J. prakt. Chem. 339 (1997) 714–720

Journal für praktische Chemie
Chemiker-Zeitung

Quinoxalines. IX [1]

Reaction of 2-(Halogenomethyl)-quinoxalines and -quinoline with Hydroxybenzoic Acids and their Esters

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Received July 29th, 1997 respectively September 22nd, 1997

Abstract. In the presence of a base the title compounds react to products with ether structure (**4**, **6**), or with ester structure (**3**), or to structure **5** containing both functionalities in dependence on the mole ratio of the starting substances, on reaction conditions and on the substituent patterns in the hydroxybenzoic acid component.

Under the influence of alkali hydroxide the *m*- and *p*-substituted compounds (**6e–g**) are saponified to the alkali salts of the carboxylic acid (**4b, c**). The *o*-substituted compounds (**6a–d**), however, are cyclized to the benzo[*b*]furanylquinoxalines (**8**). **8a, d** are also obtained by thermal water elimination of the carboxylic acids **4a, d.** The red-coloured benzofuranols **8** react with acetic anhydride and benzoyl-chloride/pyridine, resp., to the weakly yellow esters **9**.

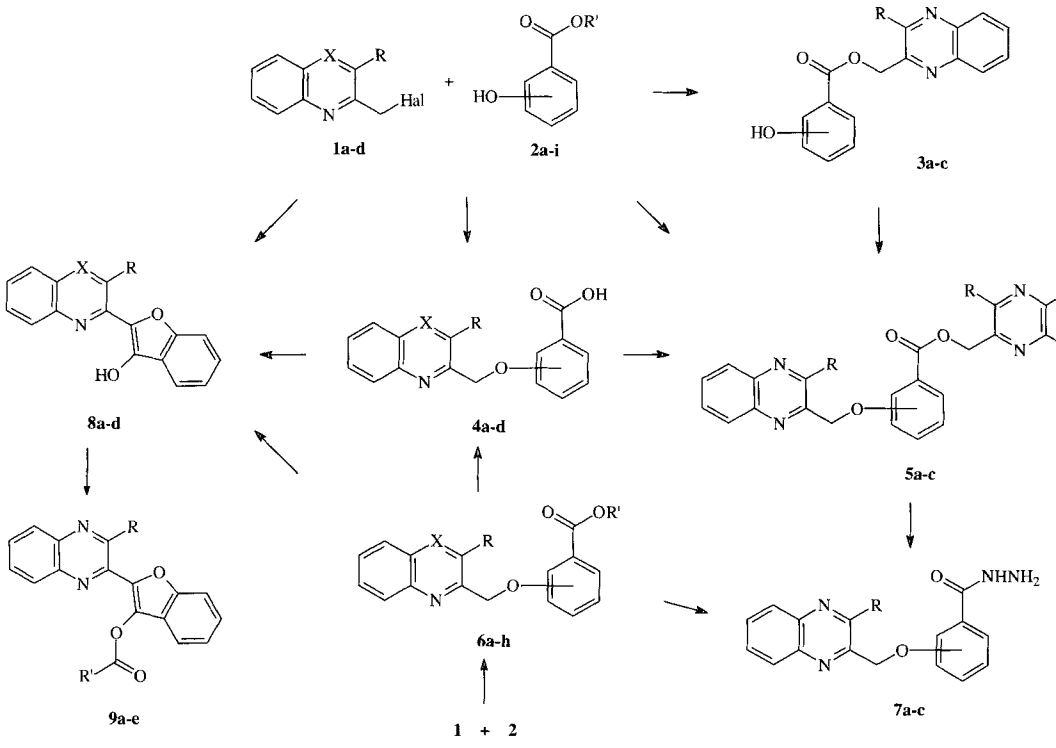
The structure of the products **8** and **9** is studied by UV-VIS derivative spectroscopy, by theoretical calculation of the dihedral angles and by ^{1}H and ^{13}C NMR spectroscopy. The ^{1}H and ^{13}C chemical shifts are completely assigned. The quinoxalines **8a–c** and the quinoline **8d** only exist in the hydroxy form.

Substituted aryloxymethylquinolines proved to be 5-lipoxygenase inhibitors and leukotrien receptor antagonists; they are in clinical testing [2–4]. The corresponding quinoxalines are mostly unknown, adequate biological activity is expected. Derivatives of quinoxalinylmethoxyphenylacetic acid were even patented as inhibitors of the arachidonic acid metabolism [5]. In this respect we studied the reaction of halogenomethylquinoxalines with the hydroxybenzoic acids and their esters, respectively. We obtained different products in dependence on mole ratio of the starting substances, on reaction conditions and on substituent patterns in the hydroxybenzoic acid component (Scheme 1).

