Synthesis of Oxazolo[4,5-*c*]quinolones by Thermolytic Degradation of 4-Azido-2(1*H*)-quinolones [1]

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4-Azido-2(1*H*)-quinolones **1** are thermolyzed in the presence of carboxylic acids and polyphosphoric acid to yield oxazolo[4,5-*c*]quinolones **3**. Formation of other possible isomeric ring closure products such as oxazolo[5,4-*c*]quinolones **2** or isoxazolo[4,3-*c*]quinolones **4** could be excluded by independent syntheses.

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Oxazoloquinolines were investigated thoroughly in the last years and many representatives were found to show antihypertensive and dopaminergic properties [2], antiulcer [3], anticancer [4], antiallergic [5], antidepressive [6] or herbicidal activity [7]. We focused our interest to oxazoloquinolines which are anellated to the *c*-side of the quinoline nucleus derived from 4-azido-2-quinolones [8]. Surprisingly,in the literature only oxazolo[4,5-*c*]-quinolones are described, derived either from 3-amino-4-hydroxy-2-quinolones [9], or obtained from isatoic anhydrides with α -isocyanoacetates [10] or by Beckmann rearrangement of the oximes of 3-acyl-4-hydroxy-2-quinolones [11]. Some of these derivatives were found to possess antiallergic, antiinflammatory and central nerve depressing activities [10]. The reversed isomer, an oxazolo[5,4-*c*]quinolone, is not described, probably due to the instability of the intermediate 4-amino-3-hydroxy-quinolones.

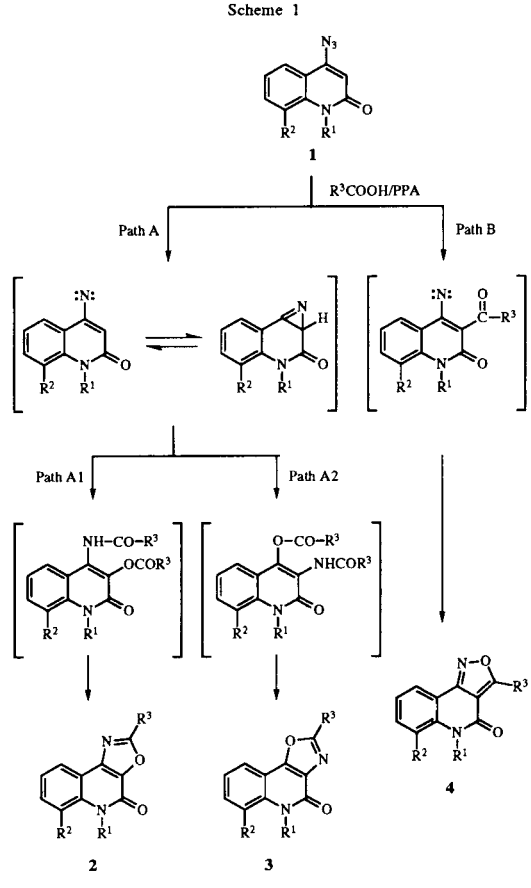
Oxazoloarenes are reported to be obtained from azidoarenes by thermolysis in the presence of acetic acid and polyphosphoric acid [12] involving nucleophilic substitution by acetoxy-oxygen at the position next to the azide group [12, 13], although a recent reexamination of this work has shown some discrepancies in the structural assignment [14]. Transformation of this reaction type to 4-azidoquinolones should lead to the hitherto unknown oxazolo[5,4-*c*]quinoline ring system.

Actually, when we reacted 4-azidoquinolones **1** with aliphatic and aromatic carboxylic acids in the presence of polyphosphoric acid, we obtained cyclization products, which were in agreement with oxazoloquinolone structures. A consideration of the available reaction offered three pathways leading to isomeric oxazolo- or isoxazoloquinolones, namely **2**, **3**, or **4**, respectively.

According to the findings obtained with azidoarenes [12-14], the formation of an oxazolo[5,4-*c*]quinolone of type **2** should be expected to occur *via* an intermediate quinolone with a nitrene function in 4-position, then *C*-acyloxylation by the carboxylic acid in 3-position followed by cyclization to the oxazolo[5,4-*c*]-quinolone **2**. In this case the nitrogen derived from the nitrene would not have changed its position.

On the other hand, nitrenes are known to exist in an equilibrium with ring closed azirines [15], which could react with carboxylic acids by addition and subsequent ring opening of the aziridine ring to quinolones bearing the nitrogen function in 3-position and the oxygen function in 4-position, resulting in an reversed anellated isomeric oxazolo[4,5-*c*]quinolone **3**. Moreover the attack of the oxygen of the carboxylic acid to the positive charged

Scheme 1



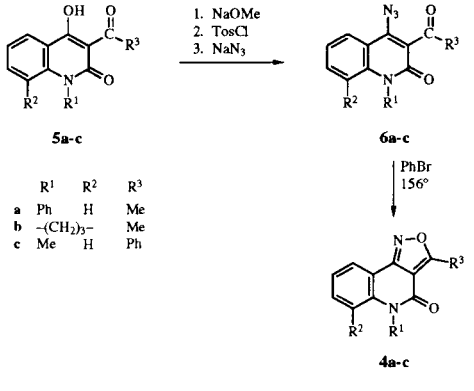
4-position of the 2-quinolone is more likely.

