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Synthesis and Spectral Properties of Substituted 4-Chlorooxazoloquinolines[#]

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Summary. The treatment of a mixture of linearly and angularly annelated 2-substituted oxazolo[4,5-*f*]-quinolones (**5a–c**) and oxazolo[5,4-*g*]quinolones (**6a–c**) and similarly the treatment of 2-substituted oxazolo[5,4-*f*]quinolones (**7a–c**) and oxazolo[4,5-*g*]quinolones (**8b, c**) with $POCl_3$ afforded substituted 4-chlorooxazolo[4,5-*f*]quinolines (**9a–c**) and 2-substituted 4-chlorooxazolo[5,4-*f*]quinolines (**10b, c**), respectively. Spectral characteristics of the synthesized derivatives (^1H and ^{13}C NMR, IR, UV, and MS) are discussed.

Keywords. Oxazoloquinolones, chlorination of; 2-Substitued 4-chlorooxazolo[4,5-*f*]quinolines; 2-Substitued 4-chlorooxazolo[5,4-*f*]quinolines.

Synthese und spektroskopische Eigenschaften von substituierten 4-Chlor-oxazolochinolinen

Zusammenfassung. Durch Umsetzung einer Mischung von linear und angulär anellierten 2-substituierten Oxazolo[4,5-*f*]chinolonen (**5a–c**) und Oxazolo[5,4-*g*]chinolonen (**6a–c**) mit $POCl_3$ beziehungsweise durch analoges Behandeln von 2-substituierten Oxazolo[5,4-*f*]chinolonen (**7a–c**) und Oxazolo[4,5-*g*]chinolonen (**8b, c**) erhält man substituierte 4-Chlor-oxazolo[4,5-*f*]chinoline (**9a–c**) bzw. 4-Chlor-oxazolo[5,4-*f*]chinoline (**10b, c**). Die spektroskopischen Eigenschaften der Verbindungen werden diskutiert (^1H- und ^{13}C-NMR, IR, UV, MS).

Introduction

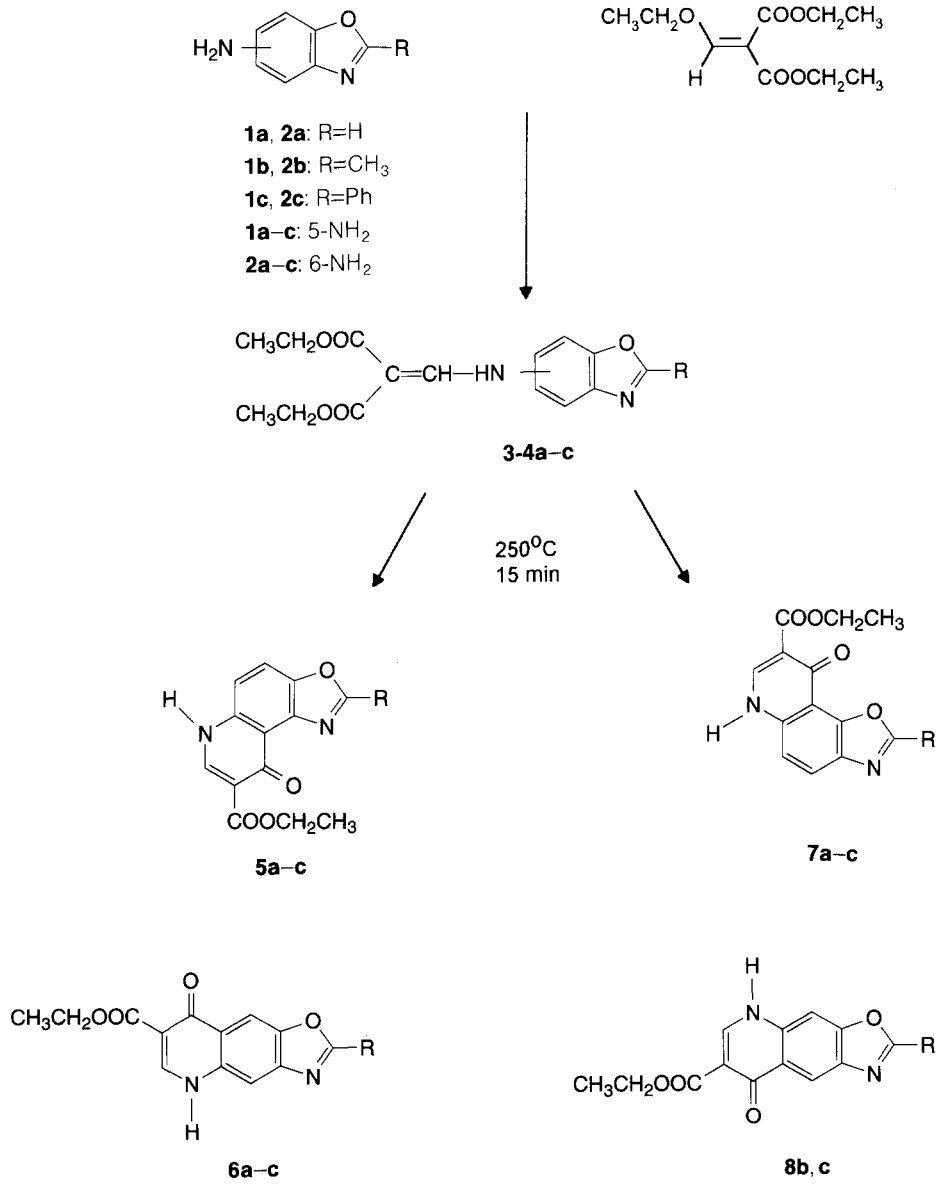
A substitution reaction at a pyridine ring carrying a halogen in position 2 or in position 4 usually affords several substitution products. This property of the pyridine ring remains unchanged even after a benzazole moiety has been fused with the pyridone skeleton.

