REACTIONS OF 3-ACYL-4-HYDROXY-2(1H)-QUINOLONES WITH NITROGEN BASES

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Dedicated to Prof. Dr. F. SAUTER, Vienna, on the occasion of his 65th birthday

ABSTRACT: 3-Acyl-4-hydroxy-2-quinolones **1** react with amines to yield 3-aminomethylene quinolinediones **2**. With hydroxylamine the corresponding oximes **3** are obtained, which cyclize on heating *via* a thermal Beckmann rearrangement to oxazolo[5,4-c]quinolones **4**. The oxazoles can be ringopened in the presence of acids to give 3-acylamino-4-hydroxyquinolones **5**. The hydrazones **6**, obtained from 3-acyl-4-hydroxy-2-quinolones **1** and hydrazines, cyclize either to pyrazolo[4,3-c]quinolones **7** or give mixtures of **7** and the dimeric azino-diethylidenequinolones **8**.

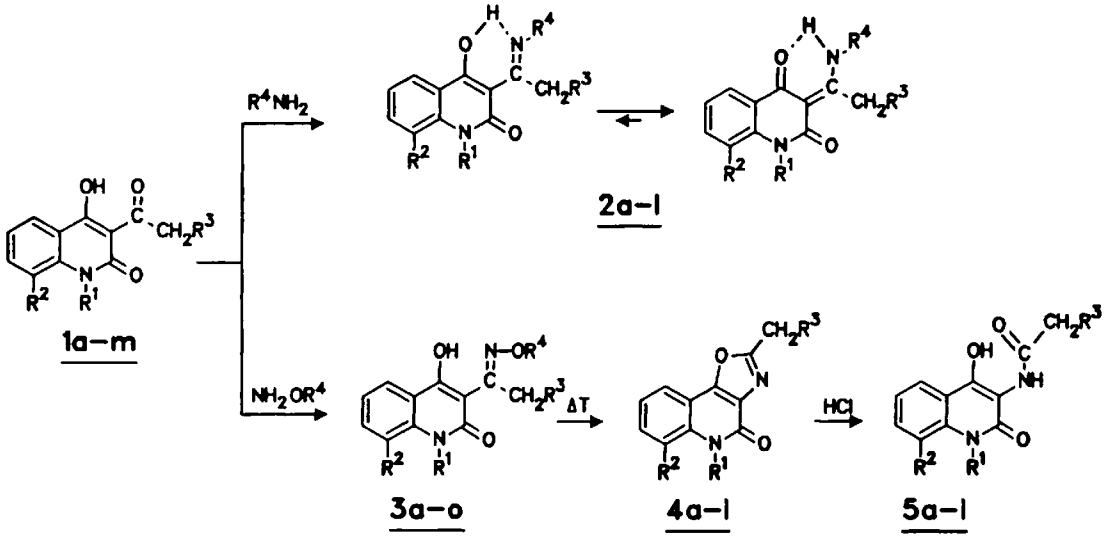
INTRODUCTION

4-Hydroxy-2-quinolines, their oxygen derivatives and the monocyclic debenzo derivatives having aliphatic acyl groups in position 3 have found great interest in the last years because of their biological properties (4). Reaction of the keto group of this class of compounds with nitrogen bases such as amines, hydroxylamines and hydrazines offers an entry to nitrogen containing carbonyl derivatives. Some of them have caused great interest because of their biological (5) or technical properties (6).

RESULTS AND DISCUSSION

We have shown recently, that 3-acyl-4-hydroxyquinolones of type **1** could be aminated in an equilibrium process at the keto moiety of the 3-acyl substituent by reaction with aqueous ammonia or amines with acetic acid as catalyst (7). The isomeric 4-amino-3-acylquinolones could be excluded by synthesis of the corresponding compounds *via* an independent pathway. Aliphatic and aromatic amines could be shown to react with **1a-f** in ethanol as solvent also by using dimethylaminopyridine as basic catalyst to obtain the 4-hydroxy-3-iminoethyl-2-quinolones **2a-l** in good yields. ^{1}H NMR spectroscopic studies have shown that compounds of this type deriving from 3-carbaldehydes (instead of 3-acyl groups in **2**) exist mainly in the tautomeric enaminoketone form (8) by using the aldehydic/olefinic proton as probe. The lack of this proton in **2** does not allow a similar assignment, and the carbonyl frequencies of the 4-oxo group in infrared spectra, which are usually a good hint for discussion of tautomers (9), are not helpful because of hydrogen bondings between the 4-hydroxy/4-oxo group with the imino/amino group, resp. Investigations by deuterium isotope effects on ^{13}C NMR chemical

shifts (10), however, give strong hints on the predominance of the enamino form, which is presented by the 3-aminoethylidene-quinoline-2,4-dione structure. Moreover, the ^1H NMR spectra (in DMSO-d_6) of the benzylamino derivatives **2a,g,i,k** show the CH_2-protons of the benzyl group as a 5 Hz coupling with the NH proton, which appears at 14.5 as broad signal. Therefore we use throughout this paper the enaminoketone structure, which is also in concordance with the results obtained in ref. (8).



R-Key: see Table 1-4

3-Oximatoacyl-4-hydroxyquinolones **3a-o** were obtained by reaction of the corresponding 3-acyl-4-hydroxyquinolones **1a-m** with excess hydroxylammonium chloride and hydrogencarbonate in ethanol-water under reflux to yield the hydroxyiminoquinolones **3a-l** (R^4 = H). To obtain the oximethers **3m-o** (R^4 = methyl), the quinolones **1a,b,m** were reacted with methyloxyammonium chloride and hydrogencarbonate. Both types of compound **3** show structural analogy to biologically interesting compounds such as ALLOXYDIM or SETHOXYDIM (11).