A third possible isomer, the isoxazolo[4,3-*c*]quinoline ring system **4**, could be formed by an acid catalyzed electrophilic attack of the carbonyl carbon of the carboxylic acid, which should be directed to the nucleophilic 3-position of the 4-azido-2-quinolone according to the findings obtained in the synthesis of 3-acetyl-4-hydroxyquinolones [20]. If this reaction step is faster than the thermolysis of the azido function, a subsequent thermolytic ring closure reaction of the intermediate nitrene should take place to form the isoxazole **4** [8a].

To obtain an unambiguous structural assignment, we decided to synthesize oxazoles **3** and isoxazoles **4** in independent synthetic pathways for a comparison of physical and spectroscopic data.

Recently we have developed syntheses for isoxazolo[4,3-*c*]quinolines starting from 3-acetyl-4-azido- or 4-azido-3-formyl-2-quinolones [8a,b,d]. According to these procedures we synthesized 5-methylisoxazolo-[4,3-*c*]quinolin-4-ones **4a,c** and 9-methyl-5,6-dihydro-4*H*-benzo[*ij*]isoxazolo[3,4-*b*]quinolizin-8-one **4b** starting from 3-acetyl-4-hydroxy-2-quinolones **5**, which were converted to tosylates and then reacted to azides **6**. Surprisingly an azide of type **6** with a 3-propionyl-substituent (R^1 = Me, R^3 = Et) could not be obtained from its tosylate, because decomposition to a dark blue, insoluble compound occurred during the attempted conversion of the tosylate to the azide. The azide **6c** could not be obtained in a pure form due to its immediate cyclization to **4c**, so that only mixtures of **6c** and **4c** could be isolated.

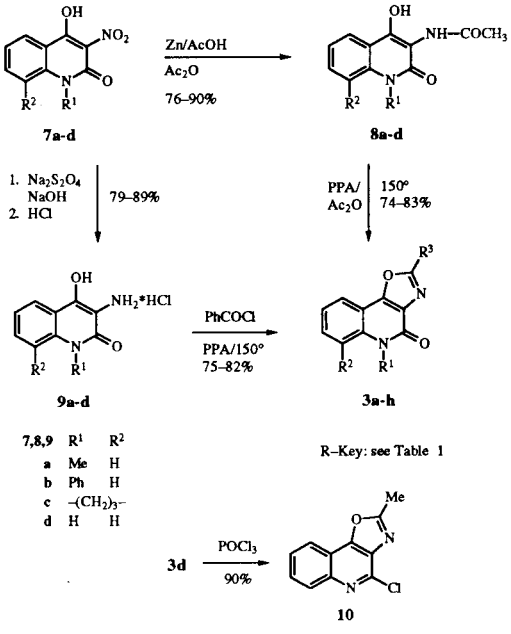
Scheme 2



Thermolysis of the azides **6a,b** (or the mixture of **6c/4c**) in boiling bromobenzene resulted in the formation of isoxazolo[4,3-*c*]quinolones **4a-c**, which could be used for comparison with reaction products from azides **1** with carboxylic acids.

Oxazolo[4,5-*c*]quinolones **3** are known to be accessible *via* three pathways as cited above [9-11]. We started from

Scheme 3



4-hydroxy-3-nitroquinolones **7** [8c], which were reduced either to the acetylaminoquinolones **8** with zinc in acetic acid in the presence of acetic anhydride similar to ref [16], to avoid the isolation of the sensitive free amino derivatives. **8d** could not be obtained, because consecutive thermal ring closure to **3d** occurred before the reduction to **8d** was complete.

Another method for reduction of 4-hydroxy-3-nitroquinolones involves treatment with sodium dithionite similar to ref [9c]; in this case the hydrochlorides of the 3-aminoquinolones **9** were isolated which are very sensitive to oxidation; they had to be dried carefully at room temperature and immediately used for further reactions. So no physical and spectroscopic data of **9** could be obtained.

Scheme 4

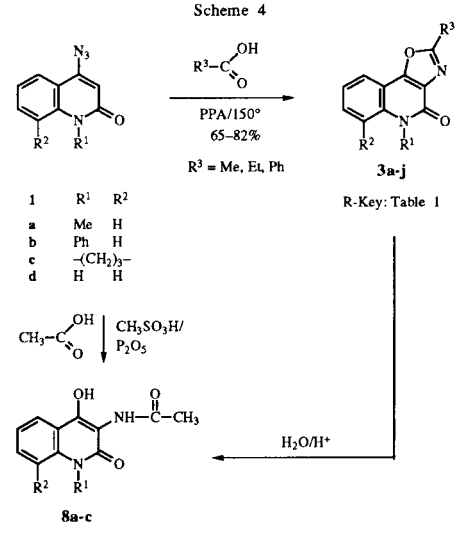


Table 1

Experimental and Analytical Data of 2,5-Disubstituted Oxazolo[4,5-*c*]quinolin-4-ones **3a,b,d-f,h-j** and 10-Substituted 5,6-Dihydro-4*H*-benzo[*ij*]oxazolo[5,4-*b*]quinolizin-8-ones **3c,g**