If there is an ester or a nitrile group adjacent to the halogen, a pyrazolone ring can be easily created [1]. We now report the preparation of 4-chlorosubstituted oxazoloquinolines by the *Gould-Jacobs* procedure [2].

[#] Dedicated to Prof. *Fritz Sauter* on the occasion of his 65th birthday

Results and Discussion

The 2-substituted 5-nitro- and 6-nitrobenzoxazoles were converted to the corresponding 2-substituted 5-amino- and 6-aminobenzoxazoles (**1a–c**, **2a–c**) by a palladium-catalyzed reduction. Further reactions of these amines with the diethylester of ethoxymethylenemalonic acid (*EMME*) afforded substitution products (**3a–c**, **4a–c**). In an aprotic medium (a mixture of biphenyl and diphenyl ether) at 250 °C, the substitution products underwent a cyclization to oxazoloquinolones (**5a–c**, **6a–c**, **7a–c**, **8a–c**). However, in contrast to such known cyclizations in the benzothiazole, benzimidazole, and benzotriazole series giving exclusively angularly annelated ring systems [3, 4], our cyclizations gave rise to a mixture of linearly and angularly annelated oxazoloquinolones (**5a–c**, **6a–c**, **7a–c**, **8a–c**). Yields, physicochemical data, and spectral characteristics of these oxazoloquinolones are described in Ref. [5].



When such a mixture of linearly and angularly annelated oxazoloquinolones is treated with phosphoroxychloride, the reagent preferentially attacks the linearly annelated ring systems of [5,4-*g*] and [4,5-*g*]quinolones (derivatives **6a–c**, **8b, c**), leaving the angularly annelated derivatives (**9a–c**, **10b, c**) unchanged. However, in spite of short reaction times and low (ambient) temperature, the yields were low (Table 1). Extending the reaction time and elevating the temperature decreased the yields even more, probably due to the concomitant ring-opening of the oxazole. The inherently lower stability of linearly annelated systems has been demonstrated by the fact that linearly annelated 4-chloro derivatives could not be isolated in spite of very mild reaction conditions. The reaction also failed to produce any chlorosubstituted derivative of **7a**.

