Ring Opening of 2-(Benzylamino)-2*H*-1,4-benzoxazin-3(4*H*)-ones and 2-Bromo-2*H*-1,4-benzoxazin-3(4*H*)-ones

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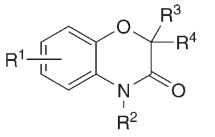
Substituted 2-(benzylamino)-2*H*-1,4-benzoxazin-3(4*H*)-ones are unstable under alkaline and acidic conditions, undergoing opening of the benzoxazinone ring. 2-Bromo-2*H*-1,4-benzoxazin-3(4*H*)-ones show similar degradation under alkaline conditions, while replacement of Br at C(2) to give 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones was observed only under mild alkaline conditions. Mechanisms of ring opening and degradation to 2-aminophenol derivatives are proposed.

Introduction. – 2*H*-1,4-Benzoxazin-3(4*H*)-ones have been studied extensively as important heterocyclic systems for building natural [1] and designed synthetic compounds [2]. They have frequently been utilized as suitable precursors for the design of biologically active compounds, ranging from herbicides and fungicides to therapeutically usable drugs, due to their rather simple preparation and various options for further functionalization [3]. Although the chemical behavior of 2*H*-1,4-benzoxazin-3(4*H*)-ones has been well explored, unexpected reaction products are obtained under certain specific conditions [4]. Whereas 2,2-disubstituted 2*H*-1,4-benzoxazin-3(4*H*)-ones **1** are relatively stable, the corresponding 2-monosubstituted 2*H*-1,4-benzoxazin-3(4*H*)-ones **2**, which possess an acidic H-atom at C(2), are more prone to various transformations [5][6].

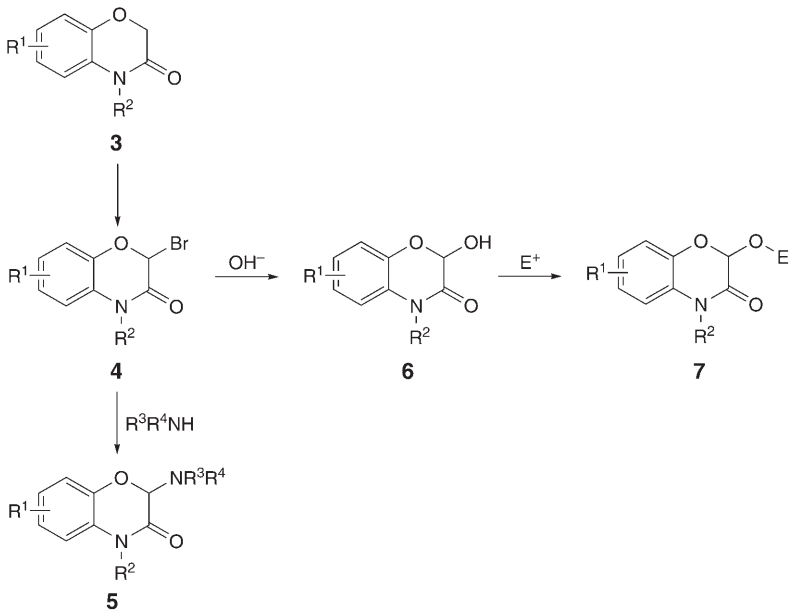


1 R^3, $R^4 \neq H$
2 $R^3 \neq H$, $R^4 = H$
3 R^3, $R^4 = H$

2-Unsubstituted 2*H*-1,4-benzoxazin-3(4*H*)-ones **3** are easily prepared and are suitable for further functionalization at C(2) among which bromination is a simple and efficient way to transform the C(2)-atom to an electrophilic center bearing a good leaving group, thus making **4** a good substrate for nucleophilic substitution with amines, allowing easy access to derivatives **5** [7]. Transformation of the Br derivative **4** to 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one **6** affords the *O*-nucleophilic compound which is further used for nucleophilic substitution on various electrophilic substrates, *e.g.*, alkyl halides to give cyclic acetals **7** (*Scheme 1*).

Results and Discussion. – During our investigations in the field of 2*H*-1,4-benzoxazin-3(4*H*)-one chemistry, we observed that opening of the 1,4-oxazin-3-one

Scheme 1

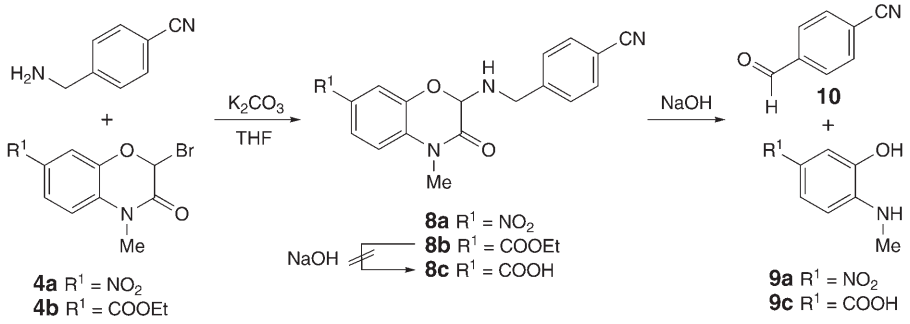


ring sometimes compromised the outcome of the synthesis. Here, we report the results of our studies on the ring opening of 2-bromo-2*H*-1,4-benzoxazin-3(4*H*)-ones **4** and 2-(benzylamino)-2*H*-1,4-benzoxazin-3(4*H*)-ones **8** which proceed differently from the ring opening of naturally occurring 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones and 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones, the only studied ring opening reactions of 2-substituted 2*H*-1,4-benzoxazin-3(4*H*)-ones. Whereas *a*) in the transformation of 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones to benzoxazolinones the ring opening step involves participation of the hydroxamic acid OH group [8][9], and *b*) ring-opening of 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones has been observed only under reductive conditions [9][10], we demonstrate in this work that substituted 2-(benzylamino)- and 2-bromo-2*H*-1,4-benzoxazin-3(4*H*)-ones undergo ring opening and degradation to 2-aminophenol derivatives under alkaline and acidic conditions following a different mechanism.

The Br-atom of 2-bromo-2*H*-1,4-benzoxazin-3(4*H*)-ones **4a** and **4b** was smoothly replaced by (4-cyanobenzyl)amino group in the presence of K_2CO_3 to give 4-{[(3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazin-2-yl)amino]methyl}benzonitrile derivatives **8a** and **8b** as solid, stable compounds (*Scheme 2*). In an attempt to hydrolyze ethyl ester **8b** to the corresponding acid **8c** by using 2 equiv. of NaOH in a H_2O/dioxane 1:1, the benzoic acid derivative **9c** and 4-formylbenzonitrile (**10**) were obtained instead of the desired carboxylic acid **8c**. Similarly, under alkaline conditions, the nitro derivative **8a** afforded degradation products **9a** and **10** (*Scheme 2*).