No.	R^1	R^2	R^3	method Yield (%)	Mp (°C) Recrystallization solvent	Molecular Formula Molecular mass	Analysis, % Calcd./Found C	H	N
3a	CH_3	H	CH_3	A: 81	191	$C_{12}H_{10}N_2O_2$	67.28	4.70	13.08
				C: 79	(toluene/hexane)	(214.2)	67.58	4.86	12.81
3b	CH_3	H	C_6H_5	A: 74	246	$C_{17}H_{12}N_2O_2$	73.90	4.38	10.14
				C: 65	(toluene/hexane)	(276.3)	73.86	4.64	10.02
3c	$-(CH_2)_3-$		CH_3	A: 83	170-71	$C_{14}H_{12}N_2O_2$	69.99	5.03	11.66
				C: 74	(toluene/hexane)	(240.3)	69.70	5.11	11.77
3d	CH_3	H	H	C: 74	309	$C_{11}H_8N_2O_2$	66.00	4.03	13.99
				D: 80	(xylene)	(200.2)	65.82	4.27	13.90
3e	C_6H_5	H	CH_3	B: 75	178-79 (ref [9c] 199)				
				C: 82	(toluene/hexane)				
3f	C_6H_5	H	C_6H_5	B: 82	234	$C_{22}H_{14}N_2O_2$	78.09	4.17	8.28
				C: 71	(cyclohexane)	(338.4)	77.89	4.39	8.19
3g	$-(CH_2)_3-$		C_6H_5	B: 77	246	$C_{19}H_{14}N_2O_2$	75.48	4.67	9.27
				C: 67	(cyclohexane)	(302.3)	75.54	5.00	9.25
3h	C_6H_5	H	H	B: 77	321 [22]	$C_{16}H_{10}N_2O_2$	73.27	3.84	10.68
				C: 75	(dimethylformamide)	(262.3)	73.05	4.03	10.76
3i	C_2H_5	H	CH_3	C: 82	203.5-204	$C_{13}H_{12}N_2O_2$	68.41	5.30	12.27
					(toluene)	(228.3)	68.32	5.31	12.14
3j	C_2H_5	H	C_6H_5	C: 73	188-189	$C_{18}H_{14}N_2O_2$	74.47	4.86	9.65
					(toluene/hexane)	(290.3)	74.58	5.08	9.95

Table 2

Spectroscopic Data of 2,5-Disubstituted Oxazolo[4,5-*c*]quinolin-4-ones and 10-Substituted 5,6-Dihydro-4*H*-benzo[*ij*]oxazolo[5,4-*b*]quinolizin-8-ones **3a-j**

No.	IR [cm^{-1}]	^1H NMR (δ ppm)
3a	1670 s, 1640 w, 1590 s.	2.70 (s, CH_3), 3.70 (s, NCH_3), 7.10-7.20 (m, H at C-7 and C-8), 7.75 (dd, J = 7 and 1.5 Hz, H at C-6), 7.85 (dd, J = 7 and 1.5 Hz, H at C-9)
3b	1680 s, 1590 m.	2.70 (s, CH_3), 6.65 (d, J = 7 Hz, 1 ArH), 7.30-7.75 (m, 7 ArH), 8.0 (dd, J = 7 and 1.5 Hz, H at C-9)
3c	1680 s, 1655 m, 1640 m, 1590 s.	2.00 (t, J = 7 Hz, CH_2), 2.65 (s, CH_3), 2.90 (t, J = 7 Hz, Ar-CH_2), 4.15 (t, J = 7 Hz, N-CH_2), 7.20 (t, J = 7 Hz, H at C-2), 7.38 (dd, J = 7 and 1.5 Hz, H at C-3), 7.60 (dd, J = 7 and 1.5 Hz, H at C-1)
3d	3150 w, 1670 s, 1610 m, 1590 m.	2.60 (s, CH_3), 7.20-7.65 (m, 3 ArH), 7.80 (dd, J = 7 and 1.5 Hz, H at C-9), 11.90 (s, NH)
3e	1690 s, 1675 s, 1590 m.	3.70 (s, N-CH_3), 7.40 (m, 1 ArH), 7.60-7.80 (m, 5 ArH), 8.10 (dd, J = 7 and 1.5 Hz, H at C-9), 8.15-8.30 (m, H at C-7 and C-8)
3f	1680 s, 1635 w, 1610 w, 1590 m.	6.65 (m, 1 ArH), 7.35-7.50 (m, 3 ArH), 7.60-7.85 (m, 7 ArH), 8.15 (dd, J = 7 and 1.5 Hz, H at C-9), 8.20-8.30 (m, H at C-7 and C-8)
3g	1675 s, 1640 s, 1610 w.	2.20 (t, J = 7 Hz, CH_2), 3.0 (t, J = 7 Hz, Ar-CH_2), 4.20 (t, J = 7 Hz, N-CH_2), 7.10-7.20 (m, 3 ArH), 7.30 (t, J = 7 Hz, H at C-2), 7.45 (dd, J = 7 and 1.5 Hz, H at C-3), 7.90 (dd, J = 7 and 1.5 Hz, H at C-1), 8.20-8.30 (m, 2 ArH)
3h	1670 s, 1635 m, 1610 m.	7.30-7.70 (m, 5 ArH), 8.05 (dd, J = 7 and 1.5 Hz, H at C-9), 8.25 (m, 3 ArH), 12.05 (s, N-H)

Table 2 (continued)