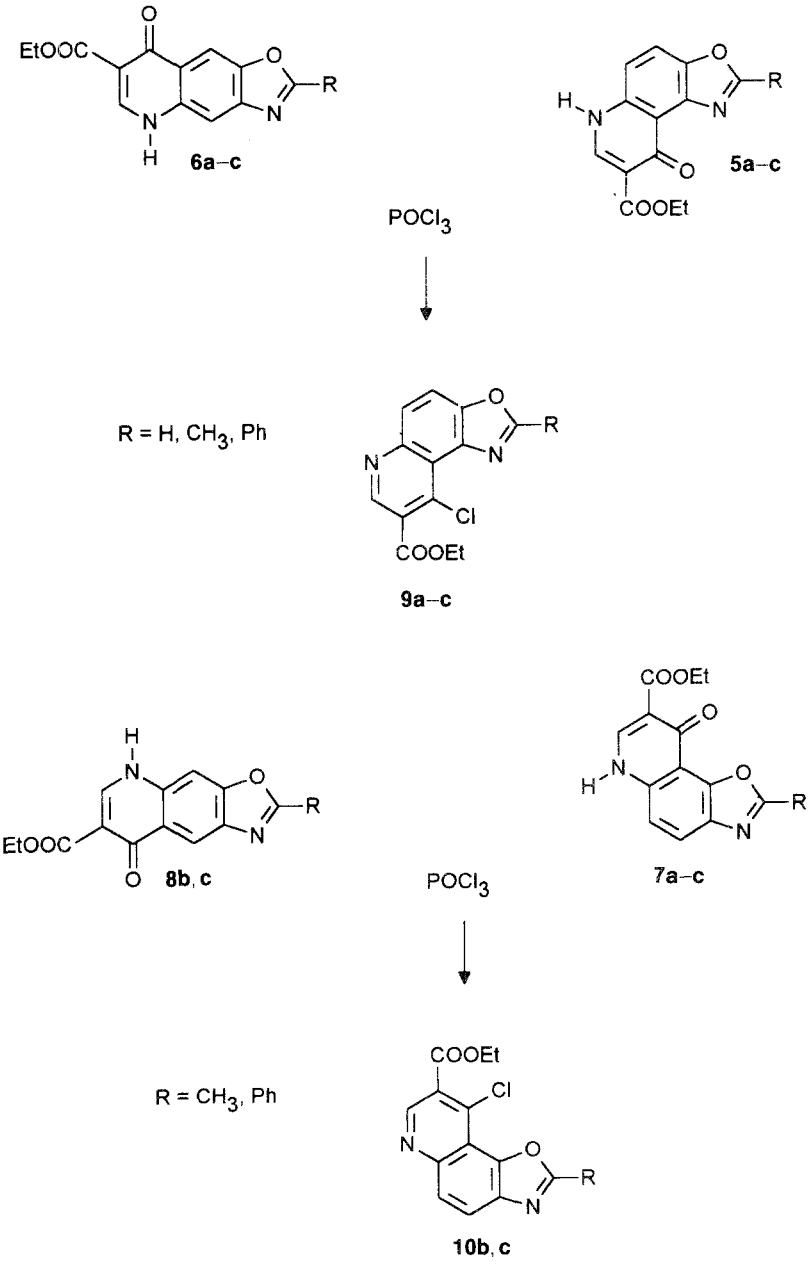
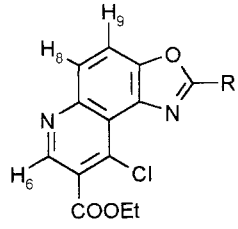


Table 1. Physical data of compounds **9a–c** and **10b, c**

	Formula[a] (M.W.)	M.p. (°C) reaction time	Yield (%) reaction temperature
9a	$C_{13}H_9N_2O_3Cl$ (276.67)	151 15 min	15 20 °C
9b	$C_{14}H_{11}N_2O_3Cl$ (290.70)	175 15 min	20 20 °C
9c	$C_{19}H_{13}N_2O_3Cl$ (352.77)	150–1 15 min	30 65 °C.
10b	$C_{14}H_{11}N_2O_3Cl$ (290.70)	147 45 min	20 20 °C
10c	$C_{19}H_{13}N_2O_3Cl$ (352.77)	160–3 60 min	25 20 °C

[a] All compounds gave satisfactory elemental analyses (C, H, N)

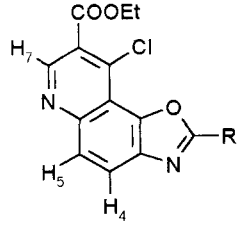
Table 2a. ^1H NMR spectra of compounds **9a–c** (δ, ppm)



	H_6	H_8[a]	H_9[a]	CH_2	CH_3	R
9a	8.49	7.30	7.63	4.25	1.30	8.92
9b	8.44	7.29	7.47	4.23	1.28	2.27
9c	8.52	7.34	8.13	4.28	1.33	8.28–8.24 7.65–7.62

[a] $J_{8,9} = 9$ Hz in all cases

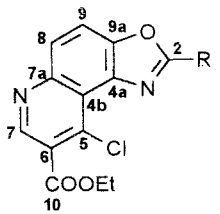
Table 2b. ^1H NMR spectra of compounds **10b, c** (δ, ppm)



	H_4[a]	H_5[a]	H_7	CH_2	CH_3	R
10b	8.22	8.07	9.11	4.46	1.40	2.77
10c	8.11	7.71	8.53	4.25	1.31	8.24–8.22 7.64–7.63

