SYNTHESIS OF 2-ARYL-3-HYDROXYQUINOLIN-4(1*H*)-ONES

Pavel HRADIL[a] and Josef JIRMAN[b]

[a] *Farmakon s.p., 771 17 Olomouc, Czech Republic*

[b] *Research Institute of Organic Syntheses s.a., 532 18 Pardubice-Rybitvi, Czech Republic*

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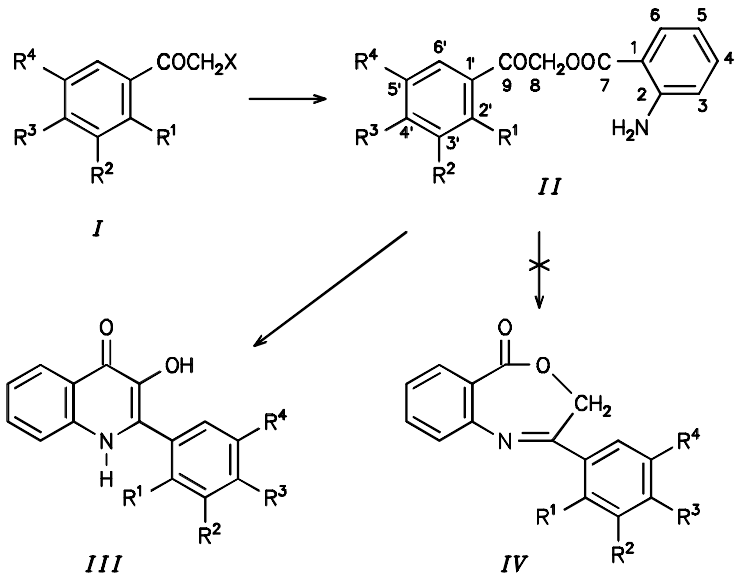
Eight substituted phenacyl anthranilates have been prepared by reaction of sodium anthranilate with substituted phenacyl halides in dimethylformamide in the yields from 31 to 93%. The phenacyl esters were cyclized in polyphosphoric acid or by mere heating to give the respective substituted 2-aryl-3-hydroxyquinolin-4(1*H*)-ones in the yields from 77 to 98%. All the compounds prepared have been characterized by their ^{1}H and ^{13}C NMR spectra.

Phenacyl bromides belong among very reactive substances and their reaction with sodium salts of lower organic acids giving the corresponding phenacyl esters is well known and has been employed for identification of these acids[1,2]. The direct reaction of anthranilic acid with bromomethyl phenyl ketone has also been described[2,3]. In boiling ethanol in the absence of base, alkylation at amino group predominated to give *N*-phenacylanthranilic acid[3]. In the presence of base, phenacyl *N*-phenacylanthranilate was formed[2,3]. Phenacyl anthranilates were prepared by reactions of 2-nitrobenzoic acid with bromomethyl aryl ketones and subsequent reduction of the phenacyl 2-nitrobenzoates formed with hydrogen on palladium[4,5]. The rates of reactions of bromomethyl aryl ketones with nucleophiles are strongly affected by the solvent used. If amides are used as the reaction medium, the reaction is smooth even at room temperature and is exothermic[6]. When these conditions were adopted for the reactions of bromomethyl phenyl ketones *I* with salts of anthranilic acid, the alkylation predominantly took place at the oxygen atom to give phenacyl anthranilates *II* mostly in high yields (Scheme 1). The substances prepared were identified by their ^{1}H and ^{13}C NMR spectra (Tables I and II). Although quinolines represent an extensively studied class of heterocyclic compounds, only few basic representatives of 2-aryl-3-hydroxyquinolin-4(1*H*)-ones have been described in literature. The described method of preparation starting from the 2-nitrophenylethylene oxide prepared by the Darzens reaction[7,8] is laborious and the yields of whole synthesis are low. The method given by us for preparation of 3-hydroxyquinolin-4(1*H*)-ones *III* was discovered during cyclizations of phenacyl anthranilates (Scheme 1). Literature[4,5] describes their cyclizations in polyphosphoric acid to give the respective 2-aryl-3*H*-benz[*e*][1,4]oxazepin-5-ones *IV* which are converted into the more stable