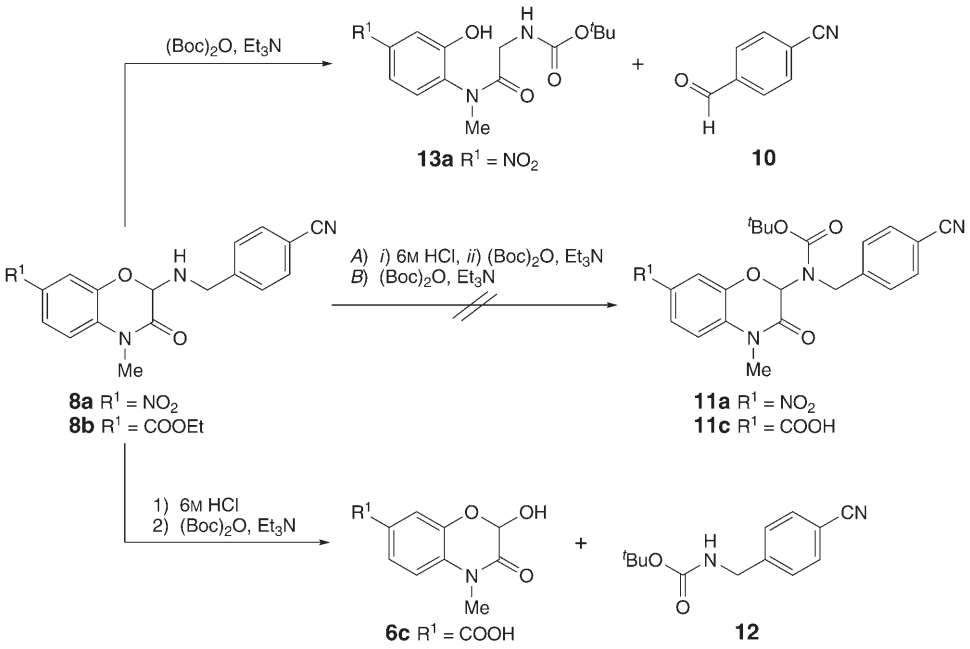
In an attempt to transform **8a** to the *N*-Boc-protected derivative **11a**, required as a key intermediate for our synthesis of potential antithrombotic compounds [11], $(Boc)_2O$ in the presence of Et_3N was employed. Although reaction conditions were

Scheme 2



mild, the expected carbamate **11a** was not obtained and, once more, 4-formylbenzonitrile (**10**) was isolated, as well as the ring-opened compound **13a** (*Scheme 3*). This reaction demonstrated that ring opening of **8a** occurred even under mild alkaline conditions. However, the benzoxazine ring was not completely decomposed, probably due to the less vigorous conditions and stabilization through carbamate formation. Ring cleavage of **8a** and **8b** observed in alkaline medium prompted us to apply acidic conditions for the hydrolysis of **8b** in order to preserve the heterocyclic ring. Thus, for the synthesis of *N*-Boc-protected carboxylic acid **11c**, a two-step procedure was envisaged. In the first step, acid hydrolysis of **8b** (6M HCl, reflux, overnight) was

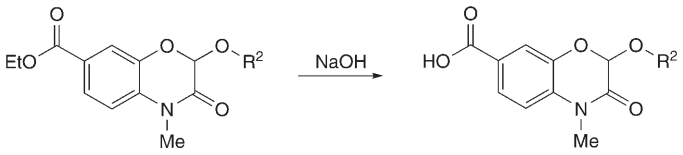
Scheme 3



performed, followed by neutralization and treatment with $(Boc)_2O$. Again, the desired product **11c** was not obtained, and the isolated products were identified as 3,4-dihydro-2-hydroxy-4-methyl-3-oxo-2*H*-1,4-benzoxazine-7-carboxylic acid (**6c**) and *tert*-butyl *N*-(4-cyanobenzyl)carbamate (**12**; *Scheme 3*).

Formation of 4-formylbenzonitrile (**10**) and carbamate **13a** (*Scheme 3*), as well as 2-aminophenol derivatives **9a** and **9c** (*Scheme 2*) provided an insight into the mechanism of ring-opening degradation of hemiaminals **8**. The amino group clearly plays the key role in the instability of 2-aminobenzoxazinones **8a** and **8b** since the benzoxazinone ring of the analogous 2-hydroxy and 2-alkoxy compounds, **6b** and **7b**, respectively, was stable under alkaline conditions. Thus, quantitative yields of carboxylic acids **6c** and **7c** was obtained on alkaline hydrolysis of ethyl esters **6b** and **7b**, respectively (*Scheme 4*).