No.	IR [cm^{-1}]	^1H NMR (δ ppm)
3i	1660 s, 1635 m 1585 m.	1.40 (t, J = 7 Hz, CH_3), 3.0 (q, J = 7 Hz, CH_2), 3.70 (s, N-CH_3), 7.40 (dd, J = 7 and 1.5 Hz, H at C-6), 7.70 (m, H at C-7 and C-8), 7.90 (dd, J = 7 and 1.5 Hz, H at C-9)
3j	1680 s, 1590 m, 1580 m.	1.95 (t, J = 7 Hz, CH_3), 3.10 (q, J = 7 Hz, CH_2), 6.70 (d, J = 7 Hz, 1 ArH), 7.40-7.80 (m, 7 ArH), 8.05 (dd, J = 7 and 1.5 Hz, H at C-9)

Ring closure to oxazoloquinolones **3a-c** having a 2-methyl substituent was achieved by heating acetylaminoquinolones **8a-c** in acetic anhydride in the presence of polyphosphoric acid. **3d** was obtained directly from **7d** during reduction *via* **8d** . Oxazoloquinolones **3e-h** with a 2-phenyl substituent were obtained from 3-aminoquinolones **9** with benzoyl chloride and polyphosphoric acid. In all cases a quick work-up of the oxazoloquinolones **3** is necessary to avoid ring opening to 3-acylaminoquinolones of type **8** . In a preparative manner ring opening of **3a-d** to **8a-c** can be performed by heating the oxazoles **3** in a mixture of ethanol and hydrochloric acid. However we failed again to obtain pure **8d** in this way, because during the workup always partial ring closure to **3d** took place. Halogenation of the *N*-unsubstituted oxazoloquinolone **3d** with phosphorylchloride resulted in the conversion to the 4-chlorosubstituted aromatic oxazoloquinoline **10**.

Comparison of the data of ring closure products of 4-azidoquinolones **1** with carboxylic acids in polyphos-

phoric acid with the data of oxazoles **3** and isoxazoles **4** showed identity in all respects with the data of oxazoles **3** obtained from 3-aminoquinolones **8** and **9**. Oxazoloquinolones **3a**, **3c** and **3d** showed also identity with oxazoloquinolones obtained *via* a thermal Beckmann rearrangement of oximes of 4-hydroxy-3-acetyl-2-quinolones [11a], which may serve also as a proof for these structures.

When other acids such as methanesulfonic acid containing 10% of phosphorus pentoxide were used as cyclization agents, *N*-alkylquinolones **1a** and **1c** formed only open chain 4-hydroxy-3-acetylaminoquinolones **8a,c,** which could be cyclized in acetic anhydride to the corresponding oxazolo[4,5-*c*]quinolones **3a,c**. *N*-Phenylquinolone **1b** cyclized directly in one step to **3b**. Structures of **3a-c** obtained *via* azidoquinolines **1** were proved additionally by ring opening to the corresponding 3-acetylaminoquinolones **8a-c**.

These findings confirm a reaction pathway *via* an aziridine intermediate [17] and open a new entry into the synthesis of oxazolo[4,5-*c*]quinolines with the possibility of broad variation of the substituent in the oxazole nucleus by use of different carboxylic acids as agents in the thermolysis reaction of the azidoquinolines **1**, but it was not possible to obtain oxazolo[5,4-*c*]quinoline systems in this way.

EXPERIMENTAL

Melting points were determined on a Gallenkamp Melting Point Apparatus Model MFB-595 in open capillary tubes. The ^{1}H nmr spectra were recorded on a Varian Gemini 200 instrument (200 MHz), ^{13}C nmr spectra on a Bruker AM 360 instrument (90 MHz). Chemical shifts are reported in ppm from internal tetramethylsilane and are given in δ-units. The solvent for nmr spectra was deuteriodimethyl sulfoxide unless otherwise stated. Infrared spectra were taken in potassium bromide pellets on a Perkin-Elmer 298 spectrophotometer. Mass spectra were recorded on a Finnigan 4021 instrument (EI: 70 eV, CI: 120 eV, methane). Elemental analyses were performed on a Carlo Erba 1106 C,H,N-automatic analyzer and are within 0.4 of the theoretical percentages. 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. Common reagent grade chemicals are either commercially available and were used without further purification or prepared by standard literature procedures.

General Procedure for the Preparation of Oxazolo[4,5-*c*]quinolin-4-ones and 5,6-Dihydro-4*H*-benzo[*ij*]oxazolo[5,4-*b*]quinolizin-8-ones **3a-j**.

Method A).

A mixture of the corresponding 3-acetylaminoquinolone **8a-c** (10 mmoles) with acetic anhydride (5.0 g, 50 mmoles) and polyphosphoric acid (10.0 g) was heated to 150° for 4 hours. The hot reaction mixture was poured into ice water (200 ml) and after 1 hour brought to *p*H 5-6 with concentrated aqueous sodium hydroxide. The formed precipitate was filtered by suction.

Method B).

A mixture of the appropriate 3-amino-4-hydroxy-2(1*H*)-quinolone hydrochloride **9a-d** (10 mmoles) and benzoyl chloride (4.5 g, 32 mmoles) in polyphosphoric acid (9.0 g) was heated to 150° for 2 hours. The hot reaction mixture was poured into ice water (300 ml) and brought to *p*H 5-6 with aqueous concentrated sodium hydroxide. The resulting precipitate was filtered by suction and recrystallized from the appropriate solvent.