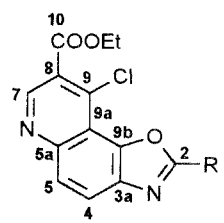
[a] $J_{4,5} = 9$ Hz in all cases

Table 3a. ^{13}C NMR spectra of compounds **9a–c** (δ, ppm)



	2	4a	4b	5	6	7	7a	8	9	9a	10	CH_2	CH_3	R
9a	164.52	116.36	127.90	177.61	109.92	142.90	146.18	116.32	120.50	137.80	171.13	59.14	14.04	
9b	164.05	116.75	125.50	177.31	109.70	142.71	144.74	116.39	125.72	133.72	171.18	59.61	14.14	23.74
9c	164.63	115.33	137.82	177.99	111.18	143.03	147.04	116.56	118.81	142.98	171.80	59.31	13.88	

Table 3b. ^{13}C NMR spectra of compounds **10b, c** (δ, ppm)



	2	3a	4	5	5a	7	8	9	9a	9b	10	CH_2	CH_3	R
10b	164.22	115.25	126.50	123.28	148.06	143.59	110.25	171.20	137.06	137.86	164.44	59.47	14.00	14.21
10c	162.71	114.72	123.83	116.07	147.26	143.71	111.01	171.27	137.71	138.35	164.48	59.56	14.17	

The ^{1}H NMR spectra (Table 2) display the characteristic doublets of H_8, H_9 and H_4, H_5 protons, respectively, the coupling constants being $J_{8,9} = 9$ Hz and $J_{4,5} = 9$ Hz. The signals of H_6 and H_9 can be found in the range of 8.44–9.11 ppm. The spectra of **9a–c** and **10b, c** show neither signals of linearly annelated products nor doubling of the signals of substituent groups (R, COOEt) – an effect typical for the starting mixture of linearly and angularly annelated oxazoloquinolones (**5a–c**, **6a–c**, **7a–c**, **8b, c**).

In the infrared spectra of derivatives **9a–c** and **10b, c**, respectively, there is only one ester carbonyl peak at 1701–1736 cm^{-1} (Table 4).

The ^{13}C NMR spectra are summarized in Tables 3a and 3b. The signal of the carbon atom carrying chlorine can be found beyond 170 ppm. There is also an anomalous shift value for C2 of the benzoxazole skeleton ($\delta > 162$ ppm). The signals of the bridgehead carbons have been assigned by the APT technique.

All the prepared chloro derivatives showed a molecular peak in their mass spectra (Table 5). Only signals with more than 10% relative intensity were taken into account.

Table 4. IR and UV spectra of compounds **9a–c** and **10b, c**

	ν(C=O) (cm^{-1})	λ_{max} (nm) $\log \varepsilon$ ($m^2 \cdot mol^{-1}$)		
9a	1713	203.6	249.0	358.2
		3.17	3.28	2.84
9b	1701		258.3	342.5
			3.48	2.92
9c	1736	205.9	249.0 282.8	346.3
		3.49	3.45 3.46	3.13
10b	1705		253.0	334.2
			3.66	2.69
10c	1730	212.9	277.2	
		3.35	3.52	

Table 5. Mass spectra of compounds **9a–c** and **10b, c**

9a	276 (M^+, 10%), 258 (43%), 213 (26%), 212 (100%), 186 (20%), 184 (29%), 57 (54%), 45 (60%), 38 (69%), 36 (98%), 31 (98%)
9b	290 (M^+, 21%), 266 (54%), 226 (35%), 221 (28%), 202 (56%), 194 (21%), 174 (22%), 83 (33%), 69 (21%), 64 (42%), 44 (98%), 43 (100%), 38 (90%), 36 (98%)
9c	352 (M^+, 100%), 324 (43%), 307 (52%), 280 (11%), 279 (11%), 244 (16%), 77 (13%), 44 (11%), 28 (32%)
10b	290 (M^+, 52%), 262 (20%), 247 (18%), 245 (48%), 218 (18%), 217 (18%), 38 (38%), 36 (100%), 28 (12%)
10c	352 (M^+, 100%), 324 (40%), 307 (38%), 280 (24%), 148 (14%), 77 (21%), 36 (31%), 28 (21%)

Experimental

Chlorination of oxazoloquinolones

A mixture of oxazoloquinolones (0.001 mol) was stirred with $POCl_3$ (reaction times given in Table 1). Then the unreacted $POCl_3$ was distilled off *in vacuo*, and the reaction mixture was neutralized by aqueous sodium acetate. The crude product was purified by column chromatography on silica gel with chloroform as eluant. The physico-chemical data of the prepared compounds are given in Table 1.

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