Nucleophilic Substitution and Ring Closure Reactions of 4-Chloro-3-nitro-2-quinolones [1]

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4-Chloro-3-nitro-2-quinolones **3** obtained from the 4-hydroxy quinolones **1** by nitration and chlorination, reacted with sodium azide to the 4-azido derivatives **4** which cyclized on thermolysis to yield the furoxanes **5**. Nucleophilic substitution reactions of **3** led to the 4-amino-, 4-fluoro- and 4-alkoxy-3-nitroquinolones **7, 8** and **9**, respectively. With thiols either 4-thio-3-nitro- **10** or 3,4-dithioquinolones **11** were obtained depending on the basic catalyst.

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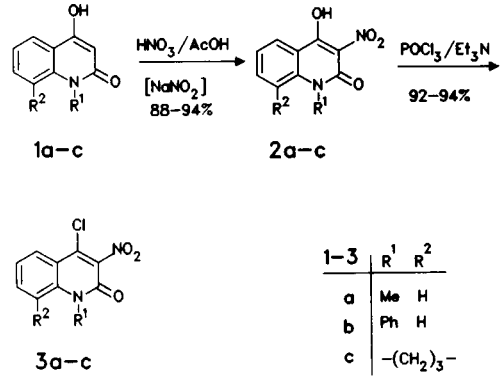
Ortho-substituted azido arenes and heteroarenes are known to give cyclization reactions induced by thermo- or photolysis [2]. Some of these reactions have been studied by us on heterocyclic systems with aryl [1,3] and carbonyl [4] groups as *ortho* substituents and are now extended to *ortho*-nitro substituents, which should cyclize to furazan oxides, as could be shown in some other systems [5-10]. As second aspect the behaviour of the reactive 4-chloro-3-nitroquinolones **3** against nucleophiles is studied.

4-Chloro-3-nitro-2(1*H*)-quinolones **3**, which were selected as starting material for the synthesis of 4-azido-3-nitroquinolones, were prepared from 4-hydroxy-2-quinolones **1**. A single step reaction to obtain the quinolones **1** using one equivalent of malonate and one equivalent of the appropriate aniline according to methods developed for alkyl malonates [11] yielded a 2:3 mixture of the desired hydroxyquinolone **1** together with a pyranoquinolone [4a,12] (as a 1:2 condensation product of the aniline with the malonate) besides some unchanged starting material. Although it is possible to separate the 2 compounds because of their different pK_S-values, the yields are poor (below 40% of crude material). For the *N*-phenyl derivative **1b** known syntheses starting from diphenylamine and malonic acid or malonate furnish low yields (15-35% [13,14]) and products of low purity, which are very difficult to purify [13]. We have adopted an improved three step preparation method [4a] starting from the appropriate aniline and two equivalents of malonate to afford the quinolone **1** in high purity and in an overall yield of 50-80%.

The nitration step, which is reported with nitric acid in boiling acetic acid [14], could be performed under substantial milder conditions - at room temperature - using sodium nitrite as catalyst. The catalytical effect of sodium nitrite can be explained by an initial nitrosation of **1** in position 3 and subsequent oxidation of the nitroso- to the desired nitro group [15].

In a former investigation we found that attempts to chlorinate 4-hydroxy-3-nitro-2-quinolones with phosphoryl chloride or phosphoryl chloride/phosphorus pentachloride resulted in long reaction times, low yields (about 10%) and a low purity [16]. Now we could show that the use of triethyl amine as a basic catalyst accelerated the exchange of the hydroxy against the chloro group and after 1 hour the reaction was finished with yields of 92-94%, an effect which can be explained in terms of the destruction of the hydrogen bonds between the 3-nitro and the 4-hydroxy group, which prevented or retarded the attack of the phosphoryl chloride. A similar hindrance was found in the chlorination of 3-acetyl-4-hydroxyquinolones [4a].

Scheme 1

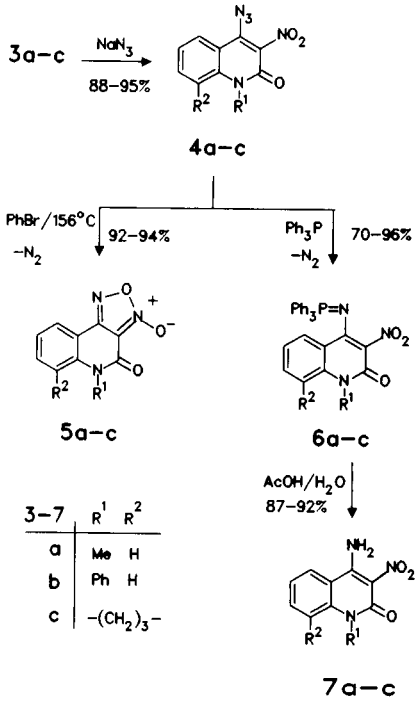


The reaction of nucleophiles with 4-chloro-2-quinolones generally affords 4-substituted 2-quinolones. The reaction rate was found to be strongly dependent on the electronic effects of substituents in position 3: electron-withdrawing substituents facilitate the substitution, whereas electron-pushing substituents impair or prevent the reaction. Based on these findings the chloro atom of **3** should be exchanged easily against nucleophiles by the influence of the nitro group. In 4-chloro-3-nitro-coumarin [6] both the 4-chloro and the 3-nitro group could be exchanged depending on the nature of the nucleophiles, a result, which should be compared with the 2-quinolone nucleus.