Method C).

A mixture of the corresponding 4-azido-2-quinolone **1a-d** [19] (10 mmoles) with the appropriate carboxylic acid (acetic acid, benzoic acid or propanoic acid, respectively) (11 mmoles) in polyphosphoric acid (20 g) was heated to 150° for 2 hours. The hot reaction mixture was poured onto ice water (300 ml), with aqueous concentrated sodium hydroxide brought to *p*H 5-6 and the formed precipitate filtered by suction. A second crop could be obtained by extraction of the filtrate with dichloromethane (2 x 100 ml), drying the organic solvents over sodium sulfate and removing the solvent *in vacuo*. The combined products were crystallized from toluene.

Method D) for the Preparation of **3d**.

A mixture of 4-hydroxy-3-nitro-2(1*H*)-quinolone (**7d**) (2.0 g, 10 mmoles) in acetic acid (70 ml) and acetanhydride (48 ml) with zinc dust (4.0 g) was heated under reflux for 30 minutes. After filtration the solvent was removed *in vacuo*, the residue was triturated with water and the product filtered by suction; yield 1.54 g (80%), experimental data are in Table 1 and spectroscopic data in Table 2.

3-Methyl-5-phenylisoxazolo[4,3-*c*]quinolin-4-one (**4a**).

A solution of 3-acetyl-4-azido-1-phenyl-2(1*H*)-quinolone (**6a**) (0.6 g, 2.3 mmoles) in bromobenzene (30 ml) was heated under reflux for 2 hours. Then the solvent was removed *in vacuo* and the residue digested with cyclohexane (20 ml). The solid product was filtered, washed with cyclohexane and dried, yield 0.47 g (86%), mp 278-280° (dioxane); ir: 1680 s, 1675 sh, 1635 s, 1615 s cm^{-1}; ^{1}H nmr: δ 2.80 (s, CH_3), 6.50 (d, J = 8 Hz, 1 ArH), 7.20-7.70 (m, 7 ArH), 8.15 (dd, J = 7 and 1.5 Hz, H at C-9); ^{13}C nmr: δ 12.4, 66.2, 110.8, 117.0, 123.0, 123.9, 128.8, 129.4, 130.0, 131.9 (3a-C), 137.0 (1'-C), 141.4 (5a-C), 155.9 (9b-C), 157.5 (4-C), 174.6 (3-C).

Anal. Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.66; H, 4.02; N, 9.96.

9-Methyl-5,6-dihydro-4*H*-benzo[*ij*]isoxazolo[3,4-*b*]quinolizin-8-one (**4b**).

From 2-acetyl-1-azido-6,7-dihydro-5*H*-benzo[*ij*]quinolizin-3-one (**6b**) (4.2 g, 15.7 mmoles) in bromobenzene (50 ml) according to **4a**, the yield was 3.3 g (88%), mp 184-185° (ethanol); ir: 1665 s, 1635 s cm^{-1}; ^{1}H nmr: δ 1.95-2.05 (m, CH_2), 2.85 (s, CH_3), 2.90(t, J = 7 Hz, aryl-CH_2), 4.0 (t, J = 7 Hz, N-CH_2), 7.30 (d, J = 7 Hz, H at C-2), 7.45 (dd, J = 7 and 1.5 Hz, H at C-3), 7.90 (dd, J = 7 and 1.5 Hz, H at C-1).

Anal. Calcd. for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.74; H, 5.20; N, 11.90.

3-Phenyl-5-methylisoxazolo[4,3-*c*]quinolin-4-one (**4c**).

4-Azido-3-benzoyl-1-methyl-2(1*H*)-quinolone (**6c**) could not

be isolated in a pure form and was reacted in a one pot reaction to **4c**. Preparation was performed according to the method described for **6a**.

A) The sodium salt of **5c** was obtained from 3-benzoyl-4-hydroxy-2(1*H*)-quinolone **5c** [11c,18] (2.8 g, 10 mmoles) and sodium (0.23 g) in methanol (10 ml), yield 2.9 g (96%).

B) 3-Benzoyl-1-methyl-4-(4-tolylsulfonyloxy)-2(1*H*)-quinolone was obtained from the sodium salt (2.9 g, 9.6 mmoles) and 4-tolylsulfonyl chloride (1.9 g, 10 mmoles) in acetonitrile (50 ml), yield 2.83 g (68%), mp 213-214° (toluene).

C) 3-Phenyl-5-methylisoxazolo[4,3-*c*]quinolin-4-one.

A mixture of the tosylate (4.0 g, 9.2 mmoles) in absolute dimethylformamide (50 ml), sodium azide (0.65 g, 10 mmoles) and *N,N*-dimethylaminopyridine (0.1 g) was stirred at 5° for 24 hours. The reaction mixture was poured in ice water, filtered and heated in bromobenzene (20 ml) for 30 minutes. Then the solvent was removed *in vacuo* and the residue triturated with cyclohexane (20 ml). The solid product was filtered, washed with cyclohexane and dried, yield 1.23 g (49%), mp 177.5-178° (ethanol); ir: 1660 s, 1610 s cm^{-1}; ^1H nmr: δ 3.60 (s, N-CH_3), 7.30-7.80 (m, 6 ArH), 8.0-8.10 (m, 2 ArH), 8.15 (dd, J = 7 and 1.5 Hz, H at C-9).