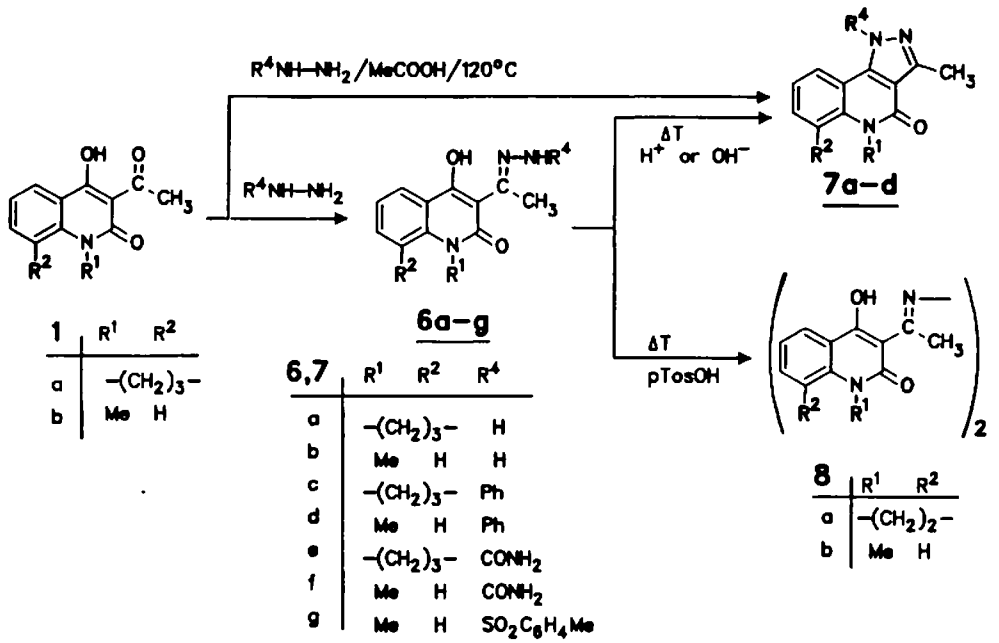
When the oximes **3** were thermolyzed in high boiling solvents such as 1,2-dichlorobenzene, diphenylether or ethylene glycol (or even without solvent, e.g. in a melting tube) in order to be cyclized to isoxazolo[4,5-c]quinolines by dehydration, a thermal Beckmann rearrangement took place and as final product the isomeric oxazolo[5,4-c]quinolones **4** were obtained in good yields, a class of compounds which was investigated recently because of its pharmacological properties (12). Attempts to achieve the cyclization to the isomeric isoxazolo[4,5-c]quinolines by dehydration even at milder temperatures in the presence of dehydrating agents such as acetic anhydride were unsuccessful.

The formation of the intermediate 3-acylamino-4-hydroxyquinolones **5** could be observed only in a few cases (e.g. from the oxime **3l** always a mixture of the oxazole **4l** and the acetylamino quinolone **5l** was obtained, whereas the oximether **3m** yielded pure oxazole **4l**). On the

other hand, hydrolysis of the oxazoles **4** with diluted hydrochloric acid led in excellent yields to 3-acylamino-4-hydroxyquinolones **5**. The structural assignment of the oxazoles **4** and the acylamino compounds **5** was performed by comparison with compounds obtained in an independent reaction pathway by reduction of 4-hydroxy-3-nitro-quinolones to the corresponding amino quinolones and acylation to compounds of type **5** followed by ring closure to compounds of type **4** (13).

Ketoximes of similar types (14) are also known to rearrange on acid catalysis to amides, but on attempts to perform this reaction sequence **3** → **5** (→ **4**) in concentrated mineral acids, only the starting 3-acylquinolone **1** could be obtained.

Hydrazines are known to give with 3-acyl-4-hydroxycoumarines the corresponding hydrazones (15). When hydrazines and similar compounds were reacted as nitrogen bases with 3-acyl-4-hydroxyquinolones **1a,b**, in the first reaction step the hydrazones **6a-d** were obtained from hydrazine or phenylhydrazine, resp. With semicarbazide or 4-toluenesulfonyl hydrazide the corresponding semicarbazones **6e,f** or the tosylhydrazone **6g** were formed.



Thermolysis of the phenylhydrazones **6c,d** in the presence of acids as catalyst led to pyrazolo[4,3-c]quinolones **7c,d** by elimination of water and cyclization. When the N-unsubstituted hydrazone **6a** was thermolyzed in boiling ethanol in the presence of p-toluenesulfonic acid, the corresponding pyrazolo[4,3-c]quinolone **7a** was obtained in only 44% yield; as byproduct in 21% yield the ketazine **8a** was obtained, a reaction sequence which is usually observed from two moles of the corresponding ketones and one mol of hydrazine. Ketazines **8a,b** were also obtained when the semicarbazones **6e,f** were thermolyzed in refluxing dimethylformamide, even without the presence of acids.

However, attempts to cyclize the N-unsubstituted hydrazone **6b** using 1-butanol as the solvent and p-toluenesulfonic acid as catalyst resulted only in the formation of the ketazine **8b**, and the pyrazole **7b** was observed only in traces. The pyrazole **7b** could be obtained in good yields when the hydrazone **6b** was thermolyzed in triethylene glycol in the presence of sodium hydroxide. Although the reaction conditions are similar to a Wolff-Kishner reaction (in its Huang-Minlon variant), no reduction product, 3-ethyl-4-hydroxy-2-quinolone, could be observed. Pyrazolo[4,3-c]quinolone **7b** was also formed in good yields in a one pot reaction from **1b** and hydrazine in boiling acetic acid.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus, Mod. MFB-595 in open capillary tubes. ^{1}H NMR spectra (200 MHz) were recorded 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 spectra was DMSO-d_6 unless otherwise stated. Infrared spectra were taken on a Perkin-Elmer 298 spectrophotometer in potassium bromide pellets. Elemental analyses werde performed on a Carlo Erba 1106 C,H,N automatic analyzer. 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.

3-Acyl-4-hydroxy-2(1H)quinolones (**1a-m**) were obtained according to ref. (16).