Our main interest was focused on the introduction of the azido group in neighbourship of the nitro group, which should be further transformed into furoxanes or amines *via* phosphazene derivatives. The reaction of the chloroquinolones **3** in *N*-methylpyrrolidone at room tem-

perature afforded in excellent yields the azido quinolones **4**, which were stable enough for recrystallization in methanol.

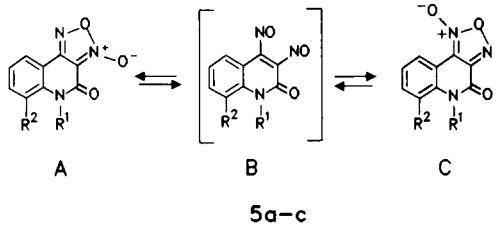
Scheme 2



Ring closure to the furoxans **5** could be achieved by thermolysis of the azide **4** in refluxing bromobenzene by loss of nitrogen and subsequent cyclization. The yields are nearly quantitative due to the *ortho*-effect of the nitro group [2].

Although the furoxans **5** were found to be chromatographically homogeneous, the ^{1}H nmr spectra of **5** showed two signals for the *N*-substituents and in the aromatic region (H-5 and H-7), which could be interpreted as a mixture of the isomeric forms **A** and **C**, although no significant high field shielding effect on the adjacent ring proton (H-5) can be observed. As explanation for this isomerisation an intermediate dinitroso form **B** can be assumed, as found in earlier benzofuroxan investigations [17].

Scheme 3



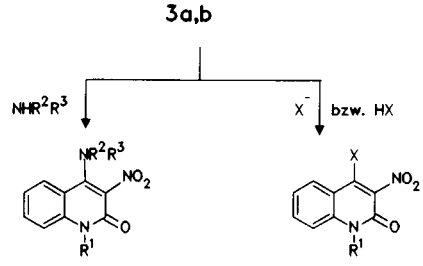
The azidoquinolones **4** react with triphenylphosphane *via* a Staudinger reaction [2,18] and spontaneous nitrogen elimination to the phosphazenes **6**, which could be hydrolyzed with aqueous acetic acid to yield the aminoquinolones **7a-c**.

Nucleophilic substitution of the chloro atom of **3** in position 4 with various nucleophiles could be carried out under mild conditions due to the high reactivity caused by the influence of the 3-nitro group. So many substitutions (*e.g.* with potassium fluoride or phenol) could be obtained, which are unknown in the 2-quinolone series with other substituents in position 3 or only possible under severe conditions. Reaction with excess ammonia and aliphatic amines leads to the 4-amino-3-nitroquinolones **7a-h**; in the case of aniline, triethyl amine was used as basic catalyst to yield **7i,j**.

The exchange of the chloro against the fluoro atom could be achieved with spray-dried potassium fluoride [19] in dry acetonitrile with 18-crown-6 as catalyst. The 4-fluoro-3-nitro-2-quinolones **8a,b** are very sensitive against traces of water during the reaction, especially in the presence of basic catalysts.

The reaction of **3** with sodium ethanolate or methanolate in excess of the corresponding alcohol yields the alkyloxy quinolones **9a-c**, the phenyl ethers **9d,e** can be obtained with phenol at room temperature in the presence of potassium carbonate.

Scheme 4



7	R^1	R^2	R^3
a	Me	H	H
b	Ph	H	H
d	Me	H	Me
e	Me	H	$PhCH_2$
f	Ph	H	$PhCH_2$
g	Me	$-(CH_2)_5-$	
h	Me	$-(CH_2)_2O(CH_2)_2-$	
i	Me	H	Ph
j	Ph	H	Ph

8	R^1	X
a	Me	F
b	Ph	F

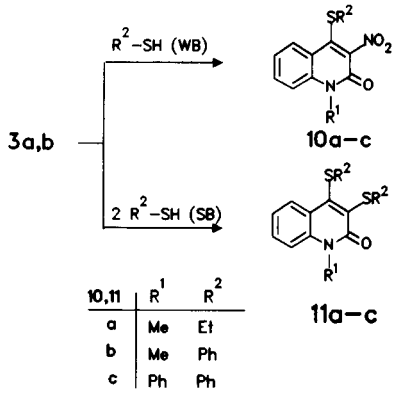
9	R^1	X
a	Me	OMe
b	Ph	OMe
c	Me	OEt
d	Me	OPh
e	Ph	OPh

Another behaviour could be observed in the reaction of **3** with thiols, which is also in opposite to some findings observed in the coumarin system [6]. Reacting ethanethiol with **3a** using triethylamine as basic catalyst substitution of the chloro atom occurred and as reaction product the 3-nitro-4-thioether **10a** was obtained, whereas in the coumarin series the nitro group in position 3 was reported to be exchanged and an 4-chloro-3-thioether was formed [6].

As explanation the difference of the electron density charges could be assumed, which causes in the 4-hydroxy form of the cyclic ester coumarin a pK_S-value of 4.20; the cyclic amide 4-hydroxy-1-methyl-2-quinolone is a more than 10 times weaker base with a pK_S-value of 5.60 [20].

On the other hand, the reaction of thiophenol with **3a,b** in the presence of triethylamine could not be stopped at the step of the monothio ethers. As reaction products only the 3,4-bis-thioethers **11b,c** could be obtained.