Anal. Calcd. for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 73.76; H, 4.48; N, 9.94.

3-Acetyl-4-azido-1-phenyl-2(1*H*)-quinolone (**6a**).

A) Sodium Salt of **5a**.

A solution of 3-acetyl-4-hydroxy-1-phenyl-2(1*H*)-quinolone (**5a**) [8c] (5.8 g, 17.9 mmoles) in dioxane (100 ml) was combined with sodium methanolate, obtained from sodium (0.5 g) in methanol (20 ml). The sodium salt precipitated and was filtered and dried, yield 4.0 g (93%).

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

A suspension of the sodium salt (4.0 g, 13.2 mmoles) in absolute acetonitrile (50 ml) was reacted with 4-tolylsulfonylchloride (3.33 g, 17 mmoles). The mixture was heated under reflux for 2 hours and then poured into ice water (250 ml). The resulting oil was allowed to become solid and then filtered by suction and dried, yield 5.64 g (98%), mp 173.5-173.8° (toluene).

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

To a solution of the tosylate (2.0 g, 4.6 mmoles) in 1-methylpyrrolidone (15 ml), sodium azide (0.65 g, 10 mmoles) was added and the mixture was stirred for 4 hours at 20°. Then the mixture was poured into ice water (200 ml) and the resulting precipitate filtered, washed with water and dried, yield 1.22 g (92%), mp 160° (methanol); ir: 2125 s, 1680 s cm^{-1}; ^1H nmr: δ 2.65 (s, CH_3), 6.60 (d, J = 7 Hz, 1 ArH), 7.30-7.45 (m, 3 ArH), 7.50-7.75 (m, 4ArH), 8.10 (dd, J = 7 and 1.5 Hz, H at C-5).

Anal. Calcd. for $C_{17}H_{12}N_4O$: C, 70.82; H, 4.20; N, 19.43. Found: C, 70.95; H, 3.98; N, 19.15.

2-Acetyl-1-azido-6,7-dihydro-5*H*-benzo[*ij*]quinolizin-3-one (**6b**).

Compound **6b** was obtained according to the method described for **6a**.

A) Sodium Salt of **5b**.

This was obtained from **5b** [8c] (5.0 g, 20 mmoles) and sodium (0.69 g) in methanol (20 ml), yield 4.95 g (91%).

B) 2-Acetyl-1-(4-tolylsulfonyloxy)-6,7-dihydro-5*H*-benzo[*ij*]-quinolizin-3-one.

This was obtained from the sodium salt (4.95 g, 18.7 mmoles) and 4-tolylsulfonyl chloride (3.8 g, 20 mmoles) in acetonitrile (50 ml), yield 6.26 g (84%), mp 181° (toluene).

C) 2-Acetyl-1-azido-6,7-dihydro-5*H*-benzo[*ij*]quinolizin-3-one.

This was obtained from the tosylate (2.29 g, 5.8 mmoles) and sodium azide (0.65 g, 10 mmoles) in 1-methylpyrrolidone (25 ml); yield 1.14 g (72%), mp 119.5° dec (methanol); ir: 2125 s, 1680 s cm^{-1}; ^1H nmr: δ 1.95-2.05 (m, CH_2), 2.85-2.95 (m, CH_2), 3.3 (s, CH_3), 4.0-4.1 (m, N-CH_2), 7.25 (d, J = 7 Hz, H at C-9), 7.50 (dd, J = 7 and 1.5 Hz, H at C-8), 7.80 (dd, J = 7 and 1.5 Hz, H at C-10).

Anal. Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.86; H, 4.68; N, 20.59.

3-Benzoyl-4-azido-1-methyl-2(1*H*)-quinolone (**6c**).

This azide could not be obtained in a pure form and was reacted in a one pot reaction to **4c**.

4-Hydroxy-3-nitro-2(1*H*)-quinolones **7a-d** were prepared according to ref [8c].

3-Acetylamino-4-hydroxy-1-methyl-2(1*H*)-quinolone (**8a**).

Method A).

A mixture of 4-hydroxy-1-methyl-3-nitro-2(1*H*)-quinolone (**7a**) (2.2 g, 10 mmoles) in acetic acid (70 ml) and acetic anhydride (48 ml) with 3.0 g of zinc dust was heated under reflux for 30 minutes and worked up according to ref [16b].

Method B).

A mixture of 4-azido-1-methyl-2(1*H*)-quinolone **1a** [19] (1.75 g, 8.7 mmoles) and acetic acid (10 g) in 10 g of methanesulfonic acid (containing 10% phosphorous pentoxide) was heated to 135° for 7 hours. The hot reaction mixture was poured into ice water (300 ml) and the product filtered by suction. A second crop was obtained when the mother liquor was extracted with dichloromethane (2 x100 ml) and the dried organic layers were taken to dryness. The combined products were crystallized from toluene, yield 1.23 g (61%).

Method C).

A solution of the oxazoloquinoline **3a** (2.1 g, 10 mmoles) in 0.5 *N* hydrochloric acid (100 ml) and ethanol (80 ml) was heated under reflux for 1 hour. The solution was allowed to cool down to form a precipitate which was filtered by suction, washed with water and dried, yield 1.9 g (87%), mp 197° (toluene); ir: 3260 s, 1640 s, 1615 s, 1590 s cm^{-1}; ^1H nmr: δ 2.20 (s, CH_3), 3.70 (s, NCH_3), 7.20-7.80 (m, 4 ArH), 9.80 (s, NH), 11.90 (s, NH).