2-aryl-1*H*-benz[*e*][1,4]oxazepin-5-ones. We have slightly modified this procedure with regard to isolation of product and used it also for further phenacyl anthranilates not described in refs[4,5]. By means of ^{1}H and ^{13}C NMR spectra it could be proved that the reaction does not produce 2-aryl-3*H*-benz[*e*][1,4]oxazepin-5-ones *IV* but produces 2-aryl-3-hydroxyquinolin-4(1*H*)-ones *III* (Scheme 1 and Tables III and IV). The correctness of



Ie X = Cl; *Ia–Id*, *If–Ih* X = Br

I–IV	R^1	R^2	R^3	R^4
a	H	H	H	H
b	H	H	Br	H
c	H	H	Cl	H
d	Cl	H	H	H
e	Cl	H	Cl	H
f	H	H	NO_2	H
g	H	Cl	NH_2	Cl
h	H	Cl	$NHCH(CH_3)_2$	Cl

SCHEME 1

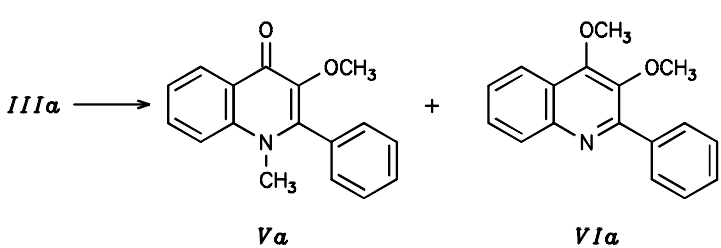
this structure was also confirmed by another reaction: alkylation of 2-phenyl-3-hydroxyquinolin-4(1*H*)-one (*IIIa*) with dimethyl sulfate gave a mixture of two products whose molecules were methylated with two methyl groups (Scheme 2). NMR spectra showed that these products are 3-methoxy-1-methyl-2-phenyl-4-quinolone (*Va*) and 3,4-dimethoxy-2-phenylquinoline (*VIa*), which was also confirmed by the literature data[9,10] concerning these compounds.

The formation of 2-aryl-3-hydroxyquinolin-4(1*H*)-ones *III* is surprising though not inexplicable. Lability of seven-membered ring compounds is well known. Hence the transformation could consist in intramolecular cyclization giving 2-aryl-3*H*-benz[*e*][1,4]oxazepin-5-ones *IV* (originally expected) immediately followed – due to low stability of seven-membered ring at the given conditions – by decomposition of lactone bond and formation of a new carbon–carbon bond with subsequent shift of protons and aromatization of the molecule to give the quinoline nucleus. However, the available data do not allow any decision about the reaction mechanism. Other cycliza-

TABLE I
^{1}H NMR spectra of compounds *II* (δ, ppm)

Compound	NH_2	H-3	H-4	H-5	H-6	H-8	H-2′	H-3′	H-4′	H-5′	H-6′
IIa	6.72	6.87	7.34	6.63	7.88	5.73	8.06	7.63	7.75	7.63	8.06
IIb	6.73	6.88	7.33	6.61	7.82	5.70	7.98	7.80	–	7.80	7.98
IIc	6.72	6.88	7.34	6.61	7.82	5.71	8.07	7.67	–	7.67	8.07
IId	6.73	7.85	7.33	6.59	7.81	5.50	–	7.62	7.54	7.62	7.87
IIe	6.73	6.85	7.32	6.59	7.81	5.50	–	7.78	–	7.61	7.91
IIf	6.70	6.85	7.34	6.60	7.86	5.77	8.28	8.41	–	8.41	8.28
IIg	6.69	6.84	7.32	6.61	7.85	5.60	7.93	–	–	–	7.93
IIh[a]	6.64	6.83	7.32	6.60	7.85	5.59	7.95	–	–	–	7.95

[a] δ(NH) = 4.93, δ(CH) = 4.20, δ(CH_3) = 1.20.