Scheme 5



10,11	R^1	R^2
a	Me	Et
b	Me	Ph
c	Ph	Ph

An explanation of the different behaviour can be found in the different acidity of ethanethiol and thiophenol and the reaction rate of the thiolate anions, which is dependant on their concentration. In the presence of triethylamine, which is a weak base (WB) relative to ethanethiol, only a small part of the thiol exists as anion and the reaction rate is slow enough to allow a selective interception of the monothio compound **10a**. Thiophenol, which is a four times stronger acid than ethanethiol, exists in the presence of triethylamine in a high rate as anion - triethylamine acts now as a strong base (SB). It is not possible to isolate the monothio compound kinetically controlled, because the mono thioethers **10b,c** formed in the first step react quickly to the bis-substituted compounds **11b,c** before they can be isolated. This hypothesis can be confirmed using a stronger base than triethylamine in the reaction with ethanethiol: in the presence of potassium carbonate as a stong base (SB) also with ethanethiol the disubstituted 3,4-diethylthioquinolone **11a** can be obtained, whereas thiophenol affords with pyridine as a weak base (WB) only the monosubstituted 3-nitro-4-thioethers **10b,c**.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus Mod. 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 solvent for nmr spectra was deuterio dimethyl sulfoxide unless otherwise stated. Elemental analyses were performed 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

Table 1

4-Amino-3-nitro-2(1*H*)-quinolones and 1-Amino-2-nitrobenzo[*ij*]quinolizin-3-one **7a-j**

No.	...3-nitro-2(1*H*)-quinolone (except **7c**)	Yield (%) (Method)	Mp (°C) Recrystalization solvent	Molecular Formula Molecular weight	Analysis, %; Calcd./Found C	H	N
7a	4-Amino-1-methyl-	A: 91	325	$C_{10}H_9N_3O_3$	54.79	4.15	19.17
		B: 91	AcOH	219.2	54.78	4.18	18.95
7b	4-Amino-1-phenyl	A: 87	348 dec	$C_{15}H_{11}N_3O_3$	64.04	3.95	14.94
		B: 92	DMF	281.3	63.66	3.98	14.87
7c	1-Amino-2-nitro-6,7-dihydro-5H-benzo[*ij*]quinolizin-3-one	A: 93	304 dec	$C_{12}H_{11}N_3O_3$	58.77	4.52	17.13
			AcOH	245.2	58.61	4.60	16.95
7d	1-Methyl-4-methylamino-	C: 97	268-270 dec	$C_{11}H_{11}N_3O_3$	56.63	4.76	18.02
			AcOH	233.3	56.15	4.88	17.73
7e	4-Benzylamino-1-methyl-	C: 94	188-189 dec	$C_{17}H_{15}N_3O_3$	65.99	4.90	13.53
			AcOH	309.4	65.87	4.94	13.52
7f	4-Benzylamino-1-phenyl-	C: 98	189 dec	$C_{22}H_{17}N_3O_3$	71.14	4.62	11.32
			AcOH	371.4	70.78	4.57	11.08
7g	1-Methyl-(4-piperidinyl)-	C: 96	179-180	$C_{15}H_{17}N_3O_3$	62.68	5.97	14.62
			tolulene	287.4	62.68	5.90	14.59
7h	1-Methyl-(4-morpholinyl)-	C: 95	199-201	$C_{14}H_{15}N_3O_4$	58.12	5.25	14.53
			tolulene	289.3	58.10	4.97	14.45
7i	1-Methyl-4-phenylamino-	C: 98	217-218 dec	$C_{16}H_{13}N_3O_3$	65.07	4.45	14.23
			ethanol	295.3	64.92	4.39	14.29
7j	1-Phenyl-4-phenylamino-	C: 98	205 dec	$C_{21}H_{15}N_3O_3$	70.57	4.24	11.76
			ethanol	357.4	70.62	4.32	11.61

Table 2

Spectroscopic Data of the 4-Amino-3-nitro-2(1*H*)-quinolones and 1-Amino-2-nitrobenzo[*ij*]quinolizin-3-one **7a-j**

Compound	IR [cm^{-1}]	^{1}H-NMR (δ ppm) [a]
7a	3420 m, 3320 m, 1610 s, 1585 m	
7b	3380 m, 3340-3100 b, 1650 w, 1615 s	
7c	3400 m, 3320-3200 b, 1615 s, 1590 m	
7d	3370 m, 1610 s, 1595 s	
7e	3350 m, 3050 w, 2940 w, 1610 s, 1585 s	3.6 (s, CH_3), 4.45 (d, J = 5 Hz, benzyl-CH_2), 7.2-8.2 (m, 8 ArH), 8.45 (dd, J = 2 and 8 Hz, H at C-5)
7f	3340 m, 3260 m, 1620 s, 1600 m, 1540 s	4.4 (s, benzyl-CH_2), 6.5 (dd, J = 2 and 8 Hz, H at C-8), 7.1-7.65 (m, 12 ArH), 8.35 (dd, J = 2 and 8 Hz, H at C-5)
7g	3080 w, 2980 w, 2950 m, 2850 m, 1650 s, 1610 m, 1595 s	[a] 1.75 (m, 3,4,5-piperidinyl-CH_2), 3.2 (m, 2,6-piperidinyl-CH_2), 3.7 (s, CH_3), 7.1-7.7 (m, 3-Ar-H), 7.9 (dd, J = 2 and 8 Hz, H at C-5)
7h	2970 w, 2900 w, 2850 m, 1640 s, 1610 s, 1590 s	[a] 3.25 (t, J = 4.5 Hz, 3,5-morpholinyl-CH_2), 3.7 (s, CH_3), 3.9 (t, J = 4.5 Hz, 2,6-morpholinyl-CH_2), 7.15-7.8 (m, 3 ArH), 7.95 (dd, J = 2 and 8 Hz, H at C-5)
7i	3310 m, 3040 w, 1625 s, 1590 s	3.6 (s, CH_3) 6.9-7.9 (m, 8 ArH), 8.25 (dd, J = 2 and 8 Hz, H at C-5), 9.35 (s, NH)
7j	3400-3100 b, 1635 m, 1615 m, 1590 m	