Scheme 4



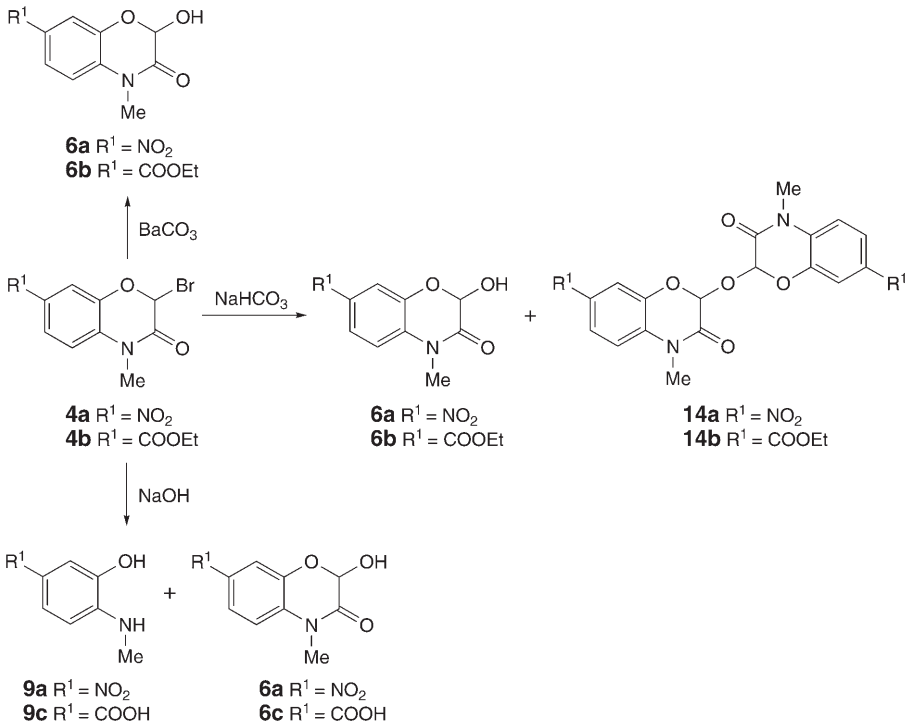
6b R^2 = H
7b R^2 = 4-(CN)–C_6H_4–CH_2

6c R^2 = H
7c R^2 = 4-(CN)–C_6H_4–CH_2

Interestingly, the 2-aminophenol derivatives **9a** and **9c** were also obtained as the main products (besides **6a** and **6c**) of the attempted replacement of the Br-atom in **4a** and **4b** by a OH group under alkaline conditions (NaOH in H_2O/dioxane 1:1; *Scheme 5*). However, since the hemiacetals **6** are stable under alkaline conditions, ring degradation of **4a** and **4b** must have taken place before substitution of the Br-atom. The 2-OH derivatives **6a** and **6b** could be obtained from **4a** and **4b**, respectively, as the main products under mild alkaline conditions (2 equiv. aq. $NaHCO_3$), whereas, in more concentrated solution, the dimeric compounds **14a** and **14b** were obtained as side products. The conversion of bromo compounds **4a** and **4b** to alcohols **6a** and **6b**, respectively, without formation of dimers **14a** and **14b**, was achieved by using $BaCO_3$ [12] instead of $NaHCO_3$ (*Scheme 5*).

Reaction mechanisms which could explain the formation of 4-formylbenzonitrile (**10**) and 4-(aminomethyl)benzonitrile (**21**) from **8a** and **8b**, respectively, under alkaline and acidic conditions are proposed in *Schemes 6* and *7*, respectively. Under alkaline conditions, after abstraction of an acidic H-atom in **8** and following delocalization of the negative charge to give **15** as an intermediate, ring opening takes place, and the resulting imine **16** undergoes tautomerization to **17**. Under mild alkaline conditions, **17** is hydrolyzed to give 4-formylbenzonitrile (**10**) and the *N*-(2-hydroxyphenyl)glycine derivative **18** which was trapped as the *N*-Boc derivative **13a** (see *Scheme 3*). Under stronger alkaline conditions, **17** is fragmented, probably by participation of the phenolate anion, to give isolated 2-(methylamino)phenol derivative **9** and 4-formylbenzonitrile (**10**). In contrast to *O*,*N*-acetals **8**, cyclic hemiacetals **6a**–**6c** were found to be stable under alkaline conditions. Although no ring-opened aldehyde forms of **6a**–**6c**

Scheme 5

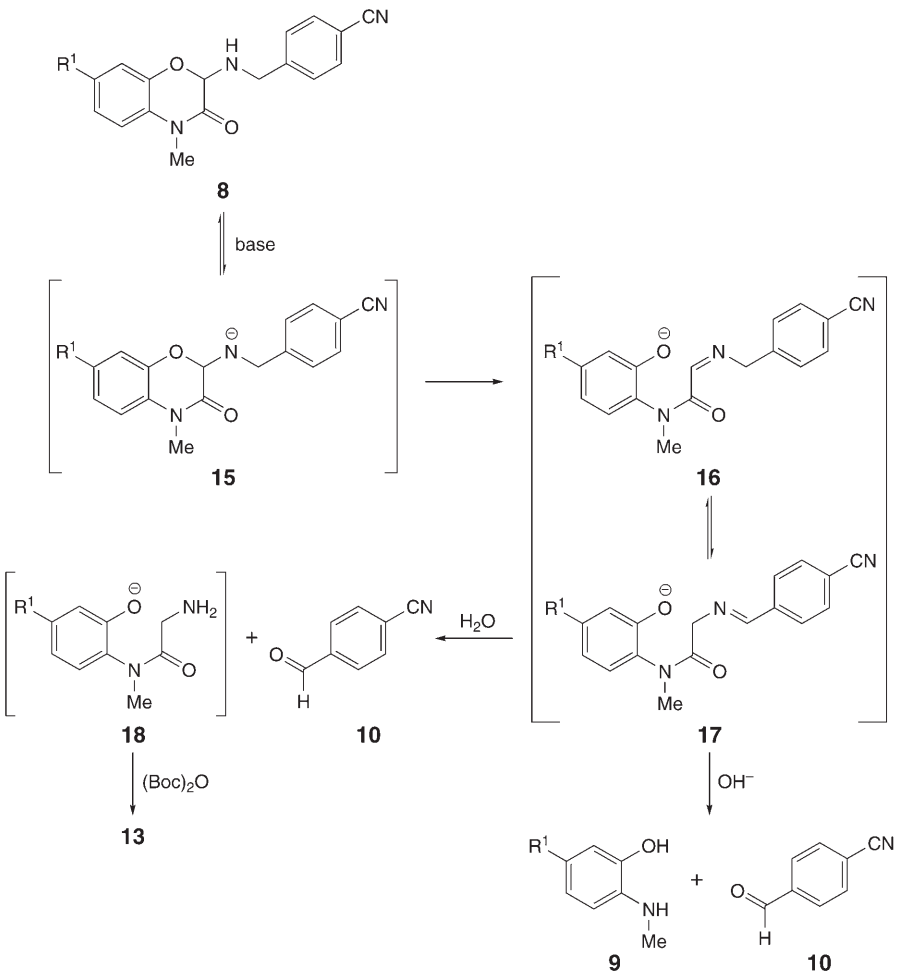


could be detected, a minor cleavage of hemiacetals **6a**–**6c** to the corresponding aldehydes cannot be excluded.

Under acidic conditions, the basis of heterocyclic ring instability is the aminal group. To account for the mechanism of the ring-cleavage step, we propose protonation of the aminal at the O-atom [13] to give *O*-protonated *O*,*N*-acetal **19**, which undergoes ring-opening. The resulting iminium ion **20** is hydrolyzed to give 4-(aminomethyl)-benzonitrile (**21**) and aldehyde **22**, which undergoes then cyclization [8][9] to yield a 3,4-dihydro-2-hydroxy-4-methyl-3-oxo-2*H*-1,4-benzoxazin-7-carboxylic acid (**6c**).