General Procedure for the Synthesis of 3-Aminoethylidene-quinoline-2,4(1H,3H)-diones and 2-Aminoethylidene-6,7-dihydro-5H-benzo[ij]quinolizin-1,3(2H)-diones (**2a-l**)

To a solution of the corresponding acyl derivative **1** (0.023 mol) in ethanol (50 ml) the appropriate amine (benzylamine or aniline, resp.) (0.047 mol) and 4-(N,N-dimethylamino)pyridine (0.2 g) as catalyst is added. The mixture is heated for 2-3 h under reflux. On cooling the product precipitates and is filtered by suction. Chemical and physical data: see table 1.

General Procedure for the Synthesis of 4-Hydroxy-3-(1-hydroxyiminoalkyl)-2(1H)-quinolones and 1-Hydroxy-2-(1-hydroxyiminoalkyl)-6,7-dihydro-5H-benzo[ij]quinolizin-3-ones (R^4= H) (**3a-l**)

A solution of the appropriate acyl derivative **1** (0.02 mol), hydroxylammonium chloride (2.50 g, 0.036 mol) and sodium hydrogencarbonate (3.00 g, 0.036 mol) in ethanol (80 ml) and water (40 ml) is heated under reflux for 60-90 min. Then the reaction mixture is cooled to 4 °C, the product precipitates and is filtered by suction. Chemical and physical data: see table 2.

General Procedure for the Synthesis of 4-Hydroxy-3-(1-methoxyiminoalkyl)-2(1H)-quinolones and 1-Hydroxy-2-(1-hydroxyiminoalkyl)-6,7-dihydro-5H-benzo[ij]quinolizin-3-ones (R^4= OMe) (**3m-o**)

A solution of the appropriate acyl derivative **1** (0.02 mol), methyloxyammonium chloride (2.08 g, 0.025 mol) (17) and sodium hydrogencarbonate (2.1 g, 0.025 mol) in ethanol (25 ml) and water (50 ml) is heated under reflux for 90 min. The oily product becomes solid on cooling to

4 °C and is filtered by suction. Chemical and physical data: see table 2.

General Procedure for the Synthesis of Oxazolo[5,4-c]quinolin-4-ones and 5,6-Dihydro-4H-benzo[i,j]oxazolo[5,4-b]quinolizin-8-ones (**4a-l**)

A solution of the appropriate hydroxyimino-alkyl derivative **3** (0.04 mol) in 1,2-dihydroxyethane (20 ml) is heated under reflux for 20 min. After cooling to 20 °C, water (25 ml) is added, the mixture stirred for 20 min and then filtered by suction. Chemical and physical data: see table 3.

General Procedure for the Synthesis of 3-Acylamino-4-hydroxy-2(1H)-quinolones and 2-Acylamino-1-hydroxy-6,7-dihydro-4H-benzo[i,j]quinolizin-3-ones (**5a-l**)

The appropriate oxazolo derivative **4** (4 mmol) is dissolved in 0.1 N hydrochloric acid (20 ml) and ethanol (30 ml) and heated under reflux for 30 min. The ring opened product precipitates in the hot solution and is separated after cooling by filtration. Chemical and physical data: see table 4.

2-(1-Hydrazonoethyl)-1-hydroxy-6,7-dihydro-5H-benzo[ij]quinolizin-3-one (**6a**) - 2-Acetyl-benzoquinolizinone **1a** (2.43 g, 0.01 mol) is dissolved in hot ethanol (25 ml) and after addition of hydrazine hydrate (0.75 g, 0.015 mol) heated under reflux for 2 h. The hot solution is poured onto ice and the precipitate filtered by suction. Yield: 1.90 g (74%), yellow prisms, mp 308 °C, dec. (ethanol). - IR: 3260 m, 3150 m, 1660 sh, 1605 s, 1585 s cm^{-1}; ^1H NMR (CF_3COOH): δ= 2.0-2.55 (m, CH_2), 2.8-3.5 (m, Ar-CH_2), 3.0 (s, CH_3), 4.37 (t, J= 6 Hz, N-CH_2), 7,3-7.95 (m, 2 ArH), 8.15 (dd, J= 2+6 Hz, 10-H). Anal. Calcd for $C_{14}H_{15}N_3O_2$: C, 65.35, H, 5.88, N, 16.33. Found: C, 65.42, H, 5.73, N, 16.24.

3-(1-Hydrazonoethyl)-4-hydroxy-1-methyl-quinolin-2(1H)-one (**6b**) - A solution of 3-acetylquinolone **1b** (4.32 g, 0.02 mol) in hot ethanol (25 ml) is reacted with hydrazine hydrate (1.5 g, 0.03 mol) and worked up as described for **6a**. Yield: 2.85 g (66%), yellow needles, mp 300 °C, dec. (methanol). - IR: 3315 m, 1600 s, 1550 m cm^{-1}; ^1H NMR (CF_3COOH): δ= 2.95 (s, CH_3), 3.9 (s, N-CH_3), 7.5-8.1 (m, 3 ArH), 8.3 (dd, J= 2+7 Hz, 5-H). Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.32, H, 5.67, N, 18.17. Found: C, 62.30, H, 5.57, N, 17.99.

1-Hydroxy-2-[1-(2-phenylhydrazono)-ethyl]-6,7-dihydro-5H-benzo[ij]quinolizin-3-one (**6c**) - To a boiling solution of the 2-acetylbenzoquinolizinone **1a** (2.43 g, 0.01 mol) in 1-butanol (10 ml), phenylhydrazine (1.08 g, 0.01 ml) is added. The product begins to precipitate slowly in the hot solution, which is refluxed for 75 min and then cooled and filtered by suction. Yield: 2.0 g (60%) yellow needles, mp 205-208 °C (ethanol). - IR: 3240 m, 2930 w, 1620 sh, 1600 s cm^{-1}; ^1H NMR (CF_3COOH): δ= 1.9-2.5 (m, CH_2), 2.85-3.25 (m, Ar-CH_2), 6.8-7.9 (m, 7 ArH), 8.1 (dd, J= 2+8 Hz, 10-H). Anal. Calcd. for $C_{20}H_{19}N_3O_2$: C, 72.05, H, 5.74, N, 12.60. Found: C, 72.28, H, 5.64, N, 12.66.