[a] If indicated, deuteriochloroform was used as the solvent.

reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using uv light for detection.

4-Hydroxy-1-phenyl-2(1*H*)-quinolone (**1b**).

1) 4-Hydroxy-6-phenyl-2*H*-pyrano[3,2-*c*]quinoline-2,5(6*H*)-dione.

A mixture of diphenylamine (16.9 g, 0.1 mole) and diethyl malonate (32.0 g, 0.2 mole) in 50 g of diphenyl ether was refluxed in a distillation apparatus equipped with a 20 cm-Vigreux-column. During 3-5 hours, the liberated ethanol (about 22 ml) was distilled until no more ethanol was formed. Then the mixture was allowed to cool to about 100° and treated with 50 ml of dioxane. After about 12 hours the precipitate was filtered by suction and washed with dioxane and diethyl ether to remove the diphenyl ether, yield 25.4 g (83%), mp 296° (dimethyl formamide), (ref [12b] 62%, 296-297°); ir: 3070 w, 1740 s, 1680 m, 1615 w, 1570 m cm^{-1}.

2) 3-Acetyl-4-hydroxy-1-phenyl-2(1*H*)-quinolone.

A suspension of the above synthesized pyrone (24.4 g, 80 mmoles) in 250 ml of glycol and of sodium hydroxide (16 g, 0.4 mole) in 25 ml of water was heated to gentle boiling for 1 hour and poured into 700 ml of ice water. The obtained solution was slowly acidified with 40 ml of concentrated hydrochloric acid to precipitate the product, filtered, washed subsequently with water and dried at 80°, yield 20.4 g (91%), mp 237-239° (toluene), (ref [12b] 86%, mp 234°); ir: 1655 s, 1600 s, 1555 m cm^{-1}.

3) 4-Hydroxy-1-phenyl-2(1*H*)-quinolone.

The acetyl compound (19.6 g, 70 mmoles) was dissolved in 40 ml of 90% sulfuric acid and heated for 15 minutes at 140°. Then the solution was poured into 100 ml of ice water and the obtained suspension filtered after standing for 12 hours. The precipitate was washed several times with water, yield 15.8 g (95%), mp 294.5-295.5° (dimethyl formamide), (ref [14] 15%, 298-300°); ir: 3100-2400 b, 1640 s, 1595 m cm^{-1}.

1-Hydroxy-3-oxo-6,7-dihydro-3*H*,5*H*-benzo[*ij*]quinolizine (**1c**).

1) 9-Hydroxy-8,11-dioxo-5,6,8,11-tetrahydro-4*H*-benzo[*ij*]pyrano-[2,3-*b*]quinolizine.

From 1,2,3,4-tetrahydroquinoline (133 g, 1.0 mole) and diethyl malonate (321 g, 2.0 moles) according to the method described for **1b**, the yield was 168.5 g (60%), mp 270-271° (xylene), (ref [21] 51%, 270°).

2) 2-Acetyl-1-hydroxy-3-oxo-3*H*,5*H*-benzo[*ij*]quinolizine.

From the above synthesized pyrone (162 g, 0.6 mole) in 1000 ml of glycol and 100 g of sodium hydroxide in 120 ml of water as described for **1b**, yield 145.8 g (99%), mp 149° (ethanol), (ref [23] 87%, 149°); ir: 3100-2800 bm, 1655 s, 1635 m, 1600 s, 1575 m cm^{-1}; ^{1}H nmr: δ 1.7-2.3 (m, $-CH_2-$), 2.7 (s, acetyl-CH_3), 2.95 (t, J = 6 Hz, Ar-CH_2), 4.0 (t, J = 6 Hz, N-CH_2), 7.0-7.5 (m, 2 ArH), 7.9 (dd, J = 2 and 7 Hz, H at C-10), 16.6 (s, OH).

3) 1-Hydroxy-3-oxo-6,7-dihydro-3*H*,5*H*-benzo[*ij*]quinolizine.

From the acetyl compound (170 g, 0.7 moles) in 300 ml of concentrated sulfuric acid as described for **1b**; the yield was 133.1 g (96%), mp 303-305°, (ref [13] 35%, 303-305°).

4-Hydroxy-1-methyl-3-nitro-2(1*H*)-quinolone (**2a**).

A suspension of **1a** (13.26 g, 76 mmoles) in 140 ml of glacial acetic acid was treated with concentrated nitric acid (14.0 ml, 213 mmoles) and then with sodium nitrite (0.40 g, 5.8 mmoles) to start the slightly exothermic reaction. The starting material dissolved, followed immediately by precipitation of the product. After stirring for 30 minutes the mixture was diluted with 500 ml of ice water. The product was filtered and washed with water, yield 15.1 g (90%), mp 155°, dec (dioxane), (ref [14] 65%, 159°).