The hydroxybenzoic acids **2a–c** react after addition of an equimolar quantity of alkali hydroxide with the bromomethylquinoxaline **1a** [6] in ethanolic solution to yield the corresponding esters **3a–c**. If the quantity of alkali hydroxide is doubled, also salicylic acid **2a** reacts to the ester **3a**, but the *m*- and *p*-substituted acids **2b,c** react to the ethers **4b,c**. When the reaction is carried out with two moles alkali hydroxide and two moles **1a** per one mole hydroxybenzoic acid then the compounds **5a–c** with ether and ester structures are obtained. The compound **5a** is obtained in small quantity beside much **3a**. The same compounds **5a–c** can be also obtained from the ethers **4a–c** by reacting with an equimolar quantity of alkali hydroxide and **1a**. But it is impossible to obtain the compounds **5** from the phenols **3** in the same way because the alkali hydroxide saponifies the esters. Sodium ethoxide as the base was used successfully to prepare **5b** from **3b**.

The hydroxybenzoic acid esters **2d–i** react with **1a**, **1b** [7] or **1d** [8] to the ethers **6a–h** when employing alkali alkoxide in alcoholic solution or potassium carbonate in acetonic or butanonic solution. Carboxylic acid hydrazides **7a–c** were synthesised through hydrazinolysis of the esters **5a–c** and **6a–c, e**. The compounds **5** reacted easier than **6** because they are activated by electron-withdrawing heteroaromatics (**7c** was obtained only from **5c**).

The *m*- and *p*-substituted compounds **6e–g** were saponified to the alkali salts of the carboxylic acids **4** under the influence of alkali hydroxide, the *o*-substituted compounds **6a–d,** however, were cyclized to the benzo[*b*]furanylquinoxalines **8a, b**. The *o*-substituted carboxylic acid **4a** was synthesised under the influence of potassium carbonate on **6a** followed by acidification with acetic acid. The colourless acid **4a** reacts at temperatures >200 °C under dehydration to the red benzofuran derivative **8a** which shows an identical IR spec-



1	X	R	Hal
a	N	CH_3	Br
b	N	C_6H_5	Br
c	N	H	Cl
d	CH	H	Cl

3, 5, 7	R	Pos.
a	CH_3	*o*
b	CH_3	*m*
c	CH_3	*p*

2	R'	Pos.
a	H	*o*
b	H	*m*
c	H	*p*
d	CH_3	*o*
e	C_2H_5	*o*
f	C_6H_5	*o*
g	C_2H_5	*m*
h	C_2H_5	*p*
i	n-C_3H_7	*p*

4	X	R	Pos.
a	N	CH_3	*o*
b	N	CH_3	*m*
c	N	CH_3	*p*
d	CH	H	*o*

6	X	R	R'	Pos.
a	N	CH_3	CH_3	*o*
b	N	CH_3	C_2H_5	*o*
c	N	CH_3	C_6H_5	*o*
d	N	C_6H_5	CH_3	*o*
e	N	CH_3	C_2H_5	*m*
f	N	CH_3	C_2H_5	*p*
g	N	CH_3	n-C_3H_7	*p*
h	CH	H	CH_3	*o*

8	X	R
a	N	CH_3
b	N	C_6H_5
c	N	H
d	CH	H

9	R	R'
a	H	CH_3
b	CH_3	CH_3
c	CH_3	C_6H_5
d	C_6H_5	CH_3
e	C_6H_5	C_6H_5

Scheme 1

Tab. 1 Physical and spectroscopic characterization of the synthesised substances **3–10**

No.	*m.p.* (°C) Solvent	Procedure [a]) Yield (%)	Mol. Formula Mol. Mass (g/mol)	IR (KBr) ν(C=O) (cm^{-1})	MS *m/z* (%)
3a	174–176.5 EtOH	58	$C_{17}H_{14}N_2O_3$ 294.31	1670	294 (16), 174 (55), 157 (100), 121 (67), 89 (90), 76 (75), 65 (94)
3b	192–195 EtOH	69	$C_{17}H_{14}N_2O_3$ 294.31	1720	295 (7,0), 294 (34), 173 (75), 143 (27), 121 (100), 93 (46), 65 (47)
3c	206–210 EtOH	76	$C_{17}H_{14}N_2O_3$ 294.31	1710	294 (6.4), 174 (43), 143 (15), 121 (100), 102 (14), 93 (20), 65 (27)
4a	198–200 EtOH	54	$C_{17}H_{14}N_2O_3$ 294.31	1710	294 (6.5), 235 (32), 157 (100), 89 (34)
4b	204–207 EtOH	a: 44 b: 92	$C_{17}H_{14}N_2O_3$ 294.31	1715	295 (6.8), 294 (31), 157 (100), 89 (18), 76 (10)
4c	206–209 EtOH	a: 68 b: 90	$C_{17}H_{14}N_2O_3$ 294.31	1690	295 (4.3), 294 (22), 158 (12), 157 (100), 156 (13), 89 (24), 76 (14)
4d	160–161 EtOH	42	$C_{17}H_{13}NO_3$ 279.30	1710	280 (7.7), 261 (13), 235 (54), 234 (37), 158 (25), 142 (100), 115 (53)
5a	174–176.5 DMF	a: 8 b: 76	$C_{27}H_{22}N_4O_3$ 450.50	1740	450 (9.2), 293 (21), 158 (57), 157 (100), 156 (34), 89 (24)
5b	144.5–146.5 DMF	a: 75 b: 73 d: 53	$C_{27}H_{22}N_4O_3$ 450.50	1705	451 (11), 450 (39), 293 (11), 158 (14), 157 (100), 156 (18), 89 (16)