Table 1: Chemical and Physical Data of 3-Aminoethylidene-quinoline-2,4(1H,3H)-diones and 2-Aminoethylidene-6,7-dihydro-5H-benzo[ij]quinolizin-1,3(2H)-diones (**2a-l**)

Compound* (from)	R^1	R^2	R^3	R^4	yield (%)	mp (°C) solvent	IR (cm^{-1}) ^1H NMR (δ ppm)
2a (**1a**)	$-(CH_2)_3-$		H	CH_2Ph	69	122-124 ethanol	2920 w, 1625 s, 1590 s 1.7-2.0, 2.5-2.8, 3.6-3.9 (m, 3 CH_2), 3.25 (s, CH_3), 4.65 (d, J= 5 Hz, NH-CH_2), 6.7-7.4 (m, 7 ArH), 7.75 (dd, J= 7+1.5 Hz, 10-H), 14.4 (b, NH).
2b (**1a**)	$-(CH_2)_3-$		H	Ph	70	111-113 ethanol	2920 w, 1620 s, 1590 s, 1550 s 1.85-2.3, 2.65-3.1, 3.9-4.2 (m, 3 CH_2), 3.4 (s, CH_3), 7.0-7.5 (m, 7 ArH), 7.95 (dd, J = 7+1.5 Hz, 10-H).
2c (**1b**)	Me	H	H	CH_2Ph	51	162-164 [lit. mp 159.5-161.5 (7)]	
2d (**1b**)	Me	H	H	Ph	58	161-162 ethanol	1625 s, 1610 m, 1590 s 2.6 (s, CH_3), 3.45 (s, N-CH_3), 7.1-7.6 (m, 8 ArH), 8.05 (dd, J= 7+1.5 Hz, 5-H).
2e (**1c**)	CH_2Ph	H	H	CH_2Ph	64	114-116 ethanol	3060 w, 1640 s, 1590 s
2f (**1c**)	CH_2Ph	H	H	Ph	61	150-151 ethanol	3020 w, 1630 s, 1610 m, 1590 m 2.6 (s, CH_3), 5.35 (s, N-CH_2), 7.0-7.5 (m, 13 ArH), 8.15 (dd, J= 7+1.5 Hz, 5-H).
2g (**1d**)	Me	H	Me	CH_2Ph	80	100-101 ethanol	2960 w, 2920 w, 1630 s, 1610 m 1.2 (t, J= 7 Hz, CH_3), 3.3 (s, NCH_3), 3.45 (q, J= 7 Hz, CH_2), 4.85 (d, J= 5 Hz, NH-CH_2), 7.0-7.6 (m, 8 ArH), 8.1 (dd, J= 7+1.5 Hz, 5-H), 14.5 (b, NH).
2h (**1d**)	Me	H	Me	Ph	60	144-145 ethanol	2940 w, 1630 s, 1590 s 1.15 (t, J= 7 Hz, CH_3), 3.1 (q, J= 7 Hz, CH_2), 3.5 (s, N-CH_3), 7.1-7.6 (m, 8 ArH), 8.05 (dd, J = 7+1.5 Hz, 5-H).
2i (**1e**)	$-(CH_2)_3-$		Me	CH_2Ph	75	113-114 ethanol	2940 m, 1620 s, 1590 s 1.2 (t, J= 7 Hz, CH_3), 1.7-2.1, 2.65-3.0, 3.7-4.05 (m, 3 CH_2), 3.3 (q, J= 7 Hz, CH_2), 4.8 (d, J= 5 Hz, NH-CH_2), 6.9-7.4 (m, 7 ArH), 7.8 (dd, J= 7+1.5 Hz, 10-H), 14.4 (b, NH).
2j (**1e**)	$-(CH_2)_3-$		Me	Ph	75	118-120 ethanol	2940 w, 1625 s, 1590 s, 1555 s 1.1.1 (t, J= 7 Hz, CH_3), 1.7-2.1, 3.0-3.4, 3.7-4.0 (m, 3 CH_2), 2.85 (q, J= 7 Hz, CH_2), 6.9-7.5 (m, 7 H), 7.85 (dd, J= 7+1.5 Hz, 10-H).
2k (**1f**)	Ph	H	Me	CH_2Ph	70	185-186 ethanol	2980 w, 2960 w, 1640 s, 1605 s 1.1 (t, J= 7 Hz, CH_3), 2.4 (q, J= 7 Hz, CH_2), 4.8 (d, J= 5 Hz, NH-CH_2), 7.0-7.6 (m, 13 ArH), 8.05 (dd, J= 7+1.5 Hz, 5-H), 14.3 (b, NH).
2l (**1f**)	Ph	H	Me	Ph	65	160-162 ethanol	2940 w, 1640 s, 1610 m, 1590 m 1.1.0 (t, J= 7 Hz, CH_3), 3.1 (q, J= 7 Hz, CH_2), 7.1-7.5 (m, 13 ArH), 8.0 (dd, J= 7+1.5 Hz, 5-H).

* The elemental analyses for C, H, and N agree within ± 0.4% of the theoretical values.

Table 2 Chemical and Physical Data of 4-Hydroxy-3-(1-hydroxyiminoalkyl)-2(1H)-quinolones and 1-Hydroxy-2-(1-hydroxyiminoalkyl)-6,7-dihydro-5H-benzo[ij]quinolizin-3-ones (**3a-o**)