4-Hydroxy-3-nitro-1-phenyl-2(1*H*)-quinolone (**2b**).

From **1b** (14.95 g, 63 mmoles), 120 ml of acetic acid, 12 ml of concentrated nitric acid and 0.3 g of sodium nitrite according to the method described for **2a**, yield 16.8 g (94%), mp 158°, dec (dioxane), (ref [14] 38%, mp 167-169°, no dec described).

1-Hydroxy-2-nitro-3-oxo-3*H*,5*H*-benzo[*ij*]quinolizine (**2c**).

From **1c** (159 g, 0.79 mole) in 1400 ml of acetic acid, 140 ml of concentrated nitric acid and 4 g of sodium nitrite according to the method described for **2a**, the yield was 172.6 g (89%), mp 185°, dec (ethanol), (ref [22] 82%, 185°).

4-Chloro-1-methyl-3-nitro-2(1*H*)-quinolone (**3a**).

Dry triethylamine (10 ml) is added to a solution of **2a** (15.1 g, 69 mmoles) in 80 ml of phosphoryl chloride. The mixture is refluxed for 1 hour, the excess solvent is removed by distillation and the residue poured on 1500 ml of ice water. The solution is brought to *p*H 6 with sodium hydroxide, filtered by suction and washed with water, yield 15.1 g (92%), mp 251-252.5° (dioxane); ir: 3040 w, 1665 s, 1620 w, 1600 s cm^{-1}.

Anal. Calcd. for $C_{10}H_7ClN_2O_3$: C, 50.34; H, 2.96; N, 11.74. Found: C, 50.07; H, 2.96; N, 11.58.

4-Chloro-3-nitro-1-phenyl-2(1*H*)-quinolone (**3b**).

From **2b** (16.1 g, 57 mmoles), triethylamine (9 ml) and 70 ml of phosphoryl chloride according to **3a**, the yield was 16.5 g (96%), mp 217-218° (toluene); ir: 3060 w, 1660 s, 1610 w, 1595 s cm^{-1}.

Anal. Calcd. for $C_{15}H_9ClN_2O_3$: C, 59.91; H, 3.01; N, 9.31. Found: C, 59.80; H, 2.92; N, 9.45.

1-Chloro-2-nitro-3-oxo-6,7-dihydro-3*H*,5*H*-benzo[*ij*]quinolizine (**3c**).

From **2c** (172.6 g, 0.7 moles) and triethylamine (120 ml) in 1200 ml of phosphoryl chloride according to **3a**, the yield was 175.1 g (94%), mp 248° (dioxane); ir: 2980 w, 1640 s, 1590 w cm^{-1}.

Anal. Calcd. for $C_{12}H_9ClN_2O_3$: C, 54.44; H, 3.43; N, 10.59. Found: C, 54.66; H, 3.53; N, 10.45.

4-Azido-1-methyl-3-nitro-2(1*H*)-quinolone (**4a**).

A suspension of **3a** (2.39 g, 10 mmoles) and sodium azide (0.98 g, 15 mmoles) in 30 ml of *N*-methylpyrrolidone was stirred at room temperature for 3 hours. Then the reaction mixture was poured into 500 ml of ice water, the precipitate filtered, washed with water and dried *in vacuo* over potassium hydroxide, yield 2.33 g (95%), mp 134° (methanol), partial dec, resolidifies and melts again at 203-205°; formation of **5a**; ir: 2125 s, 1650 s, 1610 m cm^{-1}.

Anal. Calcd. for $C_{10}H_7N_5O_3$: C, 48.98; H, 2.88; N, 28.57. Found: C, 48.96; H, 2.90; N, 28.59.

4-Azido-3-nitro-1-phenyl-2(1*H*)-quinolone (**4b**).

From **3b** (2.40 g, 8.0 mmoles) and sodium azide (0.78 g, 12 mmoles) according to **4a**, the yield was 2.34 g (95%), mp 160° (methanol), partial dec, resolidifies and melts again at 229-232°; formation of **5b**; ir: 2125 s, 1660 s, 1610 m cm^{-1}.

Anal. Calcd. for $C_{15}H_9N_5O_3$: C, 58.62; H, 2.96; N, 22.80. Found: C, 58.69; H, 2.94; N, 22.60.

1-Azido-2-nitro-3-oxo-6,7-dihydro-3*H*,5*H*-benzo[*ij*]quinolizine (**4c**).

From **4c** (2.64 g, 10 mmoles) and sodium azide (0.78 g, 12 mmoles) according to **4a**, the yield was 2.39 g (89%), mp 173°, dec (methanol); ir: 3040 w, 3980 w, 2130 sh, 2120 s, 1640 s, 1590 m cm^{-1}.

Anal. Calcd. for $C_{12}H_9N_5O_3$: C, 53.14; H, 3.35; N, 25.83. Found: C, 53.32; H, 3.45; N, 25.64.

5-Methyl-4-oxo-4,5-dihydro-1,2,5-oxadiazolo[3,4-*c*]quinolin 3-Oxide (**5a**).

