Synthesis of 3-Nitro- and 3-Aminoquinoline-2,4-diones. An Unexpected Route to 3-Hydroxyquinoline-2,4-diones

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Nitration of 3-substituted-4-hydroxy-2(1*H*)-quinolones **1** with nitric acid leads either to 3-nitro- **2** or 3-hydroxyquinolinediones **3**, depending on the reaction conditions. 3-Substituted-3-hydroxyquinolinediones **3** are also obtained by oxidative hydroxylation with peracetic acid. Amination of 3-substituted-3-chloroquinolinediones **4** with ammonium hydroxide predominantly leads again to 3-substituted-3-hydroxyquinolinediones **3**, only in one case the 3-aminoquinolinedione **5** could be isolated. With morpholine or pyridine as amines the expected 3-aminoquinolinediones **6** and **7** were obtained.

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3,3-Disubstituted quinoline-2,4-dione systems have found interest because of their biological activity (*e.g.* 3-hydroxy-3-alkylquinoline-2,4-diones as metabolites of some *Pseudomonas* species [1,2], 3-aryl-3-chloroquinoline-2,4-diones with herbicidal activity and 3,3-diazidoquinoline-2,4-diones as platelet aggregation inhibitors [3]). 3-Nitro-4-hydroxy-2(1*H*)-quinolones, which could also be considered as tautomeric 3-monosubstituted nitroquinoline-2,4-diones, show strong antiallergic activity [4]. Some monocyclic analogues, 3-nitropyridine-2,4-diones, were found to possess antiviral activity [5].

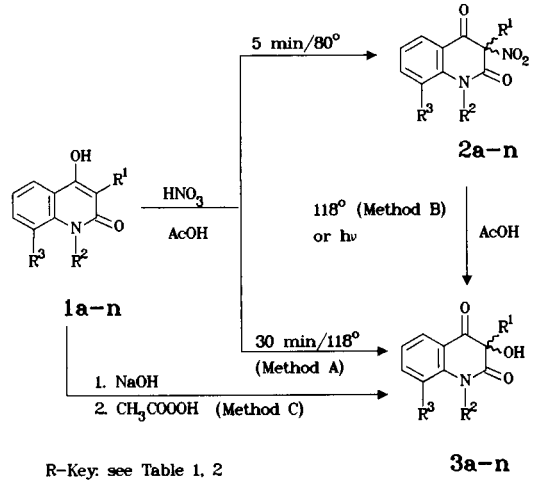
Because of these findings our interest was focused to investigate routes to other 3,3-disubstituted quinolinediones, especially 3-nitro- and 3-aminoquinolinediones, having 3-alkyl- or 3-aryl substituents in position 3 to prevent tautomerism to a 4-hydroxy-2-quinolone form. In the future an examination of the biological activities of the 3-nitro- and the 3-aminoquinolinediones is planned, particularly in the plant protection and antiviral area.

According to literature data [4,6] described for 3-unsubstituted and 3-halo-substituted 4-hydroxy-2-quinolones, nitration of 3-substituted 4-hydroxy-2-quinolones **1** was performed using concentrated nitric acid in acetic acid to afford 3-alkyl- or 3-aryl-3-nitroquinoline-2,4-diones **2**, respectively. However, always a by-product was observed, which showed a characteristic light blue fluorescence in tlc. When the nitration was performed at room temperature, no by-product was observed, but the yields of **2** were very poor. Addition of catalytic amounts of sodium nitrite, which is known to accelerate the nitration step by initial nitrosation and subsequent oxidation to the nitro group [9,10], was not successful, because both products were formed in this case in an 1:1 ratio. The best reaction conditions were found when **1** was reacted with concentrated nitric acid and acetic acid for five minutes at 80°. Using longer reaction times and temperatures higher than 80°, the amount of this by-product increased, which was found to be the only product, when the nitration was performed in boiling acetic acid for 30 minutes (method A). The structure of this by-product was eludicated to be a 3-substituted 3-hydroxyquinoline-2,4-dione **3**, a class of compounds, which could be obtained also by oxidative hydroxylation of 4-hydroxy-2-quinolones [2,7].