Conclusions. – In contrast to 2-hydroxy- and 2-alkoxy-2*H*-1,4-benzoxazin-3(4*H*)-ones, the synthetically available 4-{[(3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazin-2-yl)amino]methyl}benzonitrile derivatives **8**, comprising a structure of cyclic hemiaminal ethers, were found to be unstable under both alkaline and acidic conditions. Whereas, under alkaline conditions, the product of decomposition of **8a** and **8b** was 4-formylbenzonitrile, ring cleavage under acidic conditions afforded 4-(aminomethyl)-benzonitrile, in addition to 2-(methylamino)phenol or 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one derivatives, respectively. In 2-bromo-4-methyl-2*H*-1,4-benzoxazin-3(4*H*)-one derivatives **4a** and **4b**, the Br-atom could be replaced with a OH group only under mild alkaline conditions, while, under stronger alkaline conditions, a similar ring-opening degradation yielded also 2-(methylamino)phenol derivatives. These observa-

Scheme 6

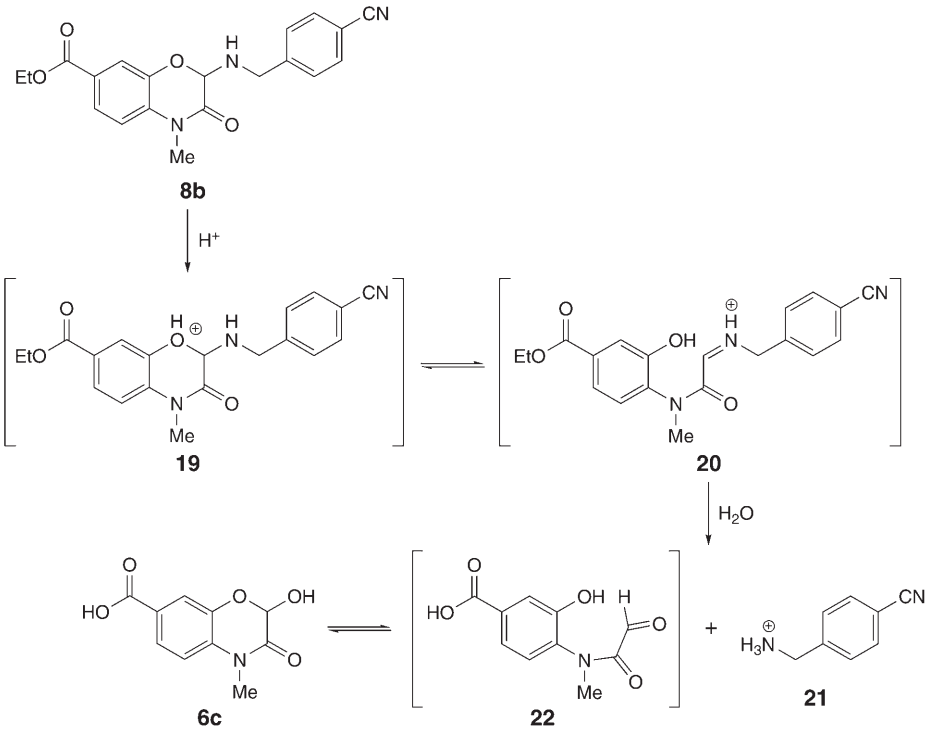


tions will help to devise optimal strategies for the synthesis of 2-substituted 2*H*-1,4-benzoxazin-3(4*H*)-ones which are pharmaceutically valuable intermediates.

Experimental Part

General. All chemicals were obtained from *Aldrich Chemical Co.* and *Fluka*, and were used without further purification. All reported yields are yields of purified products. Solvents were used without purification or drying, unless otherwise stated. Anh. solvents were prepared according to literature procedures [14]. 4-Methyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one and ethyl 4-methyl-3-oxo-3,4-dihydro-2*H*-1,4-benzoxazine-7-carboxylate were synthesized from the corresponding 2-aminophenols and chloroacetyl chloride ($ClCH_2COCl$) by analogy to published procedures [15]. Anal. TLC: *Merck* silica gel (*60 F 254*) plates (0.25 mm), visualization with UV light. Column chromatography (CC): silica gel (*Merck*, particle size 240–400 mesh). Microwave assisted reactions were performed on a *CEM Discover*

Scheme 7



microwave reactor (*CEM Corporation*, USA). M.p.: *Reichert* hot stage microscope; uncorrected. IR Spectra: *Perkin-Elmer 1600* FT-IR spectrometer; KBr pellets, in cm^{-1}. NMR Spectra: at 300 MHz (^1H) and 75 MHz (^{13}C) on a *Bruker Avance-DPX-300* spectrometer in $CDCl_3$ or (D_6)DMSO soln. with TMS as the internal standard; assignments of ^{13}C-NMR spectra on the basis of HMQC and HMBC experiments. MS: *VG Analytical Autospec Q* mass spectrometer; in *m*/*z* (rel. %). Elemental analyses: *Perkin-Elmer C,H,N analyzer 240 C*.

*Synthesis of 4-Methyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one* (**3a**) *and Ethyl 3,4-Dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazine-7-carboxylate* (**3b**). *Step 1.* $ClCH_2COCl$ (3.50 ml, 44 mmol) was added dropwise to a stirred, ice-bath cooled mixture of the corresponding 2-aminophenol derivative (40 mmol) in a biphase mixture of AcOEt (150 ml) and sat. $NaHCO_3$ soln. (50 ml). After 1 h, the org. phase was separated, and the aq. phase was extracted with AcOEt (3×40 ml). The combined org. fractions were dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was dissolved in DMF (20 ml), and the soln. was heated in a sealed vial in a microwave reactor (35 min, 120°/10 bar, 10 W) and poured into 800 ml of H_2O/ice. The precipitate was filtered of and dried at 60°.

*7-Nitro-2*H*-1,4-benzoxazin-3(4*H*)-one.* Prepared from 2-amino-5-nitrophenol (40.0 mmol, 6.16 g). Yield: 6.91 g (89%). The spectral data were identical to those reported in [9].

*Ethyl 3,4-Dihydro-3-oxo-2*H*-1,4-benzoxazine-7-carboxylate.* Prepared from ethyl 4-amino-3-hydroxybenzoate (40.0 mmol, 7.24 g). Yield: 8.33 g (94.1%). Brown crystals. M.p. 199–201°. IR: 3413, 3072, 1716, 1687, 1610, 1424, 1282, 1098, 1050, 762. ^1H-NMR ((D_6)DMSO): 11.03 (br. *s*, NH); 7.57 (*dd*, $J = 8.2, 1.8$, H–C(6)); 7.43 (*d*, $J = 1.8$, H–C(8)); 6.98 (*d*, $J = 8.2$, H–C(5)); 4.64 (*s*, 2 H–C(2)); 4.27 (*q*, $J = 7.1$, $MeCH_2$); 1.29 (*t*, $J = 7.1$, $MeCH_2$). ^{13}C-NMR ((D_6)DMSO): 165.9, 165.8 (*C*OOEt, C(3)); 143.7 (C(8a)); 132.6 (C(7)); 125.3 (C(4a)); 124.8 (C(6)); 117.5 (C(8)); 116.5 (C(5)); 67.5 (C(2)); 61.5 ($MeCH_2O$); 15.0

(*Me*CH_2O). MS (FAB): 222 (20, $[M+H]^+$), 154 (100), 137 (74). Anal. calc. for $C_{11}H_{11}NO_4$ (221.21): C 59.73, H 5.01, N 6.33; found: C 59.76, H 5.12, N 6.27.