A solution of **4a** (1.96 g, 8 mmoles) in 50 ml of bromobenzene was refluxed until evolution of nitrogen had stopped (about 20 minutes). Then the solvent was removed *in vacuo* and the remaining solid digested with 20 ml of cyclohexane. The product was filtered and washed with cyclohexane, yield 1.63 g (94%), mp 204-206.5° (toluene); ir: 1685 s, 1635 m, 1610 w, 1580 m cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.65 and 3.73 (2 s, N-CH_3), 7.25-7.48 (m, 2 ArH), 7.67 and 7.71 (2 dt, J = 2 and 8 Hz, H at C-7), 8.25 and 8.29 (2 dd, J = 2 and 8 Hz, H at C-5).

Anal. Calcd. for $C_{10}H_7N_3O_3$: C, 55.29; H, 3.26; N, 19.35. Found: C, 55.65; H, 3.30; N, 19.30.

4-Oxo-5-phenyl-4,5-dihydro-1,2,5-oxadiazolo[3,4-*c*]quinolin 3-Oxide (**5b**).

From **4b** (2.46 g, 8 mmoles) according to **5a**, the yield was 2.05 g (92%), mp 235-238° (toluene); ir: 1695 s, 1630 m, 1610 s, 1590 m cm^{-1}; ^1H nmr: δ 6.51 and 6.55 (2 dd, J = 2 and 8 Hz, H at 2'-phenyl), 7.35-7.85 (m, 7 ArH), 8.25 and 8.29 (2 dd, J = 2 and 8 Hz, H at C-5).

Anal. Calcd. for $C_{15}H_9N_3O_3$: C, 64.50; H, 3.25; N, 15.05. Found: C, 64.70; H, 3.33; N, 14.77.

8-Oxo-5,6-dihydro-4*H*,8*H*-benzo[*ij*]-1,2,5-oxadiazolo[3,4-*b*]quinolizine 9-Oxide (**5c**).

From **4c** (2.71 g, 0.01 mole) according to **5a**, the yield was 2.23 g (92%), mp 205-206° (toluene); ir: 2940 w, 1680 s, 1630 m, 1605 m cm^{-1}; ^1H nmr: δ 1.9-2.1 (m, CH_2), 2.85-3.05 (m, CH_2), 4.02 and 4.13 (2 t, J = 7 Hz, N-CH_2), 7.15-7.45 (m, 2 ArH), 7.50-7.65 (m, 1 ArH), 8.05 and 8.09 (2 dd, J = 2 and 8 Hz, H at C-1).

Anal. Calcd. for $C_{12}H_9N_3O_3$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.62; H, 3.81; N, 16.93.

1-Methyl-3-nitro-4-triphenylphosphoranylideneamino-2(1*H*)-quinolone (**6a**).

A solution of triphenylphosphane (0.79 g, 3.0 mmoles) and **4a** (0.74 g, 3.0 mmoles) in 10 ml of toluene is refluxed for 15 minutes. The reaction mixture is allowed to cool and the precipitate is filtered after standing some hours and washed with toluene and cyclohexane, yield 1.0 g (70%), mp 196° (toluene); ir: 1630 s, 1610 s cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.6 (s, N-CH_3), 6.9-7.9 (m, 18 ArH), 8.05 (dd, J = 2 and 8 Hz, H at C-5).

Anal. Calcd. for $C_{28}H_{22}N_3O_3P$: C, 70.13; H, 4.63; N, 8.77. Found: C, 70.02; H, 4.48; N, 8.76.

3-Nitro-1-phenyl-4-triphenylphosphoranylideneamino-2(1*H*)-quinolone (**6b**).

From triphenylphosphane (1.18 g, 4.5 mmoles) and **4b** (1.27 g, 4.1 mmoles) according to **6a**, the yield was 2.14 g (96%), mp 289-291.5°, dec (toluene); ir: 3060 w, 1650 s, 1610 m, 1580 m cm^{-1}.

Anal. Calcd. for $C_{33}H_{24}N_3O_3P$: C, 73.18; H, 4.48; N, 7.76. Found: C, 73.66; H, 4.55; N, 7.60.

2-Nitro-1-triphenylphosphoranylideneamino-6,7-dihydro-3*H*,5*H*-benzo[*ij*]quinolizin-3-one (**6c**).

From triphenylphosphane (1.18 g, 4.5 mmoles) and **4c** (1.11 g, 4.1 mmoles) according to **6a**, the yield was 1.65 g (80%), mp 235° (toluene); ir: 3600-3400 b, 3110 w, 2990 w, 1645 s, 1620 m, 1600 m, 1565 s cm^{-1}; ^1H nmr: δ 1.95 (t, J = 7 Hz, CH_2), 2.9 (t, J = 7 Hz, Ar-CH_2), 4.0 (t, J = 7 Hz, N-CH_2), 6.85-7.0 (m, 1 ArH), 7.3-7.4 (m, 1 ArH), 7.5-7.8 (m, 16 ArH).

Anal. Calcd. for $C_{30}H_{24}N_3O_3P$: C, 71.28; H, 4.79; N, 8.31. Found: C, 71.47; H, 4.85; N, 8.29.

General Method for the Preparation of 4-Amino-3-nitro-2(1*H*)-quinolones and 1-Amino-2-nitrobenzo[*ij*]quinolizin-3-one **7a-j**.

Method A.

A mixture of the phosphazene **6a-c** (2.1 mmoles), glacial acetic acid (8.0 ml) and water (2.0 ml) is refluxed for 1 hour. Then 40 ml

of water and 10 ml of toluene are added; the precipitate is filtered by suction and washed with water and toluene (data see Tables 1 and 2).