5c	175.5–177 DMF	a: 65 c: 81	$C_{27}H_{22}N_4O_3$ 450.50	1710	451 (4.6), 450 (16), 277 (24), 158 (12), 157 (100), 156 (14), 89 (12)
6a	110–112 Hexane, MeOH	a: 50	$C_{18}H_{16}N_2O_3$ 308.34	1730	309 (5,4), 308 (27), 157 (100), 156 (19), 89 (32)
6b	101–104 Heptene, EtOH	a: 53	$C_{19}H_{18}N_2O_3$ 322.36	1720	323 (6.1), 322 (28), 277 (10), 173 (12), 158 (12), 157 (100), 156 (18), 89 (31)
6c	112–114 Heptane	b: 34	$C_{23}H_{18}N_2O_3$ 370.41	1740	278 (17), 277 (100), 157 (79), 89 (12), 65 (6.8)
6d	135–136 MeOH	a: 20	$C_{23}H_{18}N_2O_3$ 370.41	1722	371 (10), 370 (43), 220 (16), 219 (100), 218 (56), 91 (20)
6e	87.5–89.5 Hexane, EtOH	a: 84 b: 65	$C_{19}H_{18}N_2O_3$ 322.36	1710	323(4.9), 322 (23), 158 (11), 157 (100), 156 (12), 89 (20), 76 (12)
6f	123–124.5 Heptane, EtOH	a: 72 b: 71	$C_{19}H_{18}N_2O_3$ 322.36	1695	323 (7.0), 322 (33), 277 (5.5), 158 (15), 157 (100), 156 (16), 89 (26), 76 (14)
6g	88–89.5 PropOH	a: 53	$C_{20}H_{20}N_2O_3$ 336.39	1700	337 (4.3), 336 (21), 158 (11), 157 (100), 156 (10), 89 (15)
6h	84–85 MeOH	a: 30	$C_{18}H_{15}NO_3$ 293.32	1722	294 (50), 293 (100), 264 (23), 262 (32), 261 (37), 234 (45), 142 (57), 115 (19)
7a	226–227 Pyridine	a: 58 b: 64	$C_{17}H_{16}N_4O_2$ 308,34	1610	308 (18), 277 (41), 158 (42), 157 (100), 156 (18), 121 (16), 92 (14), 89 (25)
7b	177–178 Pyridine	a: 67 b: 68	$C_{17}H_{16}N_4O_2$ 308.34	1630	309 (24), 308 (84), 277 (67), 262 (24), 158 (36), 157 (100), 156 (24), 89 (37)
7c	192–194 Pyridine/EtOH	b: 42	$C_{17}H_{16}N_4O_2$ 308.34	1629	309 (38), 308 (69), 277 (100), 158 (64), 157 (22), 117 (37), 79 (53)
8a	226–227 Pyridine	a: 63 b: 15	$C_{17}H_{12}N_2O_2$ 276.29	–	277 (18), 276 (100), 259 (32), 247 (9.0), 219 (43), 77 (15), 76 (21)
8b	202–204 DMF	a: 55	$C_{22}H_{14}N_2O_2$ 338.37	–	340 (6.6), 339 (68), 338 (100), 309 (28), 281 (25), 218 (94), 205 (14), 121 (18)
8c	225–228 Toluene	c: 16	$C_{16}H_{10}N_2O_2$ 262.27	–	263 (22), 262 (94), 206 (25), 179 (21), 130 (32), 129 (33), 121 (100)
8d	149–152 EtOH	b: 12	$C_{17}H_{11}NO_2$ 261.28	–	263 (6.8), 262 (47), 261 (100), 232 (11), 205 (28), 204 (71), 129 (5.8), 128 (7.3)
9a	133.5–134.5 Heptane	70	$C_{18}H_{12}N_2O_3$ 304.30	1776	305 (83), 304 (70), 263 (70), 262 (100), 261 (56), 206 (59), 205 (30), 179 (46)
9b	129–130 Heptane	72	$C_{19}H_{14}N_2O_3$ 318.33	1764	318 (9.0), 277 (16), 276 (100), 259 (19), 219 (27), 76 (11)
9c	159–160 EtOH	83	$C_{24}H_{16}N_2O_3$ 380.40	1740	380 (2.1), 275 (2.5), 106 (7.9), 105 (100), 77 (26)
9d	164–165 *i*-PrOH	76	$C_{24}H_{16}N_2O_3$ 380.40	1776	381 (8.5), 380 (21), 339 (40), 338 (100), 309 (8.6), 281 (10), 218 (19)
9e	128–130 EtOH	85	$C_{29}H_{18}N_2O_3$ 442.47	1746	443 (17), 442 (61), 338 (29), 337 (13), 281 (11), 218 (15), 105 (100),77 (23)
10	174–175 *n*-BuOH	64	$C_{16}H_{10}N_2O$ 246.26	–	247 (58), 246 (100) , 219 (27), 190 (48), 143 (35), 115 (21), 76 (28)

[a] *cf.* Experimental

trum with the products from the reactions of the esters **6a–c** with KOH.

