Syntheses for 2-Hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one Derivatives as Thio Analogues of Natural Hemiacetals

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Reductive cyclizations of methyl 2-(2-nitrophenylthio)acetate **2** by means of electrochemistry or by catalytic hydrogenation have been used as key steps in the syntheses of the hemiacetals 2-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one **10** and its 4-hydroxy derivative **9** representing thio analogues of allelo chemicals found in *Gramineae* and *Acanthaceae*. In contrast to its natural counterpart 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one hydroxamic acid **9** did not undergo degradation by extrusion of formic acid.

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Naturally occurring hemiacetals with the 1,4-benzoxazin-3(4*H*)-one skeleton have been found to occur in the form of 2-β-D-glucosides as allelo chemicals in different plant species. Thus, isolation procedures have been described for the glucosidic precursors like the cyclic hydroxamic acid (2*R*)-2-β-D-glucopyranosyloxy-4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one from rye (*Gramineae*) [1], its 7-methoxy derivative from maize (*Gramineae*) [2] and Coix *lachryma jobi* (*Gramineae*) [3] as well as the lactam (2*R*)-2-β-D-glucopyranosyloxy-2*H*-1,4-benzoxazin-3(4*H*)-one (*Blepharin*) from *Blepharis edulis* (*Acanthaceae*) [4]. The aglucones are set free by the cell constituent β-glucosidase when the plant is attacked by a pest and exhibit a wide variety of biological activities, *e.g.* as plant resistance factors against microbial diseases and insects [5]. Therefore, they are under continued investigation also in comparison with close synthetic analogues [6]. Investigations on the lead of 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones have proven the responsibility of their lactol unit for the bioactivity. Derivatives of the 2-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one ring system are available by means of different synthetic pathways including general [7,8] and individual [9] syntheses. Based on this work we are now interested in the syntheses of thioanalogous hemiacetals derived from the 1,4-benzothiazine skeleton.

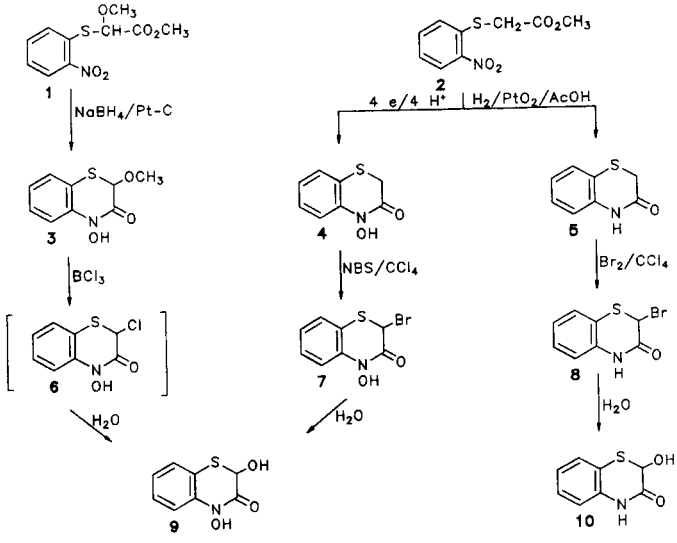
Results and Discussion.

We have started with a procedure analogous to that described for the syntheses of 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-ones [10]. The starting methyl 2-methoxy-2-(2-nitrophenylthio)acetate (**1**) was prepared from sodium 2-nitrophenolate and methyl 2-bromo-2-methoxyacetate in dry toluene. Reductive cyclization of **1** with sodium borohydride following the method of Coutts [11] with slight modifications regarding solvent and catalyst yielded the 2-methyl acetal **3**. The lactol unit was unmasked by demethylation with excess boron trichloride in methylene chloride. The intermediate 2-chloro hydroxamic acid was hydrolizable just with water to give 2,4-dihydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one (**9**). The use of silver carbonate/water for the hydrolysis was unnecessary. In contrast, this system gave rise to the quantitative formation of silver sulfide. Eventually, we have tried to apply our previously described method for 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one [9] to the syntheses of the thio analogues **9** and **10** to avoid the disadvantage of working with hazardous boron trichloride. The starting material methyl 2-(2-nitrophenylthio)acetate (**2**) (mp 91-92° (lit [12] 89-90°), 82%) was readily available by the reaction of 2-chloronitrobenzene and methyl thioglycolate in the presence of sodium methoxide. Unfortunately, all efforts to apply Coutts' method for reductive cyclization of **2** to the hydroxamic acid **4** by means of sodium borohydride [12] have failed.