Anal. Calcd. for $C_{12}H_{12}N_2O_3$: C, 62.06; H, 5.21; N, 12.06. Found: C, 62.20; H, 5.08; N, 12.31.

3-Acetylamino-4-hydroxy-1-phenyl-2(1*H*)-quinolone (**8b**).

Method A).

This compound was obtained from 4-hydroxy-3-nitro-1-phenyl-2(1*H*)-quinolone [8c] (**7b**) (2.8 g, 10 mmoles) according to the method described for **8a**, yield 2.24 g (76%).

Method C).

This compound was obtained from oxazoloquinoline **3b** (2.7 g, 10 mmoles) according to the method described for **8a**, yield

2.4 g (84%), mp 275° (dimethyl formamide); ir: 3295 m, 1640 m, 1615 s, 1590 m cm^{-1}; ^1H nmr: δ 2.25 (s, CH_3), 6.65 (d, J = 7 Hz, OH), 7.25-8.05 (m, 9 ArH), 9.80 (s, N-H).

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.79; N, 9.52: Found: C, 69.54; H, 5.03; N, 9.34.

2-Acetylamino-1-hydroxy-6,7-dihydro-5*H*-benzo[*i,j*]quinolizin-3-one (**8c**).

Method A).

This compound was obtained from 1-hydroxy-2-nitro-6,7-dihydro-5*H*-benzo[*i,j*]quinolizin-3-one (**1c**) [8c] (2.4 g, 10 mmoles) according to the method described for **8a**, yield 2.1 g (90%).

Method B).

This compound was obtained from 1-azido-6,7-dihydro-5*H*-benzo[*i,j*]quinolizin-3-one (**1c**) [19] (1.3 g, 5.7 mmoles) and acetic acid (10 g) in methanesulfonic acid (10 g, containing 10% phosphorus pentoxide) according to the method described for **8a**, yield 0.7 g (47%).

Method C).

This compound was obtained from oxazoloquinolizine **3c** according to the method described for **8a**, yield 2.3 g (89%), mp 214° (dimethyl formamide), lit mp 216° [11a,16b,21]; ir: identical with ref [16b]; ^1H nmr: δ 1.95, 2.05 (2 t, J = 7 Hz, CH_2), 2.25 (s, CH_3), 2.95 (t, J = 7 Hz, CH_2), 4.10 (t, J = 7 Hz, N-CH_2), 7.30-7.80 (m, H at C-1, C-2 and C-3), 9.75 (s, OH), 11.85 (s, N-H); ms: m/z (%) 258 (M^+, 60), 217 (100), 215 (M^+–$COCH_3$, 55).
Anal. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 65.16; H, 5.57; N, 10.60.

3-Acetylamino-4-hydroxy-2(1*H*)-quinolone (**8d**) [16].

This compound could not be obtained in a pure form by methods A-C and was reacted without purification to **3d**.

3-Amino-4-hydroxy-2(1*H*)-quinolone-Hydrochlorides **9a-d**.

According to ref [9c] sodium dithionite (10.0 g) was added to a solution of the corresponding 4-hydroxy-3-nitroquinolone **7a-d** [8c] (10 mmoles) in 1 *N* sodium hydroxide (100 ml) and the mixture was stirred for 5-10 minutes at room temperature. The reaction mixture was cooled down to 0° and brought to *p*H 1 with hydrochloric acid. The resulting precipitate was filtered by suction and dried at room temperature for 24 hours. Aminoquinolines **9** were used for further reactions without purification.

4-Chloro-2-methyloxazolo[4,5-*c*]quinoline (**10**).

A solution of 2-methyloxazolo[4,5-*c*]quinolin-4(5*H*)-one (**3d**) (2.0 g, 10 mmoles) in phosphoryl chloride (30 ml) was heated under reflux for 30 minutes. The excess phosphoryl chloride was removed *in vacuo* and the residue was poured into ice water. The solution was brought up to *p*H 6 with sodium hydroxide and filtered by suction, yield 1.96 g (90%), mp 161° (cyclohexane); ir: 1640 w, 1600 m cm^{-1}; ^1H nmr: δ 2.80 (s, CH_3), 7.75-7.90 (m, 2ArH), 8.15 (dd, J = 7 and 1.5 Hz, H at C-9), 8.25 (dd, J = 7 and 1.5 Hz, 1 ArH).

Anal. Calcd. for $C_{11}H_7ClN_2O$: C, 60.43; H, 3.23; N, 12.81. Found: C, 60.46; H, 3.39; N, 12.77.

REFERENCES AND NOTES

[1] Organic Azides in Heterocyclic Synthesis, Part **19**; Part **18**: W. Steinschifter, W. Stadlbauer, *J. Prakt. Chem.*, **336**, 311 (1994).

[2] J. M. Schaus and R. D. Titus, Eli Lilly & Co., U.S. Patent 4,659,832 (1987); *Chem. Abstr.*, **107**, 23329 (1987); B. W. Caprothe and J. C. Jaen, Warner Lambert Co., European Patent Appl. 260,642 (1988); *Chem. Abstr.*, **109**, 92992v (1988).