We synthesized the quinoxaline **8c** which is unsubstituted in 3-position from 2-(chloromethyl)-quinoxaline (**1c**) [8] and methyl salicylate (**2d**) without isolation of the intermediates. Both reactants were activated by adding potassium iodide and sodium methoxide, respectively. In contrast, the reaction with 2-(chloromethyl)-quinoline (**1d**) did not lead directly to the analogous benzofuranylquinoline **8d**. At first, the ester **6h** was obtained, which was saponified under the influence of alkali hydroxide, cyclization, however, did not happened. But the cyclization product **8d** could be obtained by thermal water elimination of the carboxylic acid **4d** (Tab. 1).

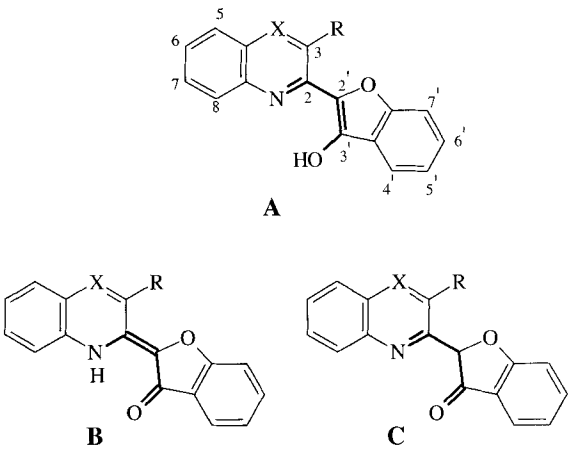
The structures of the compounds synthesized were established by CHN elemental analysis, IR, UV, NMR and mass spectroscopy.

The compounds **8** can theoretically exist in three tautomeric forms. The differences in structure are depicted in Scheme 2.

The marked structural moiety is part of both the quinoxaline and the benz[*b*]furan ring systems. In cases of this structural element being part of only the benzofuran or only the quinoxaline moiety, the tautomerism was investigated by ^{1}H NMR spectroscopy previously. It was found that the benzo[b]furan-3-ol is existing in the oxo form (analogously to **C**) but 2-acetyl-benzo[*b*]furan-3(2*H*)one in the enol form (analogously to **A**) [9, 10]. 3-Aroylmethyl-quinoxaline-2(1*H*)ones are occurring not in the ketimino form (analogously to **C**) but exclusively in the enamino form (analogously to **B**) [11]. For the hydrazone derivatives of the quinoxaline-2-(1*H*)on tautomeric equilibria between the heteroanalo-

gous forms **A** and **B** could be detected by means of ^{1}H NMR [12] and ^{13}C NMR spectroscopy [13]. The keto, enol and enamino structures of α-heterocyclic ketones (analogously to **C**, **A** and **B**, respectively) were distinguished by the differences in ^{13}C chemical shift between the carbonyl carbon atom of the ketone (193–202 ppm), of the enaminone (170–191 ppm) and enolic carbon atom of the enol (153–168 ppm) [14, 15].

It is a major objective of this paper to study the compounds **8a–d** and the corresponding esters **9a–e** particularly by ^{1}H and ^{13}C NMR spectroscopy in this respect. The results are based on the analysis of coupling patterns and on informations obtained from 2D NMR experiments (H,H-COSY, HMQC and HMBC) as described for 3'-NH_2- and other substituted 2-(benzo[*b*]furan-2-yl-quinoxalines [1]. The ^{1}H and ^{13}C NMR chemical shifts are given in Tab. 2.



Scheme 2

Tab. 2 ^{13}C (first line) and ^{1}H (second line) chemical shifts δ (ppm) of the compounds **8–9**