Step 2. A suspension of the corresponding 7-substituted 2*H*-1,4-benzoxazin-3(4*H*)-one (15.20 mmol) from *Step 1*, K_2CO_3 (5.25g, 38.00 mmol), benzyl(triethyl)ammonium chloride (0.35 g, 1.52 mmol) and MeI (0.96 ml, 15.44 mmol) in MeCN (60 ml) was stirred overnight at r.t. The suspension was filtered, and the filtrate was evaporated under reduced pressure. The obtained residue was dissolved in AcOEt (100 ml) and washed successively with 10% citric acid (2×50 ml), sat. $NaHCO_3$ soln. (2×50 ml), and sat. NaCl soln. (1×50 ml). The org. phase was dried (Na_2SO_4), and the solvent was evaporated under reduced pressure.

Compound **3a**. Prepared from 7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one (15.2 mmol, 2.95 g). Yield: 2.97 g (94%). The spectral data were identical to those reported in [16].

Compound **3b**. Prepared from ethyl 3,4-dihydro-3-oxo-2*H*-1,4-benzoxazine-7-carboxylate (3.36 g, 15.2 mmol). Yield: 3.29 g (92%). Pink crystals. M.p. 107–108°. IR: 2983, 1717, 1684, 1615, 1508, 1386, 1296, 1147, 886, 760. ^{1}H-NMR ((D$_6$)DMSO): 7.66 (*dd*, *J* = 8.4, 1.9, H–C(6)); 7.46 (*d*, *J* = 1.9, H–C(8)); 7.26 (*d*, *J* = 8.4, H–C(5)); 4.72 (*s*, 2 H–C(2)); 4.29 (*q*, *J* = 7.1, MeCH_2); 3.30 (*s*, MeN); 1.31 (*t*, *J* = 7.1, *Me*CH_2). ^{13}C-NMR ((D$_6$)DMSO): 165.7 (COO); 165.0 (C(3)); 145.2 (C(8a)); 134.5 (C(4a)); 125.6 (C(7)); 124.9 (C(6)); 117.3 (C(8)); 116.2 (C(5)); 67.8 (C(2)); 61.6 (Me*C*H$_2$); 28.7 (MeN); 15.0 (*Me*CH_2). FAB-MS: 236 (100, $[M+H]^+$), 190 (21), 154 (48), 136 (41), 71 (45), 55 (47). Anal. calc. for $C_{12}H_{13}NO_4$ (235.24): C 61.27, H 5.57, N 5.95; found: C 61.31, H 5.69, N 5.93.

Synthesis of Compounds **4a** *and* **4b**. The corresponding 2*H*-1,4-benzoxazin-3(4*H*)-one **3** (10.0 mmol) was suspended in 200 ml of CCl_4. Under stirring and irradiation with a 500-W lamp, a soln. of Br_2 (10.1 mmol) in 50 ml of CCl_4 was added dropwise over 30 min at r.t. After stirring for an additional 1.5 h at r.t., the solvent was removed under reduced pressure. Products were additionally dried at 40°.

*2-Bromo-4-methyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one* (**4a**). Prepared from 4-methyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one (2.09 g, 10.0 mmol). Yield: 2.87 g (100%). Gray powder. M.p. 172–174°. IR: 3414, 3066, 1698, 1605, 1521, 1422, 1342, 1230, 1080, 919, 808, 745, 628. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.19 (*dd*, *J* = 9.0, 2.5, H–C(6)); 8.03 (*d*, *J* = 2.5, H–C(8)); 7.23 (*d*, *J* = 9.0, H–C(5)); 6.86 (*s*, H–C(2)); 3.53 (*s*, MeN). ^{13}C-NMR ($CDCl_3$, 75 MHz): 159.3, 144.3, 140.3, 135.0, 121.2, 115.1, 114.8, 76.2, 29.7. EI-MS: 288 (23, M^+, ^{81}Br), 286 (22, M^+, ^{79}Br), 207 (100), 179 (78), 133 (81). Anal. calc. for $C_9H_7BrN_2O_4$ (287.07): C 37.66, H 2.46, N 9.76; found: C 37.88, H 2.50, N 9.66.

*Ethyl 2-Bromo-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazine-7-carboxylate* (**4b**). Prepared from ethyl 3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazine-7-carboxylate (2.35 g, 10.0 mmol). Yield: 3.14 g (100%). White powder. M.p. 144–147°. IR: 3136, 1719, 1666, 1613, 1512, 1477, 1393, 1319, 1292, 1212, 1142, 1094, 1027. ^{1}H-NMR ((D$_6$)DMSO): 7.70 (*dd*, *J* = 8.5, 1.8, H–C(6)); 7.51 (*d*, *J* = 1.8, H–C(8)); 7.32 (*d*, *J* = 8.5, H–C(5)); 5.64 (*s*, H–C(2)); 4.29 (*q*, *J* = 7.1, MeCH_2); 3.33 (*s*, MeN); 1.30 (*t*, *J* = 7.1, *Me*CH_2). ^{13}C-NMR ((D$_6$)DMSO): 164.9 (COO); 161.9 (C(3)); 141.3 (C(8a)); 132.9 (C(4a)); 124.8 (C(7)); 124.6 (C(6)); 117.9 (C(8)); 115.2 (C(5)); 90.0 (C(2)); 60.9 (Me*C*H$_2$O); 28.1 (MeN); 14.1 (*Me*CH_2O). FAB-MS: 316 (49, $[M+H]^+$, ^{81}Br), 314 (45, $[M+H]^+$, ^{79}Br), 234 (85), 206 (28), 154 (100), 136 (86). Anal. calc. for $C_{12}H_{12}BrNO_4$ (314.13): C 45.88, H 3.85, N 4.46; found: C 45.70, H 3.95, N 4.21.

Synthesis of Compounds **8a** *and* **8b**. A suspension of **4a** or **4b** (10.0 mmol), 4-(aminomethyl)benzonitrile (1.32 g, 10 mmol) and K_2CO_3 (1.38 g, 10.0 mmol) in anh. THF (150 ml) was stirred at 60° for 2 h. The mixture was cooled and poured into H_2O/ice (600 ml). The precipitate was filtered off and dried at 60°. The crude product was recrystallized from EtOH.