SCHEME 2

TABLE II
^{13}C NMR spectra of compounds *II* (δ, ppm)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
IIa	108.38	151.63	116.71	134.45	114.94	130.93	166.80	66.45	193.28	134.09	127.85	128.99	133.99	128.99	127.85
IIb	108.36	151.84	116.86	134.64	115.06	131.07	166.90	66.53	192.77	128.35	129.99	132.23	133.15	132.23	129.99
IIc	108.35	151.84	116.86	134.63	115.04	131.06	166.90	66.56	192.56	132.84	129.23	129.93	139.13	129.93	129.28
IId	108.09	151.88	116.85	134.72	115.05	130.93	166.77	68.02	195.89	130.67	135.28	133.40	127.68	130.06	130.06
IIe	108.03	151.89	116.86	134.72	115.04	130.94	166.77	67.95	194.85	132.15	133.84	130.55	137.47	127.87	131.53
IIf	108.06	151.68	116.72	134.54	114.93	130.87	166.68	66.69	192.80	138.64	129.36	124.02	150.34	124.02	129.36
IIg	108.51	151.76	116.82	134.55	115.02	131.04	166.91	66.07	189.65	122.54	128.40	117.67	146.29	117.67	128.40
IIh[a]	108.57	151.80	116.97	134.79	115.30	131.16	167.04	66.27	190.31	126.06	129.23	123.61	146.45	123.61	129.23

[a] δ(CH) = 48.05, δ(CH_3) = 23.92.

tion conditions were also adopted with the aim to preserve the 2-aryl-3*H*-benz[*e*][1,4]oxazepin-5-one or other intermediates formed but these attempts failed. No reaction took place in toluene with piperidine as a catalyst. It was found that heating of phenacyl anthranilates above their melting points – at about 180 °C – results in foaming of the reaction mixture and escaping of water. After ca 15 min, the reaction mixture solidified. Beside 2-aryl-3-hydroxyquinolin-4(1*H*)-ones *III* the reaction mixture contained large amounts of the starting substance *II*. When the melt was heated more intensively, the reaction became exothermic after reaching the temperature of 230 °C, the temperature increased and the reaction mixture quickly solidified. In all the cases, however, the reaction mixture again contained 2-aryl-3-hydroxyquinolin-4(1*H*)-ones *III*. In the cases of phenacyl anthranilates *II* with higher melting points, however, the reaction mixture was strongly contaminated with decomposition products. For phenacyl anthranilates *II* with lower melting points the yields were acceptable though lower than those of the cyclizations in polyphosphoric acid. The compounds obtained by the cyclizations in polyphosphoric acid were identical with those obtained by thermal cyclizations, which was proved by determination of melting points, by TLC and NMR.

EXPERIMENTAL

The melting points were measured in capillaries in the Kofler apparatus and were not corrected. The ^{1}H and ^{13}C NMR spectra (δ, ppm) were measured with an AMX 360 (Bruker) apparatus at 360.13 and 90.57 MHz, respectively, using an inverse tunable 5 mm probe. Saturated solutions of the substances in hexadeuteriodimethyl sulfoxide (mixed with trifluoroacetic acid in the case of compound *IIIh*) were prepared at 23 °C. The NMR spectra were interpreted and the signals of the parent com-

TABLE III
^{1}H NMR spectra of compounds *III* (δ, ppm)

Compound	H-5	H-6	H-7	H-8	H-2′	H-3′	H-4′	H-5′	H-6′
IIIa	8.24	7.33	7.64	7.80	7.87	7.59	7.54	7.59	7.87
IIIb	8.21	7.31	7.63	7.77	7.88	7.79	–	7.79	7.88
IIIc	8.21	7.32	7.64	7.77	7.89	7.68	–	7.68	7.89
IIId	8.23	7.32	7.63	7.64	–	[a]	[a]	[a]	7.70
IIIe	8.21	7.32	7.61	7.61	–	7.90	–	7.65	7.69
IIIf	8.21	7.32	7.66	7.76	8.14	8.44	–	8.44	8.14
IIIg	8.16	7.29	7.61	7.75	7.83	–	–	–	7.83
IIIh[b]	8.15	7.28	7.60	7.72	–	7.94	–	–	7.94

[a] Unresolved multiplet from 7.53 to 7.67. [b] δ(NH) = 4.47, δ(CH) = 4.02, δ(CH_3) = 1.22.