Method B.

A slow stream of ammonia is bubbled through a suspension of **3a,b** (2.0 mmoles) in 5 ml of *N*-methylpyrrolidone. After 30 minutes the product is precipitated with 100 ml of ice water and after standing for 24 hours filtered and washed thoroughly with water (data see Tables 1 and 2).

Method C.

A mixture of **3a,b** (2.0 mmoles) and the appropriate amine (10 mmoles) in 5 ml of *N*-methylpyrrolidone is stirred at room temperature for the time given in Table 1 and worked up as described for method B (data see Tables 1 and 2).

4-Fluoro-1-methyl-3-nitro-2(1*H*)-quinolone (**8a**).

A suspension of **3a** (1.19 g, 5.0 mmoles), spray-dried potassium fluoride [19] (0.35 g, 6.0 mmoles) and 18-crown-6 (0.26 g, 1.0 mmoles) in 20 ml of dry acetonitrile is refluxed for 3 hours under exclusion of moisture. Then the solvent is removed and the residue poured into 300 ml of ice water, the precipitate filtered, washed with ice cold water and dried thoroughly, yield 1.05 g (95%), mp 206.5-207.5° (toluene); ir: 3070 w, 1675 s, 1605 m, 1570 m cm^{-1}.

Anal. Calcd. for $C_{10}H_7FN_2O_3$: C, 54.05; H, 3.18; N, 12.61. Found: C, 54.01; H, 3.25; N, 12.30.

4-Fluoro-3-nitro-1-phenyl-2(1*H*)-quinolone (**8b**).

From **3b** (1.20 g, 4.0 mmoles) as described for **3a**, the yield was 1.01 g (89%), mp 224-227°, dec (toluene); ir: 1670 s, 1600 m, 1560 m cm^{-1}.

Anal. Calcd. for $C_{15}H_9FN_2O_3$: C, 63.37; H, 3.20; N, 9.86. Found: C, 63.03; H, 3.32; N, 9.64.

4-Methoxy-1-methyl-3-nitro-2(1*H*)-quinolone (**9a**).

A solution of sodium (0.12 g, 5.0 mmoles) in 10 ml of methanol is combined with 0.48 g (2.0 mmoles) **3a** and refluxed for 30 minutes. The mixture is then poured onto 100 ml of ice water and acidified with acetic acid. The precipitate is filtered and washed with water, yield 0.40 g (85%), mp 138-139.5° (toluene); ir: 3080 m, 2960 w, 1640 s, 1600 s, 1570 w cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.7 (s, N-CH_3), 4.2 (s, OCH_3), 7.1-7.7 (m, 3 ArH), 8.1 (dd, J = 2 and 8 Hz, H at C-5).

Anal. Calcd. for $C_{11}H_{10}N_2O_4$: C, 56.41; H, 4.31; N, 11.96. Found: C, 56.70; H, 4.36; N, 11.99.

4-Methoxy-3-nitro-1-phenyl-2(1*H*)-quinolone (**9b**).

From **3a** (0.60 g, 2.0 mmoles) according to **9a**, the yield was 0.58 g (98%), mp 194-195.5° (toluene); ir: 1655 s, 1620 m, 1600 m cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.25 (s, CH_3), 6.75 (dd, J = 2 and 8 Hz, H at 2'-phenyl), 7.15-7.75 (m, 7 ArH), 8.15 (dd, J = 2 and 8 Hz, H at C-5).

Anal. Calcd. for $C_{16}H_{12}N_2O_4$: C, 64.85; H, 4.09; N, 9.46. Found: C, 65.16; H, 4.08; N, 9.36.

4-Ethoxy-1-methyl-3-nitro-2(1*H*)-quinolone (**9c**).

As described for **9a** using 10 ml of absolute ethanol (instead of methanol), the yield was 0.45 g (91%), mp 152-153° (toluene); ir: 2980 w, 1640 s, 1600 m, 1565 w cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.5 (t, J = 7 Hz, ethyl-CH_3), 3.7 (s, N-CH_3), 4.35 (q, J = 7 Hz, ethyl-CH_2), 7.1-7.5 (m, 3 ArH), 8.05 (dd, J = 2 and 8 Hz, H at C-5).

Anal. Calcd. for $C_{12}H_{12}N_2O_4$: C, 58.04; H, 4.88; N, 11.28. Found: C, 58.27; H, 4.83; N, 11.26.

1-Methyl-3-nitro-4-phenoxy-2(1*H*)-quinolone (**9d**).

A mixture of **3a** (0.48 g, 2.0 mmoles), phenol (0.28 g, 3.0 mmoles) and dry potassium carbonate (0.42 g, 3.0 mmoles) in 5.0 ml of *N*-methylpyrrolidone is stirred for 3 hours at 20° and then worked up as described for **9a**, yield 0.55 g (93%), mp 140-142° (ethanol); ir: 1655 s, 1600 m, 1570 w, 1535 s cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.8 (s, CH_3), 6.9-7.75 (m, 8 ArH), 7.95 (dd, J = 2 and 8 Hz, H at C-5).

Anal. Calcd. for $C_{16}H_{12}N_2O_4$: C, 64.85; H, 4.09; N, 9.46. Found: C, 64.91; H, 4.05; N, 9.40.

3-Nitro-4-phenoxy-1-phenyl-2(1*H*)-quinolone (**9e**).