Results obtained in the reaction of alkylmalonates with nitric acid [8] indicate, that the formation of the 3-hydroxyquinolinediones **3** are not primarily formed parallel to the nitration; **3** is also formed by heating the 3-nitroquinolinedione **2** in boiling acetic acid (method B). Formation of **3** could be observed too, when a solution of **3** is irradiated (even with sunlight) in solvents containing water. Therefore we assume rather a nucleophilic displacement of the 3-nitro group by water than an oxidation of the dioxo tautomer of **1** by action of nitric acid.

Another synthesis of these 3-hydroxyquinolinediones **3** could be developed performing the oxidation of the sodium salts of quinolones **1** with peracetic acid (method C). Comparison of the pros and cons of this method with

Scheme 1



R-Key: see Table 1, 2

earlier described methods such a alkaline hydrogen peroxide oxidation [7] or oxidation with 3-chloroperoxybenzoic acid [2,7] shows that solution difficulties in the peroxide method and separation problems in the peroxybenzoic acid method can be avoided using peracetic acid as oxidizing agent.

In order to find synthetic routes to 3-amino-3-substituted-quinoline-2,4-diones, 3-chloroquinolinediones **4** [2,3, 11,13,14] as precursors were treated with various amines. Surprisingly, the reaction with aqueous ammonium hydroxide yielded again 3-hydroxyquinolinediones **3** (method D); only in the case of the 3-benzyl compound **4a** the desired 3-aminoquinolinedione **5** could be isolated as a by-product in low yield. When the amination was carried out in other solvents (like dimethylformamide, acetone, 2-propanol or pyridine, containing gaseous ammonia), a mixture of **3a**, **5** and **1a** was obtained besides unrecovered starting material.

Attempts to carry out the hydrolysis of the 3-chloroquinolinediones **4** in aqueous sodium hydroxide solution (instead of ammonia as the base), resulted in the decomposition of the 3-chloroquinolinediones **4**. At room temperature as the main product the corresponding 4-hydroxyquinolones **1** were obtained in 10-15% yield. The 3-hydroxyquinolinediones **3** could be detected by tlc monitoring, but isolation was not successful. Besides other mainly ring opened by-products, which in most cases could not be isolated in a pure form, the corresponding isatin was obtained in about 5-10% yield; its structure was eludicated by mp's and spectral comparison. When the hydrolysis of **4c,d** (R^1 = Ph) was carried out at reflux temperature, a similar decomposition was observed, and additionally benzaldehyde could be isolated by steam distillation.

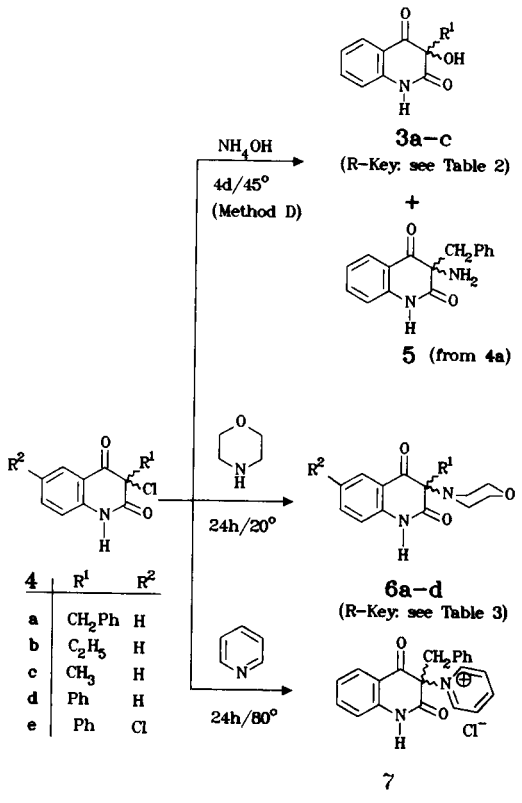
Reaction of **4** with morpholine as a secondary amine in absolute dimethylformamide was found to lead in good yields to the desired 3-morpholinoquinolinediones **6** at