TABLE IV
^{13}C NMR spectra of compounds *III* (δ, ppm)

Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-4a	C-8a	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
IIIa	131.74	137.91	170.07	124.52	122.00	130.59	118.58	121.90	138.14	132.44	129.32	128.35	129.32	128.35	129.32
IIIb	131.72	138.17	170.28	124.70	122.10	130.88	118.72	122.10	138.32	130.60	131.56	131.48	122.86	131.48	131.56
IIIc	131.17	138.01	170.20	124.54	123.03	130.74	118.52	121.93	138.17	130.29	131.16	128.40	134.01	128.40	131.16
IIId	131.91	137.97	170.18	124.81	122.12	130.82	118.48	122.62	138.66	133.19	130.38	129.70	131.31	127.41	132.24
IIIe	130.96	138.05	170.12	124.82	122.15	130.88	118.52	122.68	138.71	129.36	134.38	129.26	135.10	127.63	133.55
IIIf	129.13	[a]	170.38	124.57	122.20	131.04	118.58	121.97	[a]	[a]	130.72	123.36	147.44	132.36	130.72
IIIg	129.63	137.81	169.94	124.58	122.06	130.70	118.61	121.88	138.21	120.44	128.85	117.66	142.23	117.66	128.85
IIIh[b]	137.54	137.22	162.10	127.04	124.00	132.80	120.57	121.08	144.92	123.48	131.53	125.28	144.92	125.28	131.53

[a] 138.81 or 138.58 or 138.32. [b] Measured in a $(CD_3)_2SO–CF_3COOH$ (2 : 1) mixture, δ(CH) = 48.95, δ(CH_3) = 24.25.

TABLE V
Characteristic data of compounds *II* and *III*

Compound	M.p., °C Yield, %[a]	Formula M.w.	Calculated/Found		
			% C	% H	% N
IIa	124.5–128[ab] 74	$C_{15}H_{13}NO_3$ 255.3	70.64 70.58	5.02 5.13	5.77 5.49
IIb	136.5–140[c] 83	$C_{15}H_{12}BrNO_3$ 334.2	53.55 53.91	3.58 3.62	4.20 4.19
IIc	136–138 93	$C_{15}H_{12}ClNO_3$ 289.7	62.16 62.19	4.26 4.18	4.89 4.83
IId	73.5–75.5 31[d]	$C_{15}H_{12}ClNO_3$ 289.7	61.72 61.19	4.18 4.18	4.87 4.83
IIe	85.5–87.5 58	$C_{15}H_{11}Cl_2NO_3$ 324.2	55.37 55.58	3.40 3.42	4.29 4.32
IIf	155.5–158.5 70	$C_{15}H_{12}N_2O_5$ 300.3	60.17 60.00	4.07 4.03	9.51 9.33
IIg	182–186 79	$C_{15}H_{12}Cl_2N_2O_3$ 339.2	52.49 53.12	3.62 3.57	8.18 8.26
IIh	111–114.5 82	$C_{18}H_{18}Cl_2N_2O_3$ 381.3	57.20 56.71	4.81 4.76	7.32 7.35
IIIa	278–281[e] 95/75[f]	$C_{15}H_{11}NO_2$ 237.3	76.00 75.94	4.72 4.67	6.39 5.90
IIIb	298–305[g] 97/72	$C_{15}H_{10}BrNO_2$ 316.2	56.60 56.99	3.15 3.19	4.45 4.43
IIIc	291.5–294 98/71	$C_{15}H_{10}ClNO_2$ 271.7	66.63 66.31	3.78 3.71	5.26 5.16
IIId	291–295 93/64	$C_{15}H_{10}ClNO_2$ 271.7	65.88 66.31	3.69 3.71	5.19 5.16
IIIe	298–304 95/68	$C_{15}H_9Cl_2NO_2$ 306.2	58.34 58.85	2.96 2.96	4.58 4.58
IIIf	329–332 95/65	$C_{15}H_{10}N_2O_4$ 282.3	63.68 63.83	3.66 3.57	10.13 9.93
IIIg	290–295.5 93/72	$C_{15}H_{10}Cl_2N_2O_2$ 321.2	55.45 56.10	3.46 3.14	8.32 8.72
IIIh	237–242 98/75[h]	$C_{18}H_{16}Cl_2N_2O_2$ 363.2	59.93 59.52	4.23 4.44	8.10 7.71