*4-{[(3,4-Dihydro-4-methyl-7-nitro-3-oxo-2*H*-1,4-benzoxazin-2-yl)amino]methyl}benzonitrile* (**8a**). Prepared from **4a** (2.87 g, 10.0 mmol). Yield: 2.91 g (86%). Brown powder. M.p. 204–206°. IR: 3306, 3088, 2228, 1677, 1598, 1498, 1341, 1134, 894, 745. ^{1}H-NMR ((D$_6$)DMSO): 7.97 (*dd*, *J* = 8.9, 2.4, H–C(6)); 7.76 (*d*, *J* = 8.2, H–C(3′), H–C(5′)); 7.47–7.50 (*m*, H–C(8), H–C(2′), H–C(6′)); 7.39 (*d*, *J* = 8.9, H–C(5)); 5.42 (*d*, *J* = 11.0, H–C(2)); 4.48–4.56 (*m*, N*H*CH_2); 3.95–4.09 (*m*, NHCH_2); 3.35 (*s*, MeN). ^{13}C-NMR ($CDCl_3$, 75 MHz): 161.5; 146.3; 142.5; 142.1; 135.7; 131.9; 128.6; 118.8; 118.1; 115.6; 112.7; 109.4; 85.9; 47.9; 28.7. EI-MS: 339 (4, $[M+H]^+$), 321 (6), 168 (85), 131 (100), 116 (72). Anal. calc. for $C_{17}H_{14}N_4O_4 \cdot \frac{1}{4}\ H_2O$ (338.32): C 59.56, H 4.26, N 16.34; found: C 59.67, H 4.37, N 16.13.

*Ethyl 2-[(4-Cyanobenzyl)amino]-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazine-7-carboxylate* (**8b**). Prepared from **4b** (3.13 g, 10.0 mmol). Yield: 3.21 g (88%). Yellow powder. M.p. 152–155°. IR:

3451, 3278, 2228, 1715, 1677, 1611, 1509, 1397, 1286, 1159, 1027, 907, 818, 726. ^{1}H-NMR ((D$_6$)DMSO): 7.75 (*d*, *J* = 8.2, H–C(3′), H–C(5′)); 7.66 (*dd*, *J* = 8.5, 1.9, H–C(6)); 7.48 (*d*, *J* = 8.2, H–C(2′), H–C(6′)); 7.28 (*d*, *J* = 8.5, H–C(5)); 7.22 (*d*, *J* = 1.9, H–C(8)); 5.31 (*d*, *J* = 10.7, H–C(2)); 4.34–4.42 (*m*, N*H*CH$_2$); 4.30 (*q*, *J* = 7.1, MeC*H*$_2$); 3.92–4.07 (*m*, NHC*H*$_2$); 3.35 (*s*, MeN); 1.33 (*t*, *J* = 7.1, *Me*CH$_2$). ^{13}C-NMR ((D$_6$)DMSO): 165.8 (COO); 162.7 (C(3)); 147.4 (C(1′)); 142.7 (C(8a)); 134.6 (C(3′); C(5′)); 132.8 (C(4a)); 129.6 (C(2′); C(6′)); 125.8 (C(7)); 124.6 (C(6)); 119.8 (CN); 119.0 (C(8)); 116.2 (C(5)); 110.3 (C(4′)); 86.7 (C(2)); 61.6 (Me*C*H$_2$); 48.9 (NHCH$_2$); 29.4 (MeN); 15.1 (*Me*CH$_2$). EI-MS: 365 (4, M^+), 320 (25), 235 (75), 222 (45), 195 (100), 116 (62). Anal. calc. for $C_{20}H_{19}N_3O_4$ (365.38): C 65.74, H 5.24, N 11.50; found: C 65.59, H 5.41, N 11.21.

Alkaline Hydrolysis of **8a** *and* **8b**. A soln. of **8a** or **8b** (1.0 mmol) and 1M NaOH (2.0 ml for **8a**; 4.0 ml for **8b**) in dioxane/H$_2$O 1:1 (50 ml) was stirred for 6 h at r.t. The pH was adjusted with 1M HCl to 3, and the solvent was removed under reduced pressure. The residue was separated by CC (silica gel; CH_2Cl_2/MeOH 20:1 → 9:1) to give **9a** (119 mg, 71%) and **10** (26 mg, 20%; starting from **8a**), and **9c** (35 mg, 21%) and **10** (89 mg, 68%; starting from **8b**).

Data of 4-Formylbenzonitrile (**10**). The product was in all respects (m.p., TLC, ^{1}H-NMR, MS) identical to an authentic sample (*Sigma-Aldrich*).

Data of 2-(Methylamino)-5-nitrophenol (**9a**). Red crystals. M.p. 177–179°. IR: 3402, 1614, 1552, 1486, 1296, 1199, 855, 749. ^{1}H-NMR ((D$_6$)DMSO): 10.26 (*s*, OH); 7.72 (*dd*, *J* = 9.0, 2.4, H–C(4)); 7.47 (*d*, *J* = 2.4, H–C(6)); 6.48 (*d*, *J* = 9.0, H–C(3)); 6.42 (br. *q*, *J* = 4.8, NH); 2.83 (*d*, *J* = 5.3, Me). ^{13}C-NMR ((D$_6$)DMSO): 146.5, 143.7, 136.0, 119.6 (C(4)); 107.9 (C(6)); 107.2 (C(3)); 30.1 (Me). EI-MS: 168 (100, M^+), 138 (44), 122 (25), 94 (24). HR-MS: 168.0535 (M^+, $C_7H_8N_2O_3^+$; calc. 168.0535).

Data of 3-Hydroxy-4-(methylamino)benzoic Acid (**9c**). White crystals. M.p. 180–183°. IR: 3318, 1675, 1609, 1423, 1271, 1158, 958, 766, 715, 628. ^{1}H-NMR ((D$_6$)DMSO): 11.90 (br. *s*, COOH); 9.50 (br. *s*, OH); 7.37 (*dd*, *J* = 8.3, 1.8, H–C(6)); 7.23 (*d*, *J* = 1.9, H–C(2)); 6.42 (*d*, *J* = 8.3, H–C(5)); 5.51 (br. *s*, NH); 2.75 (br. *s*, Me). ^{13}C-NMR ((D$_6$)DMSO): 168.6 (CO); 143.8, 143.8 (C(3), C(4)); 124.0 (C(6)); 117.4 (C(1)); 114.2 (C(2)); 108.1 (C(5)); 30.2 (Me). EI-MS: 167 (100, M^+), 152 (25), 150 (19), 124 (18). Anal. calc. for $C_8H_9NO_3$ (167.16): C 57.48, H 5.43, N 8.38; found: C 57.71, H 5.51, N 8.40.