Compound*	(from)	R^1	R^2	R^3	R^4	yield (%)	mp (°C) solvent	IR (cm^{-1}) ^1H NMR (δ ppm)
3a	(**1a**)	-$(CH_2)_3$-		H	H	64	159-161 xylene	3360 bm, 3160 w, 1645 m, 1605 w, 1564 sh 1.9-2.3 (m, CH_2), 2.45 (s, CH_3), 2.94 (t, J= 5 Hz, Ar-CH_2), 4.05 (t, J= 5 Hz, N-CH_2), 6.9-7.5 (m, 2 ArH), 7.8 (dd, J= 2+7 Hz, 10-H)
3b	(**1b**)	Me	H	H	H	40	174-175 toluene	3220 b,sn, 3050 s, 1645 s, 1615 m, 1605 m, 1585s 2.45 (s, CH_3), 3.55 (s, N-CH_2), 7.0-7.75 (m, 3 ArH), 7.95 (dd, J= 2+7 Hz, 5-H), 11.55 (b, s, acidic H)
3c	(**1c**)	CH_2Ph	H	H	H	82	163-164 ethanol	2940 w, 1640 s, 1600 m, 1550 s 2.3 (s, CH_3), 5.4 (s, N-CH_2), 7.0-7.4 (m, 8 ArH), 7.85 (dd, J= 7+1.5 Hz, 5-H)
3d	(**1d**)	Me	H	Me	H	72	144-145 ethanol	2970 w, 1650 s, 1610 w, 1580 s 1.1 (t, J= 7 Hz, CH_3), 2.9 (q, J= 7 Hz, CH_2), 3.55 (s, N-CH_3), 7.2-7.7 (m, 3 ArH), 8.05 (dd, J= 7 + 1.5 Hz, 5-H).
3e	(**1e**)	-$(CH_2)_3$-		Me	H	69	162-163 ethanol	3120 w, 2940 w, 1640 s, 1600 m 1.1 (t, J= 7 Hz, CH_3), 1.75-2.3, 2.7-3.2 (m, 3 CH_2), 3.95 (q, J= 7 Hz, CH_2), 5.85 (s, OH), 6.9-7.55 (m, 2 ArH), 7.7 (dd, J= 7+1.5 Hz, 10-H).
3f	(**1g**)	-$(CH_2)_3$-		Et	H	48	69-170 ethanol	2960 w, 2870 w, 1630 s, 1605 m 0.9 (t, J= 7 Hz, CH_3), 1.2-2.3, 2.7-3.2 (m, 3 CH_2), 3.8-4.2 (m, 2 CH_2), 7.0-7.6 (m, 2 ArH), 7.9 (dd, J= 7+1.5 Hz, 10-H).
3g	(**1h**)	Ph	H	Et	H	74	179-80 ethanol	2940 w, 2860 w, 1630 s, 1600 m
3h	(**1i**)	Me	H	C_4H_9	H	76	131-133 ethanol	2940 w, 2850 w, 1660 s, 1610 m 0.9 (t, J= 7 Hz, CH_3), 1.2-1.7 (m, $(CH_2)_3$), 2.5 (q, J= 7 Hz, CH_2), 3.75 (s, N-CH_3), 7.2-7.75 (m, 3 ArH), 8.25 (dd, J= 7+1.5 Hz, 5-H).
3i	(**1j**)	-$(CH_2)_3$-		C_4H_9	H	77	145-146 ethanol	2960 m, 2860 w, 1635 s, 1605 m, 1585 s
3j	(**1k**)	Ph	H	Ph	H	74	180-181 ethanol	1630 s, 1600 m, 1580 m, 1540 s 4.3 (s, CH_2), 7.0-7.3 (m, 13 ArH), 7.45 (dd, J= 7+1.5 Hz, 5-H).
3k	(**1l**)	-$(CH_2)_3$-		Ph	H	75	165-166 ethanol	3040 w, 2930 w, 1630 s, 1600 m 0.7-2.3, 2.3-3.2 (m, 3 CH_2), 4.55 (s, CH_2), 7.1-7.6 (m, 7 ArH), 7.9 (dd, J= 7+1.5Hz, 10-H).
3l	(**1m**)	H	H	H	H	78	199-200 ethanol	3280 bm, 3180 bm, 3020 m, 1645 s, 1615 m 2.35 (s, CH_3), 6.9-7.6 (m, 3 ArH), 7.8 (dd, J= 2+7 Hz, 5-H), 11.2 (s, b, acidic H)
3m	(**1m**)	H	H	H	MeO	78	220-221 1-butanol	3160 w, 3110 w, 3010 w, 1655 s. 1615 m 2.25 (s, CH_3), 3.85 (s, OCH_3), 6.95-7.55 (m, 3 ArH, 7.9 (dd, J= 2+7 Hz, H-5), 11.3 (s, acidic H)
3n	(**1b**)	Me	H	H	MeO	80	111-112 EtOH/H_2O	2950 w,1640 s, 1595 m 2.5 (s, CH_3), 3.55 (s, N-CH_3), 4.0 (s, OCH_3), 6.95-7.6 (m, 3 ArH), 8.0 (dd, J= 2+8 Hz, 5-H), 13.55 (s, acidic H)
3o	(**1a**)	-$(CH_2)_3$-		H	MeO	56	100-102 ethanol	2960 w, 2940 w, 2900 w, 1640 s, 1595 m 1.8-2.15 (m, CH_2), 2.25 (s, CH_3), 2.65-3.05 (m, Ar-CH_2), 3.35-3.8 (m, N-CH_2), 3.9 (s, OCH_3), 6.85-7.4 (m, 2 ArH), 7.7 (dd, J= 2+7 Hz, 10-H)

* The elemental analyses for C, H, and N agree within ± 0.4% of the theoretical values.

Table 3 Chemical and Physical Data of Oxazolo[5,4-c]quinolin-4-ones and 5,6-Dihydro-4H-benzo[i,j]oxazolo[5,4-b]quinolizin-8-ones (**4a-l**)