From **3b** (0.60 g, 2.0 mmoles) according to **9d**, the yield was 0.64 g (89%), mp 228-229.5° (toluene); ir: 3060 w, 1660 s, 1605 m cm^{-1}.

Anal. Calcd. for $C_{21}H_{14}N_2O_4$: C, 70.37; H, 3.95; N, 7.82. Found: C, 70.71; H, 3.93; N, 7.70.

4-Ethylthio-1-methyl-3-nitro-2(1*H*)-quinolone (**10a**).

A mixture of **3a** (0.48 g, 2.0 mmoles), ethyl mercaptane (0.30 ml = 0.25 g, 4.0 mmoles) and triethylamine (1.0 ml) in 5.0 ml of *N*-methylpyrrolidone is stirred for 1 hour at 20°. Then the reaction mixture is poured into 100 ml of ice water, the resulting precipitate is filtered and washed diligently with water, yield 0.50 g (95%), mp 127-128° (toluene); ir: 2980 w, 1650 s, 1605 m, 1590 m cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.3 (t, J = 7 Hz, ethyl-CH_3), 2.95 (q, J = 7 Hz, ethyl-CH_2), 3.8 (s, NCH_3), 7.25-7.95 (m, 3 ArH), 8.35 (dd, J = 2 and 8 Hz, H at C-5).

Anal. Calcd. for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.59; N, 10.60. Found: C, 54.28; H, 4.45; N, 10.48.

1-Methyl-3-nitro-4-phenylthio-2(1*H*)-quinolone (**10b**).

A mixture of **3a** (0.48 g, 2.0 mmoles), thiophenol (0.27 g, 2.5 mmoles) and 1.0 ml of pyridine in 5.0 ml of *N*-methylpyrrolidone is stirred for 30 minutes at 20°. The product is worked up as described for **10a** and dried over potassium hydroxide, yield 0.60 g (96%), mp 205.5-206.5° (toluene); ir: 3050 w, 1655 s, 1605 w, 1590 w cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.8 (s, N-CH_3), 7.1-7.85 (m, 8 ArH), 8.25 (dd, J = 2 and 8 Hz, H at C-5).

Anal. Calcd. for $C_{16}H_{12}N_2O_3S$: C, 61.53; H, 3.88; N, 8.97. Found: C, 61.70; H, 3.93; N, 8.75.

3-Nitro-1-phenyl-4-phenylthio-2(1*H*)-quinolone (**10c**).

From **3b** (0.60 g, 2.0 mmoles), using the procedure of **10b**, the yield was 0.72 g (96%), mp 201.5-202.5° (toluene); ir: 3060 w, 1655 s, 1605 m, 1590 m cm^{-1}.

Anal. Calcd. for $C_{21}H_{14}N_2O_3S$: C, 67.36; H, 3.78; N, 7.48. Found: C, 67.45; H, 3.75; N, 7.42.

3,4-Diethylthio-1-methyl-2(1*H*)-quinolone (**11a**).

A suspension of **3a** (0.48 g, 2.0 mmoles), ethyl mercaptan (0.52 ml, 6.8 mmoles) and dry potassium carbonate (0.58 g, 4.2 mmoles) in 5.0 ml of *N*-methylpyrrolidone is stirred for 5 hours at 20°, then poured into 100 ml of ice water. After standing for 12 hours the precipitate is filtered and washed with water, yield 0.55 g (98%), mp 75-75° (cyclohexane); ir: 2920 w, 1635 s, 1600 m cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.25 (t, J = 7 Hz, ethyl-CH_3), 1.3

(t, J = 7 Hz, ethyl-CH_3), 3.05 (q, J = 7 Hz, ethyl-CH_2), 3.3 (q, J = 7 Hz, ethyl-CH_2), 3.8 (s, NCH_3), 7.1-7.8 (m, 3 ArH), 8.45 (dd, J = 2 and 8 Hz, H at C-5).

Anal. Calcd. for $C_{14}H_{17}NOS_2$: C, 60.18; H, 6.14; N, 5.01. Found: C, 59.94; H, 5.88; N, 5.08.

1-Methyl-3,4-diphenylthio-2(1*H*)-quinolone (**11b**).

A mixture of **3a** (0.48 g, 2.0 mmoles), thiophenol (0.44 g, 4.0 mmoles) and 1.0 ml of triethylamine in 5.0 ml of *N*-methylpyrrolidone is stirred for 50 minutes at 20° and worked up as described for **11a**, the yield was 0.66 g (89%), mp 139-140.5° (ethanol); ir: 3060 w, 1640 s, 1600 m cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.75 (s, CH_3), 7.0-7.7 (m, 13 ArH), 8.3 (dd, J = 2 and 8 Hz, H at C-5).

Anal. Calcd. for $C_{22}H_{17}NOS_2$: C, 70.36; H, 4.57; N, 3.73. Found: C, 70.48; H, 4.41; N, 3.72.

1-Phenyl-3,4-diphenylthio-2(1*H*)-quinolone (**11c**).

From **3b** (0.60 g, 2.0 mmoles) according to **11b**, the yield was 0.85 g (97%), mp 188.5-190° (toluene); ir: 3050 w, 1660 s, 1600 m cm^{-1}.

Anal. Calcd. for $C_{27}H_{19}NOS_2$: C, 74.10; H, 4.39; N, 3.20. Found: C, 74.15; H, 4.41; N, 3.12.

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