UV$_{254}$ with UV detection. Characteristic data of the prepared compounds are presented in Table I, their ^{1}H NMR spectra in Table II.

Acetonyl and Phenacyl 4,5-Dimethoxy- and 3,4,5-Trimethoxy-2-nitrobenzoates **2**. General Procedure

Chloroacetone or 2-bromacetophenone (44 mmol) was added to a solution of corresponding acid **1a** or **1b** (44 mmol) and triethylamine (6.2 ml, 44 mmol) in acetone (200 ml) and the reaction mixture was refluxed until no starting material was detected by TLC (toluene–ethyl acetate 1 : 1). Then the reaction mixture was cooled to 5 °C, the precipitated triethylammonium salt was filtered off and the filtrate was evaporated. The residual dark oil was dissolved in ethyl acetate (200 ml) and quickly washed with water. Acetonyl esters were washed only once because of their rapid hydrolysis. The organic layer was dried with sodium sulfate and the residual oil after evaporation was crystallized from ethanol. The yields and characteristic data are presented in Table I.

Acetonyl 2-Amino-3,4-dimethoxybenzoate (**3a**)

Sodium hydrogencarbonate (1.3 g, 15.5 mmol) was added to a solution of 4,5-dimethoxy-2-aminobenzoic acid (2.4 g, 12.2 mmol) in *N*,*N*-dimethylformamide (13 ml) and the reaction mixture was stirred at 95–100 °C for 2 h. Chloroacetone (0.9 ml, 12.2 mmol) was added to the suspension at 20 °C. The temperature increased spontaneously to 25 °C and the mixture was stirred for 1 h at ambient temperature. Then the reaction mixture was heated at 60 °C for 2 min, poured into water (200 ml), the precipitated solid was cooled to 0–5 °C, filtered off, and washed successively with 1% solution of $NaHCO_3$ (100 ml) and water (50 ml). Crys-

tallization from ethanol yielded **3a** (2 g, 65%), m.p. 129–132 °C. For $C_{12}H_{15}NO_5$ (253.3) calculated: 56.91% C, 5.97% H, 5.53% N; found: 57.02% C, 6.07% H, 5.40% N.

Phenacyl 2-Amino-4,5-dimethoxybenzoate (**3b**)

Iron dust (1.0 g, 18.4 mmol) was added to a solution of **2b** (1 g, 2.9 mmol) in a mixture of acetone (5 ml), water (1 ml), and acetic acid (0.12 ml, 2.1 mmol) and the mixture was stirred under reflux for 2 h. Then the reaction was diluted with acetone (15 ml) and sodium hydrogencarbonate (0.32 g, 3.8 mmol) was added. The mixture was refluxed with charcoal

TABLE I
Yields and characteristic data for compounds **2** and **4**

Compound	Reaction time, min	M.p., °C Yield, %	Formula M.w.	Calculated/Found		
				% C	% H	% N
2a	120	114–115	$C_{12}H_{13}NO_7$	50.89	4.63	4.95
		52	283.2	50.95	5.10	4.74
2b	90	144–147	$C_{17}H_{15}NO_7$	59.13	4.38	4.06
		86	345.3	59.02	4.63	3.97
2c	240	58–59	$C_{13}H_{15}NO_8$	49.84	4.83	4.47
		58	313.3	49.58	4.99	4.01
2d	40	92	$C_{18}H_{17}NO_8$	57.60	4.57	3.73
		85	375.3	57.62	4.58	3.45
4a	10[a]	315–321	$C_{12}H_{13}NO_4$	61.27	5.57	6.95
		0/69[b]	235.2	61.58	5.43	6.21
4b	60[a]	332–335	$C_{17}H_{15}NO_4$	68.68	5.09	4.71
		87/70[b]	297.3	68.19	5.01	4.63
4c	15[a]	243–245	$C_{13}H_{15}NO_5$	59.08	5.70	5.28
		48/22[b,c]	265.3	59.48	5.96	5.23
4d	180[a]	240–242	$C_{18}H_{17}NO_5$	66.05	5.23	4.28
		89/53[b]	327.3	65.89	5.33	4.09

[a] Procedure *B*; [b] procedure *A*/procedure *B*; [c] based on **2c**.

for 30 min, the hot solution was filtered and the filtrate was evaporated to dryness. Crystallization from a mixture ethanol–acetone (2 : 1) afforded **3b** (0.72 g, 79%), m.p. 142–143 °C. For $C_{17}H_{17}NO_5$ (315.3) calculated: 64.75% C, 5.43% H, 4.44% N; found: 64.58% C, 5.92% H, 4.49% N.