Table 1

Substituted 3-Nitroquinoline-2,4-diones **2**

No.	...3-nitroquinoline-2,4-(1*H*,3*H*)-dione (except **2m,n**)	Yield (%)	Mp (°C) Recrystallization Solvent	Molecular Formula Mw	Analysis, (%) Calcd./Found C	H	N
2a	3-Benzyl-...	51	146 (methanol)	$C_{16}H_{12}N_2O_4$ 296.3	64.86 64.67	4.08 4.19	9.45 9.32
2b	3-Ethyl-...	85	155.5 (EtOH/H_2O)	$C_{11}H_{10}N_2O_4$ 234.2	56.41 56.27	4.30 4.45	11.96 12.14
2c	3-Methyl-...	75	157-157.8 (EtOH/H_2O)	$C_{10}H_8N_2O_4$ 220.2	54.55 54.77	3.66 3.85	12.72 12.54
2d	1,3-Dimethyl-...	76	139 (methanol)	$C_{11}H_{10}N_2O_4$ 234.2	56.41 56.54	4.30 4.21	11.96 11.95
2e	3-Ethyl-1-methyl-...	72	65 (MeOH/H_2O)	$C_{12}H_{12}N_2O_4$ 248.2	58.06 57.89	4.87 4.96	11.28 11.09
2f	1-Methyl-3-phenyl-...	78	148-149 (MeOH/H_2O)	$C_{16}H_{12}N_2O_4$ 296.3	64.86 65.08	4.08 3.88	9.45 9.25
2g	1,3-Diethyl-...	63	73 (MeOH/H_2O)	$C_{13}H_{14}N_2O_4$ 262.3	59.54 59.23	5.38 5.52	10.68 10.36
2h	3-*n*-Butyl-1-ethyl-...	58	129.7-130 (EtOH/H_2O)	$C_{15}H_{18}N_2O_4$ 290.3	62.06 61.89	6.25 6.37	9.65 9.36
2i	1-Ethyl-3-phenyl-...	69	143-144 (ethanol)	$C_{17}H_{14}N_2O_4$ 310.3	65.80 66.07	4.55 4.32	9.03 8.75
2j	3-*n*-Butyl-1-phenyl-...	82	176 (ethanol)	$C_{19}H_{18}N_2O_4$ 338.4	67.45 67.71	5.36 5.24	8.28 8.09
2k	3-Benzyl-1-phenyl-...	84	144-145.5 (ethanol)	$C_{22}H_{16}N_2O_4$ 372.4	70.96 71.23	4.33 4.01	7.52 7.29
2l	1,3-Diphenyl-...	81	176 (ethanol)	$C_{21}H_{14}N_2O_4$ 358.4	70.39 70.30	3.94 4.04	7.82 7.45
2m	2-Ethyl-2-nitro-6,7-dihydro-5*H*-benzo[*ij*]quinolizine-1,3-dione	64	135 (EtOH/H_2O)	$C_{14}H_{14}N_2O_4$ 274.3	61.31 61.63	5.14 5.27	10.21 10.50
2n	2-Butyl-2-nitro-6,7-dihydro-5*H*-benzo[*ij*]quinolizine-1,3-dione	69	86-87 (MeOH/H_2O)	$C_{16}H_{18}N_2O_4$ 302.3	63.57 63.35	6.00 6.18	9.27 8.97

Scheme 2



room temperature. From the filtrate the corresponding 4-hydroxyquinolones **1** could be isolated in about 20% yield, formed by dehalogenation of **4**. When the amination was carried out at elevated temperature, the 4-hydroxyquinolones **1** became the main product (about 60%), and the amount of the amination products **6** decreased to about 30%. In the presence of traces of water again the formation of the hydroxyquinolinediones **3** could be observed. After purification the morpholinoquinolinediones **6** are rather stable compounds, and attempts to hydrolyze **6** in refluxing hydrochloric acid or aqueous sodium hydroxide (with methanol to mediate the solution) in order to obtain the 3-hydroxyquinolinediones **3** showed no efforts: only unrecovered starting material could be isolated.

With pyridine as tertiary amine 3-benzyl-3-chloroquinolinedione **4a** reacted in absolute dimethylformamide to give the pyridinium salt **7** in good yield.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus Model MFB-595 in open capillary tubes. Infrared spectra were taken in potassium bromide pellets on a Perkin-Elmer 298 spectrophotometer; the ^{1}H nmr spectra were recorded on a Varian Gemini 200 instrument. Chemical shifts are reported in ppm from internal tetramethylsilane and are given in δ-units. The solvents for nmr spectra was deuterio dimethyl sulfoxide unless otherwise stated. Elemental analyses were per-