Compound*		R^1	R^2	R^3	yield	mp (°C)	IR (cm^{-1})
	(from)				(%)	solvent	^1H NMR (δ ppm)
4a	(**3a**)	Me	H	H	56	206-209 [ref. mp 191 (13)]	
	(**3n**)				58	ethanol	
4b	(**3b**)	-$(CH_2)_3$-		H	52	189-191 [ref. mp 171 (13)]	
	(**3o**)				55	toluene	
4c		CH_2Ph	H	H	71	170-172 $EtOH/H_2O$	2860 w, 1650 s, 1605 m, 1560 s
4d		Me	H	Me	89	136-137 $EtOH/H_2O$	2960 w, 1650 s, 1600 m, 1580 s
4e		-$(CH_2)_3$-		Me	77	147-149 $EtOH/H_2O$	3080 w, 2930 w, 1660 s, 1600 m,
4f		-$(CH_2)_3$-		Et	70	123-124 $EtOH/H_2O$	2940 m, 2860 w, 1680 s, 1640 w 0.9 (t, J= 7 Hz, CH_3), 1.4-2.1, 2.6-2.9 (m, 3 CH_2), 3.95 (q, J= 7 Hz, N-CH_2), 7.0-7.3 (m, 2 ArH), 7.55 (dd, J= 7+1.5 Hz, 10-H).
4g		Ph	H	Et	75	135-136 $EtOH/H_2O$	2960 w, 2860 w, 1660 s, 1595 s
4h		Me	H	C_4H_9	93	129-130 $EtOH/H_2O$	2960 m, 2840 w, 1680 s, 1610 w
4i		-$(CH_2)_3$-		C_4H_9	91	70-72 $EtOH/H_2O$	2960 m, 2870 w, 1675 s, 1640 w 0.7-0.9 (m, CH_3), 1.0-3.05 (m, 6 CH_2), 3.8-4.15 (m, CH_2), 7.0-7.4 (m, 2 ArH), 7.55 (dd, J= 7+1.5 Hz, 10-H).
4j		Ph	H	Ph	75	145-147 $EtOH/H_2O$	2940 w, 1640 s, 1605 m, 1580 m
4k		-$(CH_2)_3$-		Ph	81	220-223 $EtOH/H_2O$	3030 w, 2930 w, 1670 s, 1635 m 0.7-2.3, 2.3-2.9 (m, 3 CH_2), 4.3 (s, CH_2), 7.0-7.3 (m, 7 ArH), 7.55 (dd, J= 7+1.5 Hz, 10-H).
4l	(**3l**)	H	H	H	**	310 dec	3180 w, 3010 w, 2870 m, 1670 s, 1635 sh, 1610 m
	(**3m**)				61	ethanol	2.65 (s, CH_3), 7.2-7.65 (m, 3 ArH), 7.8 (d, J= 8 Hz, H-9)

* The elemental analyses for C, H, and N agree within ± 0.4% of the theoretical values.
** only as 1:2 mixture of **4l** and **5l** obtained

4-Hydroxy-3-[1-(2-phenylhydrazono)-ethyl]-1-methyl-quinolin-2(1H)-one (**6d**) - A solution of the acetylquinolone **1b** (2.17 g, 0.01 mol) in 1-butanol (10 ml) is reacted for 15 min with phenylhydrazine (1.30 g, 0.012 mol) and worked up as described for **6c**. Yield: 2.85 g (92%) yellow plates, mp 211-212 °C (dioxane). - IR: 3320-3160 b, 3070-3000 b, 1615 s, 1590 sh; ^1H NMR (CF_3COOH): δ= 3.05 (s, CH_3), 3.9 (s, N-CH_3), 6.9-8.05 (m, 8 ArH), 8.25 (dd, J= 2+8 Hz, 5-H). Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34, H, 5.58, N, 13.67. Found: C, 70.24, H, 5.79, N, 13.41.

1-Hydroxy-2-(1-semicarbazono-ethyl)-6,7-dihydro-5H-benzo[ij]quinolizin-3-one (**6e**) - To a solution of the 2-acetyl-benzoquinolizine **1a** (2.43 g, 0.01 mol) in hot ethanol (200 ml) a solution of semicarbazide hydrochloride (1.67 g, 0.015 mol) and sodium acetate (1.23 g, 0.015 mol) in hot ethanol (20 ml) is added and heatded for 1 h. In the hot reaction mixture the product slowly

Table 4 Chemical and Physical Data of 3-Acylamino-4-hydroxy-2(1H)-quinolones and 2-Acylamino-1-hydroxy-6,7-dihydro-4H-benzo[i,j]quinolizin-3-ones (**5a-l**)