	8a	**8b**	**8c**	**8d**	**9a**	**9b**	**9c**	**9d**	**9e**
C-2	144.6	144.2	145.5	144.2	143.7	143.7	143.6	142.6	142.6
C-3	151.2	150.2	141.2	115.9	142.5	152.2	152.0	153.0	153.0
	–	–	9.26	7.67	9.45	–	–	–	–
C-4	–	–	–	137.5	–	–	–	–	–
	–	–	–	8.11	–	–	–	–	–
C-5	128.5	129.5	129.6	127.3	129.4	128.9	128.2	129.2	129.2
	7.93	8.05	8.06	7.71	8.07-8.13	7.99	7.98	8.15–8.19	7.98
C-6	128.3	128.8	128.6	124.9	130.1	129.4	129.2	130.2	130.1
	7.59	7.64	7.66	7.82	7.77	7.68	7.73	7.78	7.73
C-7	130.0	130.8	131.0	127.8	130.6	130.2	130.1	130.8	130.7
	7.68	7.72	7.72	7.39–7.46	7.79	7.73	7.76	7.80	7.76
C-8	125.4	126.0	126.9	130.8	129.4	128.4	128.8	129.2	129.2
	7.83	7.92	7.92	7.68	8.07–8.13	8.02	8.13	8.15–8.19	8.13
C-9	137.1	137.9	140.0	149.0	142.1	140.3	140.3	141.2	141.2
C-10	139.3	139.6	140.6	125.5	141.3	140.7	140.6	140.7	140.7
C-2'	132.2	131.6	131.8	132.5	140.7	141.7	141.7	141.3	141.5
C-3'	151.6	151.6	148.0	152.1	134.9	134.5	135.0	133.4	133.7
C-4'	120.3	119.9	120.0	120.4	119.5	119.1	119.5	119.6	119.8
	7.80	7.78	7.77	7.79	7.58	7.59	7.51	7.43	7.51
C-5'	122.9	122.7	123.0	122.5	123.8	123.6	123.7	123.4	123.4
	7.31	7.20	7.32	7.26	7.34	7.33	7.28	7.25	7.28
C-6'	128.0	127.7	127.8	125.3	127.1	126.5	126.5	126.2	126.2
	7.44	7.31	7.44	7.39–7.46	7.45	7.42	7.37	7.34	7.37
C-7'	112.1	112.0	112.1	112.0	112.5	112.1	112.2	112.2	112.3
	7.48	7.00	7.50	7.39–7.46	7.64	7.56	7.44	7.34	7.44
C-8'	154.1	153.4	154.0	154.8	153.3	152.6	152.8	153.0	153.1
C-9'	121.4	121.2	121.6	122.8	123.1	123.1	123.4	122.8	123.0
3-CH_3	24.8	–	–	–	–	24.4	24.5	–	–
	3.15	–	–	–	–	3.06	3.10	–	–
3'-CH_3	–	–	–	–	21.0	20.8	–	20.4	–
	–	–	–	–	2.59	2.47	–	2.18	–
C=O	–	–	–	–	168.0	168.0	164.1	167.1	163.0
Ph–C-1	–	138.7	–	–	–	–	129.1	138.6	a)
Ph–C-2	–	129.4	–	–	–	–	130.6	128.7	b)
	–	7.66–7.72	–	–	–	–	8.30	7.70	c)
Ph–C-3	–	127.7	–	–	–	–	128.7	128.4	d)
	–	7.47–7.55	–	–	–	–	7.54	7.40	e)
Ph–C-4	–	129.1	–	–	–	–	133.8	129.3	f)
		7.47–7.55	–	–	–	–	7.67	7.43	g)
	h)	i)							

a) R, R': 138.5, 128.5 b) 128.8, 130.5 c) 7.64, 8.03 d) 128.4, 128.4 e) 7.27, 7.50 f) 129.1, 133.8 g) 7.37, 7.64
h) H–O: 12.1 i) H–O: 11.9

The assignment of the present tautomeric structure of **8a–c** is based on the ^{13}C chemical shifts of the carbon atoms C-2' and C-3'. Characteristic for the tautomeric form **C**, the sp^3-hybridized carbon atom C-2' could not be found in the NMR spectrum; therefore **C** was excluded. Furthermore, the hydroxy form **A** was expected to be different from the keto tautomers **B** and **C** in the ^{13}C chemical shift of C-3'; a significant downfield shift was expected for **B** and **C** [14] but not observed. On this basis, it was concluded that the quinoxalines **8a–c** exist exclusively in the hydroxy form **A**. The hydroxy protons could be observed in the ^1H NMR spectra of **8a** and **8b;** they are in the range of protons intramolecularely hydrogen bonded.

The low basicity of the present quinoxaline derivatives and especially of N-1, obviously, seems to be very unfavourable for tautomer **B.** Because the basicity of pyrazine was found 10^5-fold lower than that of pyridine [16], *the quinoline* derivative **8d** was expected to exist in the keto form **B** or in an equilibrium of **A** and **B**. But the ^{13}C NMR spectrum did not show a downfield shift for C-3' (**B** and **C**) or the presence of an sp^3-hybridized carbon atom, characteristic for **C**; *i.e.* **8d** also exists exclusively in the hydroxy form **A**.

The compounds **1–7** are colourless but the compounds **8** are red-coloured. The UV-VIS-spectra of the compounds **8** measured in dioxane showed >250 nm two intensive ($\varepsilon > 15000$) absorption maxima. For the quinoxalines **8a–c** the ranges between the two maxima are structureless but in the quinoline derivative **8d** a fine structure in the form of three maxima did appear.

At the long-wave end of the spectra a weak absorption (**8a–c**: $\varepsilon < 1500$) was observed over a wide range (480–580 nm) without maxima and minima. If the absorbance curves $A = f(\lambda)$ were derivated then the functions $\frac{dA}{d\lambda} = f'(\lambda)$ display maxima and minima corresponding to points of inflection of the corresponding absorbance curves. These values determined by means of derivative spectroscopy are characteristic for the present substances and are structurally relevant.

The remarkable long-wave absorption of **8** is initiated by the hydroxy group. For comparison, 2-(benzo[*b*]furan-2-yl)-quinoxaline **10** [17, 18] was synthesised by means of a simplified procedure from 2-acetyl-benzo[*b*]furan without isolation of the intermediate benzo[*b*]fur-2-ylglyoxal. The 3'-unsubstituted 2-(benzo[*b*]furan-2-yl)-quinoxaline **10** (= **8** with X=N, R=H and H instead of OH) absorbs considerably at shorter wave length and is weakly yellow coloured. The hydroxy group in **8**, obviously forms a hydrogen bond between the nitrogen N-1 of the quinoxaline/quinoline moiety and the 3'-OH group of the benzo[*b*]furan fixing on this way the adjacent heterocyclic systems into a favourable planar position.