[a] For compounds *III*, yield for crude/crystalline product is given. [b] Ref.[4]: m.p. 122–124 °C. [c] Ref.[4]: m.p. 133–134 °C. [d] The yield is related to methyl-2-chlorophenyl ketone. [e] Ref.4: 271–275 °C. [f] The yields of the method *B*: 76/60. [g] Ref.[4]: 297–300 °C. [h] The yields of the method *B*: 80/61.

pounds *IIa* and *IIIa* were assigned with the use of the following technique of measurement: H,H-homonuclear correlated spectrum[11], inverse H,C-heteronuclear correlated spectrum via heteronuclear zero and double quantum coherence using BIRD sequence, phase sensitive using TPPI with decoupling during acquisition[12]; inverse H,C-heterocorrelated spectrum via heteronuclear zero and double quantum coherence optimized on long range couplings with low-pass *J*-filter to suppress one-bond correlations without decoupling during acquisition[13]. For the other substances we only measured the current unidimensional proton spectra and ^{13}C *J*-modulated NMR spectra, and the assignment made use of the substituent chemical shifts[14,15]. The ^{1}H and ^{13}C NMR spectra of compounds *IIa–IIh* are given in Tables I and II. The ^{1}H and ^{13}C NMR spectra of compounds *IIIa–IIIh* are given in Tables III and IV. The characteristics of compounds *II* and *III* are summarized in Table V. The IR spectra were measured in KBr disc using a Genesis Series FTIR apparatus (ATI Mattson, U.S.A.). The characteristic absorption bands are presented in Table VI.

Chemicals used. The bromomethyl phenyl ketones *Ia–Ic* were prepared from the corresponding methyl phenyl ketones (Fluka) by known procedures[16]. Bromomethyl 2-chlorophenyl ketone *Id* was prepared by the same procedure but, as the substance could not be obtained in crystalline state, the oil layer washed with water and petroleum ether was used for the reaction, and the yield was calculated with respect to the starting methyl 2-chlorophenyl ketone. The bromomethyl phenyl ketones *Ig*

TABLE VI
IR spectra of compounds *II* and *III* ($\tilde{\nu}$, cm^{-1})

Compound	$\tilde{\nu}$(C=O)	$\tilde{\nu}$(N–H)	$\tilde{\nu}$(C=C_{arom})
IIa	1 615, 1 685	3 368, 3 483	
IIb	1 615, 1 689	3 364, 3 485	
IIc	1 616, 1 689	3 364, 3 484	
IId	1 614, 1 687	3 362, 3 474	
IIe	1 615, 1 692	3 375, 3 464, 3 484	
IIf	1 621, 1 685	3 375, 3 480	
IIg	1 615, 1 682	3 374, 3 478	
IIh	1 619, 1 692	3 346–3 358, 3 460	
IIIa	1 631		1 488, 1 549
IIIb	1 635		1 488, 1 546
IIIc	1 635		1 489, 1 547
IIId	1 636		1 490, 1 553
IIIe	1 636		1 478, 1 569
IIIf	1 635		1 486, 1 522
IIIg	1 645		1 496, 1 555
IIIh	1 637		1 489, 1 557

and *Ih* were obtained from Chemopharma Usti nad Labem; bromomethyl 4-nitrophenyl ketone (*If*) was obtained from Leciva s.a. Prague. Chloromethyl 2,4-dichlorophenyl ketone (Fluka) was used for the synthesis of compound *IIe*. Anthranilic acid, pure (Lachema).