Compound*	R^1	R^2	R^3	yield (%)	mp (°C) solvent	IR (cm^{-1}) ^1H NMR (δ ppm)
5a	Me	H	H	75	190 toluene	ref. (13): mp 191.7-192.8
5b	$-(CH_2)_3-$		H	80	216	ref. 13, 18, 19: mp 212-216
5c	CH_2Ph	H	H	71	175-176 ethanol	3260 s, 1670 s, 1640 s, 1600 m 2.3 (s, CH_3), 5.55 (s, N-CH_2), 7.05-7.45 (m, 8 ArH), 7.85 (dd, J= 7 + 1.5 Hz, 5-H), 9.4 (s, OH), 11.95 (s, NH).
5d	Me	H	Me	76	150-152 ethanol	3200 s, 1660 s, 1640 m, 1605 m 1.15 (t, J= 7 Hz, CH_3), 2.85 (q, J = 7 Hz, CH_2), 3.45 (s, N-CH_3), 7.2-7.7 (m, 3 ArH), 8.05 (dd, J=7 +1.5 Hz, 5-H), 11.4 (s, NH).
5e	$-(CH_2)_3-$		Me	76	162-163 ethanol	3260 s, 2960 w, 1670 s, 1630 s 1.1 (t, J= 7 Hz, CH_3), 1.75-2.2, 2.7-3.3 (m, 3 CH_2), 3.95 q , J= 7 Hz, CH_2), 6.9-7.6 (m, 2 ArH), 7.7 (dd, J = 7+1.5 Hz, 10-H), 11.3 (s, 1 H, NH).
5f	$-(CH_2)_3-$		Et	81	147-148 ethanol	3290 s, 2940 m, 1640 s , 1610 s 0.85 (t, J = 7 Hz, CH_3), 1.5-2.2, 2.2-2.5 (m, 3 CH_2), 2.6-3.0 (m, CH_2), 3.8-4.1 (m, CH_2-CO), 7.0-7.5 (m, 2 ArH), 7.65 (dd, J = 7 + 1.5 Hz, 10-H), 9.5 (s, OH), 11.8 (s, NH).
5g	Ph	H	Et	62	157-158 ethanol	3240 s, 1670 s, 1630 s, 1600 m 0.95 (t, J = 7 Hz, CH_3), 3.05-3.25 (m, CH_2-CH_2), 3.4 (q, J= 7 Hz, CH_2-CO), 7.2-7.7 (m, 8 ArH), 8.15 (dd, J= 7+1.5 Hz, 5-H), 9.3 (s, OH), 11.8 (s, NH).
5h	Me	H	C_4H_9	82	143-144 ethanol	3260 s, 1680 s, 1640 s, 1600 m 0.95 (t, J = 7 Hz, 3 H, CH_3), 1.25-1.75, 1.75-2.25 (m, 6 H, CH_2-CH_2-CH_2), 2.5 (q, J= 7 Hz, 2 H, CH_2-CO), 3.7 (s, 3 H, N-CH_3), 7.2-7.5 (m, 3 H, ArH), 8.25 (dd, J = 7 + 1.5 Hz, 1 H, 5-H), 12.2 (s, 1 H, NH).
5i	$-(CH_2)_3-$		C_4H_9	84	111-113 ethanol	3230 s, 2950 m, 1650 s, 1630 s, 1600 s 0.7-0.9 (m, CH_3), 1.0-1.5 (m, CH_2), 1.5-2.1, 2.1-2.5 (m, 3 CH_2), 2.7-3.0 (m, 2 CH_2), 3.8-4.1 (m, CH_2-CO), 7.0-7.4 (m, 2 ArH), 7.55 (dd, J = 7 + 1.5 Hz, 10-H), 11.4 (s, NH).
5j	Ph	H	Ph	70	163-164 ethanol	3220 s, 1660 s, 1630 , 1600 m 4.3 (s, CH_2), 7.0-7.7 (m, 13 ArH), 8.0 (dd, J= 7 + 1.5 Hz, 5-H), 9.3 (s, 1OH), 11.7 (s, NH).
5k	$-(CH_2)_3-$		Ph	86	184-185 ethanol	3280 s, 1640 s, 1610 s, 1570 s 0.7-2.3, 2.3-2.9 (m, 3 CH_2), 4.3 (s, CH_2), 7.0-7.3 (m, 7 ArH), 7.55 (dd, J= 7+ 1.5 Hz, 10-H), 9.3 (s, OH), 11.5 (s, NH).
5l	H	H	H	75	216	ref. (18), (19): mp 214-218

* The elemental analyses for C, H, and N agree within ± 0.4% of the theoretical values.

precipitates. The mixture is cooled and the product filtered by suction. Yield: 2.0 g (67%) pale yellow microcrystals, mp 303 °C, dec. (ethanol). - IR: 3320 m, 3180 m, 1705 s, 1620 s, 1585 s cm^{-1}; ^1H NMR (CF_3COOH): δ= 2.0-2.5 (m, CH_2), 2.8-3.25 (m, Ar-CH_2), 2.9 (s, CH_3), 4.35 (t, J= 6 Hz, N-CH_2), 7.3-8.0 (m, 2 ArH), 8.35 (dd, J= 2+8 Hz, 10-H). Anal. Calcd. for $C_{15}H_{16}N_4O_3$: C, 59.99, H, 5.37, N, 18.66. Found: C, 60.15, H, 5.27, N, 18.11.

4-Hydroxy-1-methyl-3-(1-semicarbazono-ethyl)-quinolin-2(1H)-one (**6f**) - A solution of the 3-acetylquinolone **1b** (2.17 g, 0.01 mol) in hot ethanol (200 ml) and of semicarbazide hydrochloride (1.67 g, 0.015 mol) and sodium acetate (1.23 g, 0.015 mol) in hot ethanol (20 ml) is combined and reacted for 1 h and worked up as described for **6e**. Yield: 2.30 g (84%) pale yellow prisms, mp 273 °C, dec. (ethanol). - IR: 3410 m, 3330-3170 bm, 1680 s, 1615 s, 1585 s cm^{-1}; ^1H NMR (CF_3COOH): δ= 2.95 (s, CH_3), 3.97 (s, N-CH_3), 7.5-8.2 (m, 3 ArH), 8.35 (dd, J= 2+7 Hz, 5-H). Anal. Calcd. for $C_{13}H_{14}N_4O_3$: C, 56.93, H, 5.14, N, 20.43. Found: C, 56.88, H, 4.99, N, 20.32.

4-Hydroxy-1-methyl-3-{1-[2-(4-methylphenylsulfonyl)-hydrazono]-ethyl}-quinolin-2(1H)-one (**6g**) - A solution of the 3-acetylquinolone **1b** (1.09 g, 5 mmol) and 4-tolylsulfonylhydrazide (1.21 g, 6.5 mmol) in 1-butanol (10 ml) is heated for 90 min under reflux. On cooling the product precipitates and is filtered by suction. Yield: 1.30 g (73%), yellow needles, mp 195-198 °C (glacial acetic acid). - IR: 3080 m, 1630 sh, 1620 s, 1590 s cm^{-1}; ^1H NMR (CF_3COOH): δ= 2.4 (s, tosyl-CH_3), 2.97 (s, CH_3), 3.83 (s, N-CH_3), 7.2-8.1 (m, 7 ArH), 8.32 (dd, J= 2+7 Hz, 5-H). Anal. Calcd. for $C_{19}H_{18}N_3O_4S$: C, 59.20, H, 4.71, N, 10.90. Found: C, 59.45, H, 4.81, N, 10.80.

9-Methyl-5,6-dihydro-4H,11H-benzo[ij]pyrazolo[3,4-b]quinolizin-8-one (**7a**) - When the filtrate of the ketazine **8a** is cooled for 1 h to 4 °C, **7a** precipitates and can be separated by filtration. Yield: 0.53 g (44%), pale yellow prisms, m.p. 310 °C, dec. (dimethylformamide). - IR: 3200-3080 b, m, 2950 m, 1650 s, 1625 sh, 1590 s cm^{-1}; ^1H NMR (CF_3COOH): δ= 2.0-2.6 (m, CH_2), 3.0-3.4 (t, J= 5 Hz, Ar-CH_2), 3.1 (s, CH_3), 4.45 (t, J= 5 Hz, N-CH_2), 7.4-8.0 (m, 2 ArH), 8.15 (dd, J= 2+7 Hz, 1-H). Anal. Calcd. for $C_{14}H_{13}N_3O$: C, 70.28, H, 5.48, N, 17.56. Found: C, 70.13, H, 5.40, N, 17.39.