Also theoretical calculations on the semiempirical (PM3-method) level [19] were carried out for the compounds **8a–d** and **9a, b, d**. For **8a–d** a dihedral angle ϕ (C-3 - C-2 - C-2' - C-3') of 180° was found which confirms the results of the interpretation of the UV-VIS spectra.

The esters **9** obtained by acylation of **8** with acetic anhydride and benzoylchloride/pyridine, respectively, are unable to form the discussed hydrogen bond. Accordingly, they appear as colourless or weakly yellow substances. The UV spectra of **9** are similar to the parent compound **10** which has three maxima and the last absorption not longer than 430 nm. The planar conformation of the two heterocyclic moieties are disturbed by steric hindrance of the substituents in 3- and 3'-position. Consequently, dihedral angles ϕ for **9a:** ϕ = 180° (R=H!), **9b:** ϕ= 134.6° and for **9d** : ϕ= 136.1° were calculated.

The support of the BAYER AG and the Fonds der Chemischen Industrie is gratefully acknowledged.

Experimental

Melting points were determined on a Boëtius micro hotstage microscope (Fa. Analytik Dresden). The IR spectra were recorded on a Perkin Elmer FTIR 1600 spectrometer (KBr) and the UV spectra on a ATI Unicam UV3 (Dioxane); λ_{max} means a maximum of the absorbance curve $A = f(\lambda)$, λ'_{max} means a maximum of the first derivative $A' = f'(\lambda)$, λ_{end} means the end of the absorbance curve, *i.e.* $\varepsilon = 0$, all values of λ are given in nm; the molar decadic absorption coefficient $\varepsilon = A/c\ l$ is given in the unit 0,1 $m^2\ mol^{-1} = dm^3\ cm^{-1}\ mol^{-1}$. Mass spectra were obtained on a Finnigan-MAT SSQ 710 (70 eV). Elemental analyses were performed on the autanalyser CHNS-932 (Fa. Leco Instrumente GmbH). Satisfactory microanalyses were obtained for all new substances (C, H, N ± 0.5%).

The ^1H and ^{13}C NMR spectra were recorded on a Bruker ARX 300 NMR spectrometer at 300.13 MHz and 75.47 MHz, respectively. Samples were measured in $CDCl_3$ (5 mm probe tubes, ambient temperature, deuterated solvents as internal lock). ^1H and ^{13}C NMR chemical shifts are reported: δ (ppm) downfield from TMS (internal).

COSY 45: sweep width in both dimensions 3.5 kHz, 1 K data points in F2, 512 experiments in F1, relaxation delay 1 s, pulse width (^1H, 90°) 10.2 µs.

HMBC: sweep width in F1 10 kHz and in F2 3.5 kHz, 1 K data points in F2, 512 experiments in F1 (96 scans), relaxation delay 1 s, pulse width (^1H, 90°) 10.2 µs, (^{13}C, 90°) 10.4 µs, delay for evolution of long-range couplings: 55 ms, zero filling, filter function squared 2/3 π shifted sine bell in both dimensions.

HMQC: sweep width in F1 10 kHz and in F2 3.5 kHz, 1 K data points in F2, 512 experiments in F1 (96 scans), relaxation delay 1 s, pulse width (^1H, 90°) 10.2 µs, (^{13}C, 90°) 10.4 µs, zero filling, filter function squared 2/3 π shifted sine bell in both dimensions. The HMQC spectra were recorded in the phase-sensitive mode.

2/3/4-Hydroxy-benzoic acid 3-methyl-quinoxaline-2-ylmethyl esters (**3a–c**)

To a stirred solution of **1a** (23.7 g, 100 mmol) in EtOH (300 ml) a solution of KOH (5.6 g, 100 mmol) and **2a–c** (13.8 g, 100 mmol) in EtOH (250–400 ml) was added. The mixture was heated under reflux for 2 hours. The hot solution was filtered and concentrated *in vacuo*. The solid product was collected, washed with water and recrystallised (solvent and data *cf.* Table 1).

2-(3-Methyl-quinoxaline-2-ylmethoxy)-benzoic acid (**4a**)

Solutions of **6a** (30.8 g,100 mmol) in EtOH (750 ml) and of soda (35 g, 122 mmol) in 1.5 l water were combined, gradually boiled and refluxed for 15 minutes. The EtOH was removed in vacuo. The red by-product was filtered off by suction and washed with soda solution. The combined filtrates were slowly acidified with AcOH. The precipitate was filtered under suction and recrystallized.