General Procedure of Preparation of Phenacyl Anthranilates *II*

Hydrogen carbonate (23.5 g, 0.28 mol) was added to a solution of anthranilic acid (32.9 g, 0.24 mol) in dimethylformamide (350 ml), and the reaction mixture was heated at 90–100 °C until the foaming ceased, whereupon it was cooled to 20 °C and treated with the respective substituted phenacyl bromide *I* (0.2 mol). The temperature increased spontaneously to 25–28 °C. After 1 h stirring (while monitoring the decrease of compound *I* in the reaction mixture by TLC), the mixture was poured onto a mixture of 20 g Na_2CO_3 and 1.5 kg ice and water. The precipitated solid was collected by suction and thoroughly washed with water and dried at 60 °C in a drying oven. In the case of compound *IId* the product separated in a paste consistency after pouring the reaction mixture into water: it was extracted with ethyl acetate, the extract was washed with distilled water, dried with sodium sulfate, filtered, and evaporated until dry. The dried product or evaporation residue was dissolved in boiling ethanol, filtered with 2.5 g charcoal, cooled to 0 °C, and the precipitated solid was collected by filtration, washed with cold ethanol, and dried.

General Procedure of Preparation of 2-Aryl-3-hydroxyquinolin-4(1*H*)-ones *III*

A. Phenacyl anthranilate (*II*, 0.01 mol) was stirred with polyphosphoric acid (10 g, containing 88.4% P_2O_5) at 100 °C for 2 h. Then the reaction mixture was poured into 150 ml hot water, and the precipitated product was hot filtered, and washed with 100 ml saturated $NaHCO_3$ solution and with hot water until neutral. After thorough suction and drying, the product was used as such in subsequent synthesis or recrystallized from dimethylformamide and ethanol for analysis.

B. A melt of phenacyl anthranilate (*II*, 0.1 mol) was gradually heated to 230 °C. Foaming of the reaction mixture began at a temperature of 170–190 °C with concomitant escaping of steam. After reaching 230 °C, exothermic cyclization took place with concomitant spontaneous heating of reaction mixture up to ca 250 °C, and after several minutes the mixture solidified. 15 min after reaching the temperature of 200 °C, the reaction mixture was cooled to room temperature and treated with 75 ml ethyl acetate. The solid was stirred and the mixture was refluxed 30 min, whereafter it was cooled to 0 °C and the solid was collected by filtration. After washing with cold ethyl acetate it was dried. For analysis the product was recrystallized, for synthesis it was used without recrystallization.

3-Methoxy-1-methyl-2-phenyl-4-quinolone (*Va*) and 3,4-Dimethoxy-2-phenylquinoline (*VIa*)

Compound *IIIa* (3.64 g, 15.3 mmol) was added to a solution of NaOH (3.6 g, 90 mmol) in 30 ml water. It did not dissolve until the temperature of 60 °C. Then the reaction mixture was cooled to 20 °C and treated with dimethyl sulfate (5 ml, 52 mmol) added slowly drop by drop. During the addition, the temperature increased and a precipitate separated. The reaction mixture was stirred at 25–30 °C for 1 h, then 0.8 g NaOH was added and the solution was heated at 80 °C 20 min. After cooling to 0–5 °C, the reaction mixture was stirred ca 20 min and the solid was collected by filtration and washed with water until neutral. Aqueous mother liquors were extracted with ethyl acetate, the extract was dried with sodium sulfate, filtered, and evaporated until dry. The evaporation residue was added to the main product, mixed with 25 ml toluene, and refluxed 10 min. After cooling, the separated solid was collected by filtration, washed with toluene, and the mother liquors were filtered with charcoal through a thin layer of silica. The filtrate was evaporated until dry in a vacuum rotary evaporator to give 0.2 g yellowish oil which crystallized on standing. This fraction was identified by

NMR as 3,4-dimethoxy-2-phenylquinoline (*VIa*); yield 5%, m.p. 65 °C (ref.[9] gives m.p. 62–64 °C). ^{13}C NMR spectrum: 61.15, 61.36 ($2 \times OCH_3$). The solid portion was recrystallized from ethanol. The isolated product was identified as 3-methoxy-1-methyl-2-phenyl-4-quinolone (*Va*). The yield inclusive of the product from the mother liquors was 2.66 g, i.e. 65%, m.p. 227–231 °C (ref.[9] gives m.p. 222–224 °C, ref.[10] gives m.p. 220–222 °C). For $C_{17}H_{15}NO_2$ (265.3) calculated: 76.96% C, 5.70% H, 5.28% N; found: 76.67% C, 5.76% H, 5.36% N. ^{13}C NMR spectrum: 59.24 (OCH_3), 37.18 (NCH_3).

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