Table 2

3-Substituted 3-Hydroxyquinoline-2,4-diones 3

No.	...3-hydroxyquinoline-2,4(1*H*,3*H*) -dione (except **3n**)	Yield (%) Method	Mp (°C) Recrystallization Solvent	Molecular Formula Mw	Analysis, (%) Calcd./Found C	H	N
3a	3-Benzyl-...	A: 92 B: 78 D: 41	202-204	[7]			
3b	3-Ethyl-...	A: 94 C: 91 D: 69	170-172	[7]			
3c	3-Methyl-...	A: 97 D: 79	200-201	[7]			
3f	1-Methyl-3-phenyl-...	A: 96 C: 95	160-162 (EtOH/H_2O)	$C_{16}H_{13}NO_3$ 267.3	71.90 71.60	4.90 4.86	5.24 5.13
3g	1,3-Diethyl-...	A: 95 C: 97	92 (methanol)	$C_{13}H_{15}NO_3$ 233.3	66.94 66.76	6.48 6.13	6.00 5.93
3h	3-*n*-Butyl-1-ethyl-...	A: 52	40 (cyclohexane)	$C_{15}H_{19}NO_3$ 261.3	68.94 69.32	7.33 7.42	5.36 4.94
3i	1-Ethyl-3-phenyl-...	A: 93 C: 97	170 (methanol)	$C_{17}H_{15}NO_3$ 281.3	72.58 72.75	5.37 5.17	4.98 4.92
3l	1,3-Diphenyl-...	A: 97 B: 80 C: 90	167-168	[7]			
3n	2-Butyl-2-hydroxy-6,7-dihydro-5*H*-benzo[*ij*]quinolizine-1,3-dione	A: 92 C: 87	187 (MeOH/H_2O)	$C_{16}H_{19}NO_3$ 273.3	70.31 70.09	7.01 6.54	5.12 5.03

Table 3

3-Substituted 3-Morpholinoquinoline-2,4-diones **6**

No.	...3-morpholinoquinoline--2,4(1*H*,3*H*)-dione	Yield (%)	Mp (°C) Recrystallization Solvent	Molecular Formula Mw	Analysis, (%) Calcd./Found C	H	N
6a	3-Benzyl-...	66	210-212 ($EtOH/H_2O$)	$C_{20}H_{20}N_2O_3$ 336.4	71.41 / 71.08	5.99 / 5.91	8.33 / 8.30
6b	3-Ethyl-...	70	164-166 ($MeOH/H_2O$)	$C_{15}H_{18}N_2O_3$ 274.3	65.68 / 65.45	6.61 / 6.47	10.21 / 10.48
6c	3-Phenyl-...	72	180-182 ($MeOH/H_2O$)	$C_{19}H_{18}N_2O_3$ 322.4	70.79 / 71.08	5.63 / 5.34	8.69 / 9.01
6d	6-Chloro-3-phenyl-...	73	191-193 ($EtOH/H_2O$)	$C_{19}H_{17}ClN_2O_3$ 356.8	63.96 / 64.17	4.80 / 4.56	7.85 [a] / 7.97

[a] Cl- Analysis: Calcd. Cl, 9.94. Found Cl, 10.03.

Table 4

Spectroscopic Data for 3-Nitroquinoline-2,4-diones **2**, 3-Hydroxyquinoline-2,4-diones **3** and 3-Morpholinoquinoline-2,4-diones **6**