3-(3-Methyl-quinoxaline-2-ylmethoxy)-benzoic acid (**4b**)

a) To a stirred solution of **2b** (13.8 g, 100 mmol) and KOH (11.2 g, 200 mmol) in EtOH (125 ml) was gradually added a warm solution of **1a** (23.7 g, 100 mmol) in EtOH (500 ml). The mixture was stirred at 50 °C for 30 minutes and then refluxed for 30 minutes. The solids were removed by filtration of the hot mixture and the filtrate was acidified with diluted AcOH. The precipitate was filtered under suction and dissolved in a boiling excessive soda solution. After separation of insoluble components, the solution was acidified with AcOH. The solid product was collected and recrystallized.
b) A solution of KOH (8 g, 143 mmol) in EtOH (250 ml) was added to a solution of **6e** (32.2 g, 100 mmol) in warm EtOH (500 ml). The mixture was heated under reflux for 1 hour and than acidified with 5% aqueous solution of AcOH. Upon cooling the separated product was filtered off by suction and crystallized.

4-(3-Methyl-quinoxaline-2-ylmethoxy)-benzoic acid (**4c**)

a) A solution of **1a** (23.7 g,100 mmol) in warm EtOH (500 ml) was slowly added to a stirred solution of **2c** (13.8 g, 100 mmol) and KOH (11.2 g, 200 mmol) in EtOH (500 ml). The mixture was heated under reflux for 15 minutes. After cooling the separated solids were filtered off by suction and dissolved in boiling 5% solution of aqueous $NaHCO_3$ (850 ml). The insoluble by-product (**5c**) was removed by filtration. The filtrate was acidified with AcOH and the product **4c** precipitated. It was filtered by suction and recrystallized.
b) A boiling solution of **6f** (32.2 g, 100 mmol) in EtOH (500 ml) was mixed with a solution of KOH (8 g, 143 mmol) in EtOH (500 ml) and refluxed on a steam bath for 15 minutes. After cooling the solids were collected and washed twice with EtOH to give the potassium salt of **4c** (27.9 g, 84% yield). This salt melted under decomposition over 325 °C.

The potassium salt was dissolved in heated 5% aqueous solution of $NaHCO_3$ (300 ml) and after acidification with dilute AcOH the acid **4c** was obtained. The product was collected, washed with water and recrystallized from EtOH.

2-(Quinoline-2-ylmethoxy)-benzoic acid (**4d**)

A solution of KOH (2.8 g, 50 mmol) in MeOH (50 ml) was added to a solution of **6h** (2.93 g, 50 mmol) in MeOH (50 ml) and the resulting mixture was refluxed for 15 minutes. After cooling the stirred solution of the potassium salt of **4d** was acidified with 2N HCl (30 ml) and the resulting mixture was allowed to stand over night in the refrigerator. The separated product (**4d**) was filtered under suction and recrystallized.

2/3/4-(3-Methyl-quinoxaline-2-ylmethoxy)-benzoic acid 3-methyl-quinoxaline-2-ylmethyl esters (**5a–c**)

a) A solution of **1a** (47.4 g, 200 mmol) in EtOH (1 l) was added to a solution of **2a–c** (13.8 g, 100 mmol) and KOH (11.2 g, 200 mmol) in EtOH (500 ml) and the resulting mixture was refluxed for 3 hours. After cooling the solids were filtered under suction, washed with water and recrystallized (**5a** was obtained, after separation of **3a** and concentration of the mother liquid. The product was collected and recrystallized from toluene and DMF).
b) A solution of **1a** (23.7 g, 100 mmol) in EtOH (500 ml) was added to a heated solution of **4a, b** (29.4 g, 100 mmol) and KOH (5.6 g,100 mmol) in EtOH (2 l). The resulting mixture was refluxed for 2 hours and concentrated *in vacuo*. The product was filtered under suction when cold, washed with water and recrystallized.
c) The potassium salt of **4c** (33.2 g,100 mmol) was dissolved in $EtOH/H_2O$ (165 ml/165 ml) under heating. The solution of **1a** (23.7 g, 100 mmol) in EtOH (500 ml) was added and the mixture was refluxed with stirring for 2 hours. After cooling, the product was filtered under suction, washed with water and recrystallized.
d) An ethanolic ethoxide solution [prepared from Na (2.3 g, 100 mmol) and absol. EtOH (125 ml)] was added to a solution of **3b** (29.4 g, 100 mmol) in absol. EtOH (875 ml). With stirring a solution of **1a** (23.7 g, 100 mmol) was added. The mixture was refluxed for 2 hours and concentrated *in vacuo*. After cooling, the product was filtered under suction, washed with water and recrystallized.

2/3/4-(3-subst.-Quinoxaline-2-ylmethoxy)-benzoic acid alkyl/aryl esters (**6a–h**)

a) The methyl/ethyl/propyl ester **2d,e,g,h,i** (105 mmol) was dissolved in alcoholic sodium alkoxide, prepared from sodium (2.3 g,100 mmol) and absol. MeOH/EtOH/PrOH (250 ml). The solution of **1a,b,d** (100 mmol) in absol. MeOH/EtOH/PrOH (600 ml) was added. The mixture was refluxed for 2 hours. The hot filtered solution was concentrated *in vacuo*. The product which crystallized after cooling was collected and recrystallized from a polar and/or unpolar solvent.
b) **1a** (23.7 g, 100 mmol) and **2f,g,h** (105 mmol) were dissolved in acetone or butanone (400 ml) and K_2CO_3 (20 g, 145 mmol) added to the solution. The mixture was stirred and heated under reflux for 4 hours. After hot filtration the solvent was evaporated and the residue was recrystallized.