[3] D. L. Decktor, L. R. Fitzpatrick and H. F. Campbell, Rorer Pharmaceutical Corporation, U.S. Patent 4,831,040 (1989); *Chem. Abstr.*, **112**, 16278p (1990).

[4] Y. Inamoto, S. Kawai, K. Sanada and T. Endo, Fuji Chemical Industry Co. Ltd., Japan Kokai Tokkyo 03 109388 [91 109388](1991); *Chem. Abstr.*, **115**, 279995 (1991).

[5] J. H. Musser and R. E. Brown, USV Pharmaceutical Corporation, U.S. Patent 4,563,463 (1986); *Chem. Abstr.*, **106**, 50187u (1987).

[6] A. Renaud, A. R. Schoofs, J. M. Guiraudie and D. Brochet, Delalande SA, European Patent Appl. 322263 (1989); *Chem. Abstr.*, **112**, 216909g (1990).

[7] G. Brill, H. Hagen, K. O. Westphalen and B. Würzer, BASF AG, European Patent Appl. 401582 (1990); *Chem. Abstr.*, **114**, 122372r (1991); German Offen. 3,917,883 (1990); *Chem. Abstr.*, **114**, 185503e (1991).

[8] P. Roschger and W. Stadlbauer, *Liebigs Ann. Chem.*, 821 (1990); P. Roschger and W. Stadlbauer, *Liebigs Ann. Chem.*, 401 (1991); P. Roschger, W. Fiala. and W. Stadlbauer, *J. Heterocyclic Chem.*, **29**, 225 (1992); W. Fiala and W. Stadlbauer, *J. Prakt. Chem.*, **335**, 128 (1993).

[9] J. R. Merchant and S. S. Shirali, *Bull. Chem. Soc. Japan*, **50**, 3075 (1977); J. R. Merchant, M. S. Venkatesh and S. S. Shirali, *Curr. Sci.*, **49**, 20 (1980); *Chem. Abstr.*, **92**, 181095u (1986); O. A. Ponomarev, Yu. N. Brusilt'sev, V. Kh. Grif and V. G. Mitina, *Ukr. Khim. Zh.*, **56**, 272 (1990).

[10] M. Miyoshi, N. Yoneda, K. Matsumoto and M.Suzuki, Tanabe Seiyaku Co. Ltd., Japan Kokai 7746083, 7746085 (1977); *Chem. Abstr.*, **87**, 135109j, 135110c (1977); M. Suzuki, K. Matsumoto, M. Miyoshi, N. Yoneda and R. Ishida, *Chem. Pharm.Bull.*, **25**, 2602 (1977); P. Albaugh, Neurogen Corp., U.S. Patent 5,182,290 (1993); *Chem. Abstr.*, **119**, 49380p (1993).

[11] M. Jöbstl, Dissertation, University of Graz, Austria 1984; H. H. Zoorob and W. S. Hamama, *Egypt. J. Chem.*, **29**, 325 (1986); *Chem. Abstr.*, **111**, 7250a (1987); B. Schnell, Dissertation, University of Graz, Austria 1994; R. Aigner, Dissertation, University of Graz, Austria 1990.

[12] R. Garner, E. B. Mullock and H. Suschitzky, *J. Chem. Soc. (C)*, 1980 (1966); R. Garner and H. Suschitzky, *J. Chem. Soc. (C)*, 74 (1967), E. B. Mullock and H. Suschitzky, *J. Chem. Soc.*, 1937 (1968).

[13] R. K. Smalley and H. Suschitzky, *J. Chem. Soc.*, 5571 (1963); R. K. Smalley, W. A. Strachan and H. Suschitzky, *Tetrahedron Letters*, 825 (1974).

[14] H. Gershon, D. D. Clarke and M. Gershon, *Monatsh. Chem.*, **124**, 367 (1993).

[15] P. A. S. Smith, in Azides and Nitrenes, E. F. V. Scriven, ed, AcademicPress, New York, 1984; E. F. V. Scriven and K. Turnbull, *Chem. Rev.*, **88**, 297 (1988).

[16] S. Gabriel, *Ber.*, **51**, 1501 (1918); G. Lang, Dissertation, University of Graz, Austria 1972.

[17] K. Ito, Y. Higuchi, C. Tame and J. Hariya, *Heterocycles*, **35**, 937 (1993).

[18] W. Stadlbauer and Th. Kappe, Z. Naturforsch., **36B**, 739 (1981).

[19] W. Stadlbauer, *Monatsh. Chem.*, **117**, 1305 (1986).

[20] J. Klosa, *Arch. Pharm.*, **288**, 356 (1955); *ibid*, **289**, 104 (1956); E. Ziegler, G. Wildtgrube and H. Junek, *Monatsh. Chem.*, **87**, 439 (1956).

[21] H. Wittmann, W. Dreveny and E. Ziegler, *Monatsh. Chem.*, **99**, 1564 (1968).

[22] O. A. Ponomarev, Yu. N. Brusil'tsev and A. A. Sukhorukov, *Zhur. Fiz. Khim.*, 2723 (1990); *Chem. Abstr.*, **114**, 100938c (1991); A. A. Sukhorukov, O. A. Ponomarev, Yu. N. Brusil'tsev and V. G. Mitina, *Zhur. Fiz. Khim.*, 1838 (1991); *Chem. Abstr.*, **115**, 182274r (1992).