Similarly, reduction with zinc dust in ammonium chloride solution as well as different catalytical hydrogenations yielded lactam **5** as major product accompanied with minor amounts of hydroxamic acid **4** up to only 10%. These observations prompted us to investigate electrochemical reduction which is well adapted for the synthesis of phenylhydroxylamines or their cyclization products, as shown in the preparation of 4-hydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one from 2-nitrophenoxyacetic acid or the corresponding methyl ester [13]. Preliminary experiments on **2** showed a short life-time of the corresponding phenylhydroxylamine in acidic medium [14]. Controlled potential electrolysis has been carried out at a mercury pool cathode in a mixture of sulphuric acid (0.5 *M*) and ethanol (1:4, v/v), at −0.4 V SCE (corresponding to the polarographic plateau of the 4 electron-wave). The expected hydroxamic acid **4** was obtained in a 80% yield. A small amount of a by-product, not fully purified, has been isolated. On the basis of spectroscopic data it has been identified as 7-ethoxy-2*H*-1,4-benzothiazine-3(4*H*)-one, resulting from the re-

arrangement of **4** (or its phenylhydroxylamine precursor) in the acidic ethanolic medium [15].

Bromination of **4** with bromine in carbon tetrachloride led to the bromo compound **7** only as an oil with several dark by-products. Obviously, the known rearrangment of hydroxamic acids in strongly acidic medium to the corresponding 7-OH or 7-halogen lactams [15] caused under these conditions by the hydrogen bromide liberated on bromination is responsible for the failure. However, bromination of **4** with *N*-bromosuccinimide proceeded very well and gave rise to **7** as pale yellow crystals. In contrast to **4** lactam **5** should be insensitive towards hydrogen bromide. Catalytical hydrogenation of nitro ester **2** over platinum oxide in glacial acetic acid gave access to **5**, (mp 179-179.5 (lit [16] 176°), 94%) which indeed could be transferred by means of bromine in carbon tetrachloride to the 2-bromolactam **8**, (mp 223-225° (lit [17] 220°), 86%). Finally, hydrolyses of the very reactive bromo compounds **7** and **8** with water formed the lactols **9** and **10**.



In summary, procedures starting from nitro ester **2** proved to be convenient methods for the syntheses of the hemiacetals **9** and **10** as thio analogues of allelo chemicals from *Gramineae*.

Based on our recent results on the resolution of enantiomers of 2-methoxy-2*H*-1,4-benzoxazin-3(4*H*)-ones by hplc using a β-cyclodextrin-modified stationary phase [18] also enantioseparation of the thio analogous methyl acetal **3** could be achieved. However, using a series of eluents it was impossible to separate the enantiomers of **9**. This is obviously a consequence of a rapid oxo-thiocyclo tautomerism of the thiohemiacetal unit, which occurs fast in comparison to the separation procedure. Hence, the racemization effect at 2,4-dihydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one (**9**) originates in the same kind of isomerization that causes the mutarotation of anomeric thiosugars, *e.g.* that of 5-thio-D-glucose [19].

Surprisingly, hydroxamic acid **9** did not undergo a degradation by extrusion of formic acid to form benzothiazol-2(3*H*)-one, which might have been expected from the known decomposition of the oxo analogue 2,4-dihydroxy-2*H*-1,4-benzoxazin-3(4*H*)-one to benzoxazol-2(3*H*)-one. The mechanism of this ring contraction has been extensively studied [7,20]. Presumably, benzothiazinone **9** is stable towards decomposition because of the higher nucleophily of the mercapto group in the intermediate ring opened form of the equilibrium in comparison to that of a phenolic hydroxy group. Thereby, in the benzothiazinone case only the tautomerism occurs, whereas in the benzoxazinone case besides this process a concurrent reaction can take place leading to the slow degradation of the six membered ring.

EXPERIMENTAL

Melting points were determined on a Boetius micro hot stage apparatus and are corrected. The nmr spectra were recorded on a 200 MHz spectrometer Varian Gemini 200 with hexamethyldisiloxane as the internal standard. The ir spectra were obtained on a Carl Zeiss Jena Specord M 80 spectrometer in potassium bromide. Mass spectra were recorded on a Varian MAT CH6 mass spectometer (70 eV EI ionization, source temperature 200°). Elemental analyses were performed on a Hereaus CHN-O-Rapid analyzer. The hplc instrument consisted of a Merck/Hitachi L-6200 intelligent pump, Rheodyne 7125 injector, Merck/Hitachi A 4200 variable wavelength UV-detector, Merck/Hitachi D 2500 integrator and a LiChroCART hplc cartridge 250 x 5 mm ChiraDex (5 μm).