3,5-Dimethyl-1H-pyrazolo[4,3-c]quinolin-4(5H)-one (**7b**) - *Method a)* A solution of 3-acetylquinolone **1b** (2.17 g, 0.01 mol) in hot glacial acetic acid (40 ml) is treated with hydrazine hydrate (0.60 g, 0.012 mol) and heated under reflux for 2 h. On cooling the products precipitates and is filtered by suction. Yield: 1.37 g (64%) yellow needles, mp 301 °C, dec. (glacial acetic acid).

Method b) A mixture of the hydrazone **6b** (1.16 g, 0.005 mol) and powdered sodium hydroxide (0.60 g) are heated for 30 min in triethyleneglycol (50 ml) to 190-220 °C, and then for a short period under reflux. The hot solution is poured onto ice and kept overnight at 4 °C to start crystallization. Yield: 0.82 g (77%), colorless needles, mp 301°C, dec. (toluene). - IR: 3230-3090 b, m, 1640 s, 1625 s, 1575 s cm^{-1}; ^1H NMR (CF_3COOH): δ= 3.05 (s, CH_3), 3.95 (s, N-CH_3), 7.5-8.2 (m, 3 Ar-H), 8.3 (dd, J= 2+7 Hz, 5-H). Anal. Calcd. for: $C_{12}H_{11}N_3O$: C, 67.59, H, 5.20, N, 19.71. Found: C, 67.28, H, 5.22, N, 19.60.

9-Methyl-11-phenyl-5,6-dihydro-4H-benzo[ij]pyrazolo[3,4-b]quinolizin-8-one (**7c**) - A hot solution of the phenylhydrazone **6c** (1.00 g, 0.003 mol) in glacial acetic acid (50 ml) is treated with some drops of conc. sulfuric acid and then heated under reflux for 90 min. The hot reaction mixture is poured onto ice and the precipitate is filtered by suction. Yield: 0.78 g (82%), colorless prisms, mp 204-207 °C (ligroin). - ^1H NMR (CF_3COOH): δ= 1.9-2.5 (m, CH_2), 2.85-

3.35 (m, Ar-CH_2), 3.08 (s, CH_3), 4.3 (t, J= 6 Hz, N-CH_2), 6.9-8.0 (m, 8 ArH). Anal. Calcd. for $C_{20}H_{17}N_3O$: C, 76.17, H, 5.44, N, 13.32. Found: C, 76.34, H, 5.20, N ,13.26.

3,5-Dimethyl-1-phenyl-pyrazolo[4,3-c]quinolin-4(5H)-one (**7d**) - A hot solution of the phenylhydrazone **6d** (1.23 g, 0.004 mol) in glacial acetic acid (50 ml) is reacted as described for **7c**. Yield: 0.95 g (82%) colorless prisms, mp 190-193 °C (ligroin). - IR: 1655 s, 1570 m cm^{-1}; ^1H NMR (CF_3COOH): δ= 3.0 (s, CH_3), 3.9 (s, N-CH_3), 7.1-7.4 (m, 3 ArH), 7.5-8.0 (m, 6 ArH). Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72, H, 5.23, N, 14.52. Found: C, 74.98, H, 5.25, N, 14.50.

1,1'-Azino-di-(2-ethylidene-1-hydroxy-3-oxo-6,7-dihydro-5H-benzo[ij]quinolizin-3-one) (**8a**) - A hot solution of the hydrazone **6a** (1.29 g, 0.005 mol) in ethanol (200 ml) is treated with a catalytical amount of p-toluenesulfonic acid and the mixture heated under reflux for 3 h. The precipitate begins to crystallize in the hot solution and after cooling the product is filtered by suction. Yield: 0.25 g (21%) yellow needles, mp 355 °C, dec. (dimethylformamide). - IR: 1635 s, 1595 s cm^{-1}; ^1H NMR (CF_3COOH): δ= 2.0-2.6 (m, 2 CH_2), 2.95-3.35 (m, 2 Ar-CH_2), 3.2 (s, 2 CH_3), 4.48 (t, J= 5 Hz, 2 N-CH_2), 7.4-8.1 (m, 4 ArH), 8.25 (dd, J= 2 + 7 Hz, 2 10-H). Anal. Calcd. $C_{28}H_{26}H_4O_4$: C, 69.69, H, 5.43, N, 11.61. Found: C, 69.78, H, 5.40, N, 11.59.

1,1'-Azino-di-(3-ethylidene-4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline) (**8b**) - *Method a)* A hot solution of the hydrazone **6b** (0.92 g, 0.004 mol) in 1-butanol (20 ml) is treated with a catalytical amount of p-toluenesulfonic acid. Immediately crystallization starts and the mixture is heated under reflux for 10 min. The precipitate is filtered by suction. Yield: 0.54 g (63%).
Method b) A solution of the semicarbazone **6f** (0.81 g, 3 mmol) in dimethylformamide (20 ml) is heated for 3 h under reflux. The solvent is removed *i.vac.* and the residue digested with water. Yield: 0.58 g (72%), yellow needles, mp 342 °C, dec. (dioxane). - IR: 1635 s, 1590 s cm^{-1}; ^1H NMR (CF_3COOH): δ= 3.13 (s, 2 CH_3), 3.97 (s, 2 N-CH_3), 7.35-8.2 (m, 6 ArH), 8.4 (dd, J= 2 + 8 Hz, 2 5-H), 10.25 (s, 2 acidic H). Anal. Calcd. for $C_{24}H_{22}N_4O_4$: C, 66.96, H, 5.15, N, 13.02. Found: C, 67.01, H, 5.36, N, 13.00.

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