Compound	IR [cm^{-1}]	^{1}H-NMR (δ ppm)
2a		3.70 (s, Ph-CH_2), 6.60-7.50 (m, 8 ArH), 7.60 (dd, J = 2 and 8 Hz, 5-H)
2b		1.90 (t, J = 7 Hz, ethyl-CH_3), 2.40 (q, J = 7 Hz, CH_2), 3.40 (s, 1-CH_3), 7.00-7.65 (m, 3 ArH), 7.8 (dd, J = 2 and 8 Hz, 5-H)
2c	3240-2880 m, 1720 m, 1685 s, 1610 s	2.00 (s, CH_3), 7.20-7.35 (m, 2 ArH), 7.75-7.95 (m, 2 ArH), 11.75 (s, NH)
2d		1.95 (s, 3-CH_3), 3.45 (s, 1-CH_3), 7.00-7.70 (m, 3 ArH), 7.80 (dd, J = 2 and 8 Hz, 5-H)
2e		1.85 (t, J = 7 Hz, ethyl-CH_3), 2.40 (q, J = 7 Hz, ethyl-CH_2), 3.40 (s, 1-CH_3), 7.00-7.65 (m, 3 ArH), 7.80 (dd, J = 2 and 8 Hz, 5H)
2f	3420 w, 1710 s, 1680 m, 1605 m	
2g	2980 w, 1700 s, 1665 s, 1600 s	
2h	3350-3040 b, 2950 m, 1710 m, 1680 s, 1605 m	0.80 (t, J = 7 Hz, butyl-CH_3), 1.2 (t, J = 7 Hz, ethyl-CH_3), 1.35-1.55 (m, 2 butyl-CH_2), 2.6 (t, J = 7 Hz, butyl-CH_2), 4.25 (t, J = 7 Hz, ethyl-CH_2), 7.00-7.70 (m, 3 ArH), 7.80 (dd, J = 2 and 8 Hz, 5H)
2i	1710 s, 1675 s, 1600 s	
2j	3460 m, 2950 m, 1710 s, 1675 s, 1600 s	
2k	1710 s, 1680 s, 1605 s	
2l	3420-3080 b, 2960 m, 1710 m, 1680 s, 1605 m	
2m	2960-2870 m, 1710 s, 1670 s, 1590 m	0.8 (t, J = 7 Hz, ethyl-CH_3), 1.8-2.1 (m, trimethylene-CH_2), 2.3 (t, J = 7 Hz, Ar-trimethylene-CH_2), 2.9 (q, J = 7 Hz, ethyl-CH_2), 4.1 (t, J = 7 Hz, N-trimethylene-CH_2), 7.0-7.5 (m, 9-H), 7.6-7.95 (m, 8-H, 10-H)
2n	2940 w, 1705 m, 1665 s, 1595 m	0.8 (t, J = 7 Hz, butyl-CH_3), 1.2 (m, 2 butyl-CH_2), 1.9-2.1 (m, trimethylene-CH_2), 2.3 (t, J = 7 Hz, Ar-trimethylene-CH_2), 2.9 (t, J = 7 Hz, butyl-CH_2), 4.1 (t, J = 7 Hz, N-trimethylene-CH_2), 7.0-7.5 (m, 9-H), 7.65 (d, J = 7 Hz, 8-H), 7.8 (dd, J = 2 and 7 Hz, 10-H)
3f	3620 m, 3520 s, 1710 s, 1665 s, 1600 m	
3g	3470 s, 2970 m, 1710 s, 1660 s, 1605 s	0.85 (t, J = 7 Hz, 3-ethyl-CH_3), 1.15 (t, J = 7 Hz, ethyl-CH_3), 1.8 (t, J = 7 Hz, 3-ethyl-CH_2), 4.05 (q, J = 7 Hz, N-CH_2), 5.8 (s, OH), 7.15-7.45 (m, 2 ArH), 7.65-7.9 (m, 2 ArH)
3h	3530 m, 3420 s, 1710 s, 1660 s, 1600 m	
3i	3460 s, 2980 m, 1705 s, 1660 s, 1605 s	1.25 (t, J = 7 Hz, ethyl-CH_3), 4.15 (q, J = 7 Hz, N-CH_2), 6.4 (s, OH), 7.1-7.45 (m, 7 ArH), 7.65-7.8 (m, 2 ArH)
3n	3420 s, 2960-2890 m, 1705 s, 1665 s, 1590 m	
6a	3200-3020 m, 2940-2830 m, 1685 s, 1660 s, 1600 m	
6b	3190-3040 m, 2950-2840 m, 1690 m, 1655 s, 1605 m	
6c	3190 m, 3040 m, 2980-2830 m, 1695 s, 1665 s, 1605 m	
6d	3190 m, 3050 m, 2950-2840 m, 1700 s, 1660 s, 1605 m	

formed on a C,H,N-automatic Carlo Erba 1106 and are within 0.4 of the theoretical percentages. Common reagent-grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using uv light (254 and 366 nm) for detection.

General Procedure for the Synthesis of 3-Nitroquinoline-2,4(1*H*,3*H*)-diones **2a-o.**

To a solution of the appropriate 4-hydroxy-2(1*H*)-quinolone **1** [11,12] (0.01 mole) in 20 ml of glacial acetic acid 3 ml of concentrated nitric acid was added and the mixture heated for 5 minutes to 80°. After cooling the nitroquinoline **2** precipitated (completing the precipitation by addition of water increased the amount of **3**, which was formed as by-product). The crude material, which was rather pure, was collected by filtration. Experimental data: see Table 1; spectroscopic data: see Table 4.