2/3/4-(3-Methyl-quinoxaline-2-ylmethoxy)-benzoic acid hydrazides (**7a–c**)

a) Hydrazine hydrate (72% aqueous solution) in excess was added to the ethanolic solution of **6a–c,e** and the mixture was refluxed for 4 hours. After cooling, the solids were filtered

under suction and recrystallized.
b) Hydrazine hydrate (72% aqueous solution) in excess was added to the solution of **5a–c** in warm pyridine and the mixture was refluxed for 4 hours. After cooling, the solids were filtered under suction and recrystallized.

2-(3-subst.-Quinoxaline-2-yl)-benzo[b]furan-3-ol and 2-(Quinoline-2-yl)-benzo[b]furan-3-ol (**8a–d**)

a) A solution of KOH (2.8 g, 50 mmol) in MeOH (75 ml) was added to the solution of **6a–c, d** in warm MeOH (300 ml). The mixture was refluxed for 15 minutes and diluted AcOH (20 ml of 20% aqueous solution) was added under stirring. After cooling, the solids were filtered under suction, washed with water and MeOH and recrystallized giving the products **8a/8b. 8a** UV: λ_{max} (ε) 301 (17220), 407 (18310) λ'_{max} (ε) 497 (1380), 518 (1150), 534 (800), 551 (460) λ_{end} 580. **8b** UV: λ_{max} (ε) 310 (18830), 417 (15050) λ'_{max} (ε) 518 (580), 560 (310), 572 (230) λ_{end} 600.
b) The substances **4a/4d** were heated for 10 minutes to a temperature of 20 °C over the melting point by means of a heating bath and the obtained crude product was recrystallized giving **8a/8d. 8d** UV: λ_{max} (ε) 294 (15520), 308 (11010), 320 (12090), 333 (11810), 378 (15790) λ'_{max} (ε) 459 (2070), 485 (2350), 530 (1820) λ_{end} 560.
c) Compound **2d** (12.16 g, 80 mmol) dissolved in methanolic methoxide [prepared from Na (1.73 g, 75 mmol) and absol. MeOH (100 ml)] was treated with the solution of **1c** (12.5 g,70 mmol) in absol. MeOH (100 ml). After adding potassium iodide (0.5 g, 3 mmol) the mixture was refluxed for 2 hours, mixed with of 5N KOH (20 ml) and refluxed for further 2 hours. AcOH (12 g, 200 mmol) was poured into the hot solution. The product was precipitated by gradually dilution with water (200 ml), filtered under suction when cold, washed with MeOH and water and recrystallized to give **8c**. UV: λ_{max} (ε) 300 (22380), 404 (18440) λ'_{max} (ε) 486 (735), 514 (570), 554 (200), 572 (100) λ_{end} 600.

Acetic acid 2-(3-subst.-quinoxaline-2-yl)-benzofuran-3-yl esters (**9a,b,d**)

A mixture of **8a/8b/8c** (5 mmol), acetic anhydride (10.2 g, 100 mmol) and powdered anhydrous sodium acetate (0.82 g, 10 mmol) was stirred and heated to reflux for 10 minutes. The mixture was allowed to stand over night at 0 °C, filtered under suction, washed with water and recrystallized. **9a** UV: λ_{max} (ε) 280 (17960), 293 (20190), 368 (22770) λ_{end} 415. **9b** UV: λ_{max} (ε) 278 (15900), 290 (15030), 366 (17970) λ_{end} 430. **9d** UV: λ_{max} (ε) 280 (16300), 294 (15390), 372 (11910) λ_{end} 437.

Benzoic acid 2-(3-subst.-quinoxaline-2-yl)-benzofuran-3-yl esters (**9c, 9e**)

Benzoylchloride (2.5 g,18 mmol) was added dropwise to a stirred solution of **8a/8b** (5 mmol) in pyridine (30 ml) at 0 °C. The mixture was gradually warmed and heated to reflux for 5 minutes. After cooling the solution was poured onto crashed ice (50 g). The product crystallized after several hours was collected, washed with water and recrystallized. **9c** UV: λ_{max} (ε) 278 (17770), 287 (16650), 366 (18360) λ_{end} 435. **9e** UV: λ_{max} (ε) 280 (21180), 284 (19210), 373 (14020) λ_{end} 435.

2-(Benzo[b]furan-2-yl)-quinoxaline (**10**)

A solution of 2-acetyl-benzo[*b*]furan (16.0 g, 100 mmol) in dioxane (25 ml) was added to a heated solution of SeO_2 (11,1 g, 100 mmol) in dioxane/water (72ml/3ml). The mixture was refluxed for 3 hours. The resulting solid (Se) was separated by filtration. The filtrate was mixed with a solution of *o*-phenylendiamine (10,8 g, 100 mmol) in dioxane (30 ml). The mixture was refluxed for one hour and concentrated *in vacuo*. After cooling, the product was filtered under suction and recrystallised from butanol or DMF. **10:** UV: λ_{max} (ε) 278 (15700), 293 (16320), 366–376 (20150), λ_{end} 430.

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