Acid Hydrolysis of **8b**. Compound **8b** (1.095 g, 3.0 mmol) and 6M HCl (30 ml) in dioxane (30 ml) were refluxed overnight. The soln. was then cooled and neutralized with 3M NaOH. (Boc)$_2$O (720 mg, 3.3 mmol) and NaHCO$_3$ (504 mg, 6 mmol) were added, and the soln. was stirred at r.t. overnight. The dioxane was removed under reduced pressure, the pH was adjusted to 3.5, and the products were extracted with AcOEt (3 × 40 ml). The combined org. fractions were dried (Na$_2$SO$_4$) and the solvent evaporated under reduced pressure. The residue was separated with CC (CH_2Cl_2/MeOH 50:1 → 9:1) to give **6c** (288 mg, 43%) and **12** (432 mg, 62%).

*Data of 4-Methyl-3-oxo-3,4-dihydro-2-hydroxy-2*H*-1,4-benzoxazine-7-carboxylic Acid* (**6c**). White crystals. M.p. 249–251°. IR: 3163, 1701, 1612, 1478, 1388, 1241, 1148, 1026, 926, 805, 760, 515. ^{1}H-NMR ((D$_6$)DMSO): 12.89 (*s*, COOH); 8.12 (*s*, OH); 7.70 (*dd*, *J* = 8.4, 1.9, H–C(6)); 7.51 (*d*, *J* = 1.9, H–C(8)); 7.30 (*d*, *J* = 8.4, H–C(5)); 5.65 (*s*, H–C(2)); 3.34 (*s*, MeN). ^{13}C-NMR ((D$_6$)DMSO): 167.4; 162.8; 142.2; 133.5; 126.8; 125.2 (C(6)); 119.0 (C(8)); 115.9 (C(5)); 91.0 (C(2)); 29.0 (MeN). EI-MS: 223 (25, M^+), 194 (100). Anal. calc. for $C_{10}H_9NO_5$ (223.18): C 53.82, H 4.06, N 6.28; found: C 54.13, H 4.13, N 6.34.

Data of tert-*Butyl (4-Cyanobenzyl)carbamate* (**12**). White crystals. M.p. 90–92°. IR: 3351, 2977, 2228, 1675, 1504, 1366, 1246, 1160, 1053, 872, 846, 784. ^{1}H-NMR ((D$_6$)DMSO): 7.80 (*d*, *J* = 8.2, H–C(3), H–C(5)); 7.50 (br. *t*, *J* = 6.1, NH); 7.43 (*d*, *J* = 8.2, H–C(2), H–C(6)); 4.21 (*d*, *J* = 6.1, CH$_2$); 1.40 (*s*, *t*-Bu). ^{13}C-NMR ($CDCl_3$, 75 MHz): 156.3 (CO); 145.1 (C(1′)); 132.8 (C(3′); C(5′)); 128.2 (C(2′); C(6′)); 119.2 (CN); 111.5 (C(4′)); 80.4 (Me$_3$*C*); 44.6 (CH$_2$); 28.7 (3 Me). EI-MS: 233 (32, $[M+H]^+$), 177 (70), 116 (35), 57 (100). Anal. calc. for $C_{13}H_{16}N_2O_2$ (232.28): C 67.22, H 6.94, N 12.06; found: C 66.88, H 6.95, N 12.46.

Attempted Boc Protection of **8a**. A soln. of (Boc)$_2$O (1.31 g, 6 mmol) in THF (25 ml) was added dropwise to a stirred soln. of **8a** (1.69 g, 5 mmol), 4-(dimethylamino)pyridine (100 mg, 0.8 mmol), and Et$_3$N (707 mg, 7 mmol), cooled on ice bath. The mixture was stirred overnight at r.t., THF was removed under reduced pressure, and the obtained residue was dissolved in AcOEt (100 ml) and washed successively with 5% citric acid (2 × 25 ml) and brine (1 × 25 ml). The org. phase was dried (Na$_2$SO$_4$),

and the solvent was evaporated under reduced pressure. The crude product was separated by radial chromatography (petroleum ether/AcOEt 3:1) to give **13a** (666 mg, 41%) and **10** (334 mg, 51%).

Data of tert-*Butyl {2-[(2-Hydroxy-4-nitrophenyl)(methyl)amino]-2-oxoethyl}carbamate* (**13a**). White crystals. M.p. 101–103°. IR: 3366, 1677, 1529, 1353, 1246, 1163, 1082, 956, 816, 736. ^{1}H-NMR ((D$_6$)DMSO): 11.08 (br. *s*, OH); 7.77 (*d*, *J* = 2.5, H–C(3)); 7.74 (*dd*, *J* = 8.4, 2.5, H–C(5)); 7.52 (*d*, *J* = 8.4, H–C(6)); 6.76 (*t*, *J* = 5.8, CONH); 3.49 (br. *s*, CH$_2$); 3.10 (*s*, MeN); 1.35 (*s*, *t*-Bu). ^{13}C-NMR ((D$_6$)DMSO): 169.4 (*C*ONMe); 156.4 (NHCOO); 154.6, 148.2, 136.5 (C(1), C(2), C(4)); 131.2 (C(6)); 115.6 (C(5)); 112.2 (C(3)); 78.8 (Me$_3$*C*); 42.8 (CH$_2$); 36.4 (MeN); 29.03 (3 Me). FAB-MS: 326 (41, [*M* + H]$^+$), 270 (95), 226 (58), 169 (32), 57 (100). Anal. calc. for C$_{14}$H$_{19}$N$_3$O$_6$ · ¾ H$_2$O (325.32): C 50.98, H 5.96, N 12.74; found: C 50.94, H 6.12, N 12.61.

Data of **10**. Compound **10** was in all respects (m.p., TLC, ^{1}H-NMR, MS) identical to an authentic sample (*Sigma-Aldrich*).

*Alkaline Hydrolysis of Ethyl 3,4-Dihydro-3-oxo-2*H*-1,4-benzoxazine-7-carboxylates* **6b** *and* **7b**. A soln. of **6b** or **7b** (1 mmol) and 2 ml of 1M NaOH in EtOH/H$_2$O 1:1 (50 ml) was stirred for 6 h at r.t. The pH was then adjusted to 1 with 1M HCl, the precipitate was filtered off and dried at 60°. The corresponding carboxylic acids **6c** and **7c** were obtained in 96 and 94% yield, resp.

Data of **6c**. Yield: 214 mg (96%) The spectral data of **6c** were identical to those described above.

*Data of 2-[(4-Cyanobenzyl)oxy]-3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazine-7-carboxylic Acid* (**7c**). Yield: 317 mg (94%) The spectral data of **7c** were identical to those reported in [9].

Synthesis of **6a**, **6b**, *and* **6c**. *Method A* (with NaOH). A soln. of **4a** (1.0 mmol) and 1M NaOH (1.2 ml), or **4b** (1 mmol) and 1M NaOH (10 ml) in dioxane/H$_2$O 1:1 (50 ml) was stirred overnight at r.t. The pH was then adjusted to 3 with 1M HCl, and the solvent was evaporated under reduced pressure. The crude products were separated by radial chromatography using petroleum ether/AcOEt 1:1 as eluant giving **6a** (123 mg, 55%) and **9a** (50 mg, 30%), or **6c** (14 mg, 6%) and **9c** (135 mg, 81%), resp.