General Procedure for the Synthesis of 3-Hydroxyquinoline-2,4(1*H*,3*H*)-diones **3a-o**.

Method A.

The appropriate 4-hydroxy-2-quinolone **1** [11,12] (0.01 mole) was dissolved in a mixture of 20 ml of glacial acetic acid and 10 ml of concentrated nitric acid and then heated for 30 minutes to 110°. Then the dark reaction mixture was poured onto 100 g of ice and stirred until the precipitate had solidified. After filtration the precipitate was washed subsequently with 100 ml of 5% sodium bicarbonate solution and 100 ml of water. Experimental data: see Table 2; spectroscopic data: see Table 4.

Method B.

The corresponding 3-nitroquinolinedione **2** (0.01 mole) was refluxed in 50 ml of 80% acetic acid for 90 minutes, then the acetic acid removed *in vacuo* and the residue digested with 10 ml of ethanol and filtered. Experimental data: see Table 2; spectroscopic data: see Table 4.

Method C.

The appropriate 4-hydroxy-2-quinolone **1** [11,12] (0.01 mole) was dissolved in 150 ml of 0.5 *N* sodium hydroxide solution. Then 35% peracetic acid was added dropwise during 30 minutes at room temperature under stirring until *p*H = 2 was reached. The reaction product precipitates and was filtered and washed with 100 ml of 5% sodium bicarbonate solution and 100 ml of water. Experimental data: see Table 2; spectroscopic data: see Table 4.

Method D.

A suspension of the appropriate 3-chloroquinoline-2,4-dione **4** [2,3,11,13,14] was suspended in 25 ml of concentrated ammonia solution and held for 4 days at 45°. The resulting solution was concentrated *in vacuo* to the half volume, cooled, filtered by suction and recrystallized from the appropriate solvent. Experimental data: see Table 2; spectroscopic data: see Table 4.

3-Amino-3-benzylquinoline-2,4(1*H*,3*H*)-dione **5.**

To a solution of 3-benzyl-3-chloroquinoline-2,4-dione (**4a**) [13] (1.42 g, 0.005 mole) in 20 ml of dimethylformamide 25 ml of concentrated ammonia solution was added and held for 4 days at 45°. The solvents were removed *in vacuo* and the residue brought to *p*H = 1 with diluted hydrochloric acid. The insoluble residue was filtered off and the filtrate neutralized with 10% sodium carbonate solution. The precipitate was filtered and recrystallized from ethanol/water, yield 0.45 g (34%) yellow prisms, mp 193-195° (ethanol); ir: 3380 w, 3190-2810 m, 1690 s, 1645 s, 1605 w cm^{-1}.

Anal. Calcd. for $C_{16}H_{14}N_2O_2$: C, 72.17; H, 5.30; N, 10.52. Found: C, 72.35; H, 5.16; N, 10.18.

General Procedure for the Synthesis of 3-Morpholinoquinoline-2,4(1*H*,3*H*)-diones **6a-d.**

A solution of the appropriate 3-chloroquinolinediones **4** [2,3, 11,13,14] (0.01 mole) in 2 ml of absolute dimethylformamide is treated with absolute morpholine (2.6 ml, 0.03 mole) and then stirred at 20° for 24 hours. Then the reaction mixture is cooled with ice and precipitated with 50 ml of ice-water. The precipitate is filtered and recrystallized from acetone/methanol/water. Experimental data: see Table 3; spectroscopic data: see Table 4.

3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydroquinolin-3-ylpyridinium Chloride (**7**).

To a solution of 3-benzyl-3-chloroquinoline-2,4-dione (**4a**) [13] (2.85 g, 0.01 mole) in 6 ml of absolute dimethylformamide absolute pyridine (2.4 ml, 0.03 mole) was added and the reaction mixture stirred for 24 hours at 80°. The resulting precipitate was filtered and then subsequently washed with dimethylformamide, pyridine and diethyl ether, yield 2.6 g (72%) yellow prisms, mp 210°; ir: 3500-3300 m, 3100-2820 m, 1705 , 1660 s, 1620 sh, 1605 m cm^{-1}.

Anal. Calcd. for $C_{21}H_{17}ClN_2O_2$: C, 69.14; H, 4.70; Cl, 9.72; N, 7.68. Found: C, 69.51; H, 4.94; Cl, 9.98; N, 7.97.

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