TABLE II
^{1}H NMR data (δ, ppm; *J*, Hz) for compounds **2**, **3** and **4**

Compound	CH_3	CH_2	C_6H_5	CH_3O	Others
2a	2.21 s (3 H)	5.05 s (2 H)	–	3.96 s (3 H) 3.97 s (3 H)	7.37 s (1 H) 7.70 s (1 H)
2b	–	5.81 s (2 H)	7.63 t; 8 (2 H) 7.64 t; 8 (1 H) 8.07 d; 8 (2 H)	3.98 s (3 H) 4.00 s (3 H)	7.42 s (1 H) 7.72 s (1 H)
2c	2.15 s (3 H)	5.03 s (2 H)	–	3.96 s (3 H) 4.00 s (3 H) 4.02 s (3 H)	7.39 s (1 H)
2d	–	5.82 s (2 H)	7.63 t; 8 (2 H) 7.77 t; 8 (1 H) 8.05 d; 8 (2 H)	3.96 s (3 H) 4.00 s (3 H) 4.02 s (3 H)	7.49 s (1 H)
3a	2.14 s (3 H)	4.89 s (2 H)	–	3.66 s (3 H) 3.76 s (3 H)	6.39 s (1 H) 7.19 s (1 H)
3b	–	5.67 s (2 H)	7.60 t; 8 (2 H) 7.75 t; 8 (1 H) 8.05 d; 8 (2 H)	3.72 s (3 H) 3.82 s (3 H)	6.45 s (1 H) 7.29 s (1 H)
3d	–	5.72 s (2 H)	7.63 t; 8 (2 H) 7.76 t; 8 (1 H) 8.06 d; 8 (2 H)	3.78 s (3 H) 3.79 s (3 H) 3.91 s (3 H)	7.22 s (1 H)
4a	2.33 s (3 H)	–	–	3.83 s (3 H) 3.85 s (3 H)	6.90 s (1 H) 7.39 s (1 H)
4b	–	–	7.55 t; 7.5 (1 H) 7.60 t; 7.5 (2 H) 7.86 t; 7.5 (2 H)	3.90 s (3 H) 3.91 s (3 H)	7.23 s (1 H) 7.48 s (1 H)
4c	2.41 s (3 H)	–	–	3.88 s (6 H) 3.95 s (3 H)	7.28 s (1 H)
4d	–	–	7.53–7.59 m; (3 H) 7.76 d; 7 (2 H)	3.93 s (3 H) 3.95 s (3 H) 3.99 s (3 H)	7.37 s (1 H)

Acetonyl 2-Amino-3,4,5-trimethoxybenzoate (**3c**)

Zinc dust (2 g, 30.6 mmol) and acetic acid (20 ml, 0.35 mol) was added to a solution of **2c** (5 g, 16 mmol) in ethyl acetate (130 ml) and the reaction mixture was stirred under reflux and the reaction was checked by TLC (toluene–ethyl acetate 20 : 1). After 1 h, an additional amount of zinc dust (0.5 g, 7.6 mmol) and acetic acid (1 ml, 17.5 mmol) were added and the reaction continued for another 1 h. Then the reaction mixture was cooled, the precipitate zinc acetate was collected by filtration, the filtrate was diluted with ethyl acetate (150 ml) and washed successively with water (50 ml) and 5% solution of sodium hydrogencarbonate to pH 7. The organic layer was dried with sodium sulfate, filtered with charcoal (0.5 g) and evaporated to dryness. Compound **3c** was obtained as a yellowish oil and the crude product was used for the next step without further purification.

Phenacyl 2-Amino-3,4,5-trimethoxybenzoate (**3d**)

This compound was prepared from **2d** in the same way as described for the preparation of **3c** (reaction time 4 h). The crude product after evaporation of the solvent was crystallized from a minimum amount of ethanol to provide **3d** (68%), m.p. 144–146 °C. For $C_{18}H_{19}NO_6$ (345.4) calculated: 62.60% C, 5.55% H, 4.06% N; found: 62.35% C, 6.04% H, 3.98% N.

2-Substituted-3-hydroxy-6,7-dimethoxy- and 6,7,8-Trimethoxyquinolin-4(1*H*)-ones **4**. General Procedures

A) An anthranilate **3** (1 mmol) was added to polyphosphoric acid (5 g) at 100 °C and the reaction mixture was stirred at this temperature for 1 h. Reaction was continued until no starting material was detected by TLC (toluene–ethyl acetate 1 : 1, ethyl acetate–acetone 4 : 1 or toluene–ethyl acetate 4 : 1). Then the reaction mixture was diluted with cold water (80 ml), the mixture was cooled to room temperature and neutralized to pH 7 with a 10% solution of sodium hydroxide. The precipitated crystalline material was filtered off, washed with water (20 ml), dried at 60 °C and crystallized from *N*,*N*-dimethylformamide. The yields and characteristic data are given in Table I.

B) A solution of an anthranilate **3** (2.5 mmol) in *N*-methylpyrrolidone (1.5 ml) was refluxed until no starting material was detected by TLC (see Table II). The reaction mixture was cooled to 60 °C, ethyl acetate (20 ml) was added, the suspension was stirred at 0–5 °C for 30 min and then left to stand overnight in a refrigerator. The precipitated product was collected by filtration, successively washed with water (30 ml) and cold ethanol (10 ml), and dried at 100 °C. The yields and characteristic data are presented in Table I.

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