Method B (with NaHCO$_3$). A soln. of **4a** or **4b** (10 mmol) in THF (300 ml) was added dropwise, over a period of 1 h, to a soln. of NaHCO$_3$ (1.68 g, 20 mmol) in THF/H$_2$O 4:1 (400 ml). The solvent was then evaporated under reduced pressure. The products obtained from **4a** were separated by recrystallization from H$_2$O or AcOEt to give **6a** (1.37 g, 61%) and **14a** (1.12 g, 26%). Products obtained from **4b** were separated by recrystallization from EtOH/AcOEt mixture to give **6b** (2.16 g, 86%) and **14b** (388 mg, 8%).

Method C (with BaCO$_3$). A suspension of **4a** or **4b** (10.0 mmol) and BaCO$_3$ (11.0 mmol) in H$_2$O (150 ml) was refluxed for 15 min, cooled to r.t., and extracted with AcOEt (3 × 40 ml). The combined org. fractions were dried (Na$_2$SO$_4$), filtered and the solvent was evaporated under reduced pressure to yield **6a** (2.06 g, 92%) or **6b** (2.36 g, 94%), resp.

The spectral data of **9a**, **6c**, and **9c** were identical to those given above.

*Data of 2-Hydroxy-4-methyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one* (**6a**). Yellow powder. M.p. 183–186°. IR: 3401, 1613, 1552, 1468, 1455, 1432, 1397, 1260, 1199, 1170, 1088. ^{1}H-NMR ((D$_6$)DMSO): 8.37 (*d*, *J* = 6.2, OH); 7.98 (*dd*, *J* = 9.0, 2.6, H–C(6)); 7.82 (*d*, *J* = 2.6, H–C(8)); 7.40 (*d*, *J* = 9.0, H–C(5)); 5.72 (*d*, *J* = 6.2, H–C(2)); 3.37 (*s*, MeN). ^{13}C-NMR ((D$_6$)DMSO): 162.6 (C(3)); 143.5 (C(7)); 142.4 (C(8a)); 135.7 (C(4a)); 119.5 (C(6)); 116.3 (C(5)); 113.5 (C(8)); 91.0 (C(2)); 29.3 (MeN). EI-MS: 224 (13, *M*$^+$), 195 (100), 149 (45). Anal. calc. for C$_9$H$_8$N$_2$O$_5$ (224.17): C 48.22, H 3.60, N 12.50; found: C 48.25, H 3.56, N 12.56.

*Data of Ethyl 3,4-Dihydro-2-hydroxy-4-methyl-3-oxo-2*H*-1,4-benzoxazine-7-carboxylate* (**6b**). Violet crystals. M.p. 147–148°. IR: 3126, 1717, 1656, 1614, 1513, 1394, 1286, 1247, 1154, 1043, 762, 701. ^{1}H-NMR ((D$_6$)DMSO): 8.15 (*s*, OH); 7.71 (*dd*, *J* = 8.4, 1.9, H–C(6)); 7.53 (*d*, *J* = 1.9, H–C(8)); 7.32 (*d*, *J* = 8.4, H–C(5)); 5.66 (*s*, H–C(2)); 4.30 (*q*, *J* = 7.1, MeC*H*$_2$); 3.35 (*s*, MeN); 1.32 (*t*, *J* = 7.1, *Me*CH$_2$). ^{13}C-NMR ((D$_6$)DMSO): 164.8, 161.8, (COO, C(3)); 141.3, 132.8, 124.8 (C(4a), C(8a), C(7)); 124.0 (C(6)); 117.8 (C(8)); 115.1 (C(5)); 90.0 (C(2)); 60.6 (Me*C*H$_2$); 28.0 (MeN); 14.0 (*Me*CH$_2$). EI-MS: 251 (31, *M*$^+$), 222 (100), 206 (25), 194 (48). Anal. calc. for C$_{12}$H$_{13}$NO$_5$ (251.24): C 57.37, H 5.22, N 5.58; found: C 57.65, H 5.25, N 5.80.

*Data of 2,2′-Oxybis(4-methyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one* (**14a**). The product gave two spots on TLC (R_f 0.32 and 0.43; silica gel, CH$_2$Cl$_2$/MeOH 50:1). ^{1}H-NMR showed the presence of two diastereoisomers. The lower spot was isolated and characterized. Red crystals. M.p. 273–276°. IR: 3446,

1602, 1529, 1489, 1303, 1249, 1211, 1156, 1106, 1076. ^{1}H-NMR ((D$_6$)DMSO): 8.00 (*dd*, *J* = 8.9, 2.5, H–C(6), H–C(6′)); 7.78 (*d*, *J* = 2.5, H–C(8), H–C(8′)); 7.04 (*d*, *J* = 8.9, H–C(5), H–C(5′)); 5.97 (*s*, H–C(2), H–C(2′)); 3.42 (*s*, 2 MeN). EI-MS: 430 (6, M^+), 400 (4), 208 (100), 179 (80), 133 (53). HR-MS: 430.0770 (M^+, $C_{18}H_{14}N_4O_9^+$; calc. 430.0761).

*Diethyl 2,2′-Oxybis(3,4-dihydro-4-methyl-3-oxo-2*H*-1,4-benzoxazine-7-carboxylate)* (**14b**). The product was obtained as a mixture of diastereoisomers showing two spots on TLC (R_f 0.31 and 0.44; silica gel, CH_2Cl_2/MeOH 50 : 1) and duplication of some resonances in the ^{1}H-NMR spectrum. The lower spot was isolated and characterized. Gray crystals. M.p. 249–253°. IR: 2987, 1716, 1615, 1514, 1385, 1290, 1249, 1102, 990, 766. ^{1}H-NMR ((D$_6$)DMSO): 7.75 (*dd*, *J* = 8.5, 1.9, H–C(6), H–C(6′)); 7.71 (*d*, *J* = 1.9, H–C(8), H–C(8′)); 7.33 (*d*, *J* = 8.5, H–C(5), H–C(5′)); 6.11 (*s*, H–C(2), H–C(2′)); 4.33 (*q*, *J* = 7.1, 2 MeC*H*$_2$); 3.38 (*s*, 2 MeN); 1.35 (*t*, *J* = 7.1, 2 *Me*CH$_2$). EI-MS: 484 (5, M^+), 439 (13), 250 (40), 234 (100), 206 (59), 178 (30). Anal. calc. for $C_{24}H_{24}N_2O_9$ (484.46): C 59.50, H 4.99, N 5.78; found: C 59.13, H 5.00, N 5.78.

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