Methyl 2-Methoxy-2-(2-nitrophenylthio)acetate (**1**).

To a solution of 2-nitrothiophenol (7.75 g, 50 mmoles) in dry toluene (100 ml) sodium methoxide (2.65 g, 50 mmoles) was added under nitrogen at room temperature. After stirring the mixture for twenty minutes a solution (20 ml) of methyl 2-bromo-2-methoxyacetate in toluene (9.2 g, 50 mmoles) was added dropwise. After 1 hour the resultant sodium bromide was filtered and the filtrate was evaporated *in vacuo*. Distillation in a Kugelrohr apparatus afforded 9.5 g (71%) of **1** as a yellow oil, bp 150-155° (0.5 mm) which crystallized after several hours at room temperature, mp 47-49°; ir: ν 1520 (NO_2), 1750 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.47 (s, 3H, OCH_3), 3.66 (s, 3H, CO_2CH_3), 5.81 (s, 1H, SCH), 7.52-8.13 (m, 4H, aromatics).

Anal. Calcd. for $C_{10}H_{11}NO_5S$: C, 46.69; H, 4.31; N, 5.44; S, 12.46. Found: C, 46.73; H, 4.08; N, 5.41; S, 12.65.

4-Hydroxy-2-methoxy-2*H*-1,4-benzothiazin-3(4*H*)-one (**3**).

To a rapidly stirred suspension of sodium borohydride (0.75 g, 20 mmoles) and 5% Pt/C (100 mg) in 30 ml of methanol:water (1:1, v/v) a solution (15 ml) of 1.3 g (5 mmoles) methyl 2-methoxy-2-(2-nitrophenylthio)acetate **1** in dry methanol was added dropwise within 30 minutes at 25° with external cooling and under nitrogen. After complete addition of the nitro ester the mixture was stirred for another thirty minutes. The filtrate was acidified with 2 *M* hydrochloric acid, evaporation to 15 ml *in vacuo* gave a precipitate which was recrystallized from methanol to yield 0.75 g (71%) of **3**, mp 144-145°; ir: ν 1680 (C=O) cm^{-1}; ^1H nmr

(DMSO-d_6): δ 3.33 (s, 3H, OCH_3), 5.36 (s, 1H, C2-H); 7.07-7.46 (m, 4H, aromatics), 10.93 (s, 1H, NOH); ^{13}C nmr (DMSO-d_6): δ 55.7 (OCH_3), 80.5 (C-2), 115.6 (C-5), 116.5 (C-8), 124.1 (C-7), 127.5 (C-6), 128.7 (C-9), 138.6, (C-10), 156.9 (C=O); ms: m/z 211 (M^+, 41), 194 (5), 151 (100), 122 (35), 96 (33).

Anal. Calcd. for $C_9H_9NO_3S$: C, 51.17; H, 4.29; N, 6.63; S, 15.18. Found: C, 51.04; H, 4.62; N, 6.93; S, 15.42.

For enantio separation of **3** a 20 μl volume of a 0.1% solution of **3** in methanol was injected into the hplc system using methanol:water (20:80, v/v) at *p*H 3.56 (triethylamine/acetic acid buffer) as eluent at 0.8 ml min^{-1}.

t_R[min]	t'_R[min]	k'
18.84	14.24	3.09
22.08	17.48	3.80

4-Hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one (**4**).

Electrolyses were performed in the cell described by Moinet and Peltier [21]. The working potential was made constant by the means of a Tacussel PRT potentiostat and the electricity consumption measured with a Tacussel IG5 coulometer. In a typical run 0.5 mmoles (due to its low solubility) of the nitro ester **2** was introduced into the catholyte and a continuous stream of nitrogen was bubbled into the cell during the electrolysis. After evaporation of the catholyte to dryness the crude precipitate was filtered off and stirred with a 0.1 *M* sodium hydroxide solution. Acidification with dilute sulphuric acid led to the major product **4**, mp 151° (lit [12] 151-152°) in 80% yield. The minor non soluble product, mp 165° after recrystallization from aqueous ethanol, has been postulated as 7-ethoxy-2*H*-1,4-benzothiazine-3(4*H*)-one on the basis of spectroscopic data; ir: ν 1680 (C=O), 2800-3300 (large, NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.40 (t, 3H, CH_2CH_3), 3.40 (s, 2H, SCH_2), 4.03 (q, 2H, CH_2CH_3), 6.50-7.21 (m, 3H, aromatics), 9.7 (s, 1H, NH).

2-Bromo-4-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one (**7**).

To a suspension of 4-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one **4** (3.62 g, 20 mmoles) in dry carbon tetrachloride (100 ml) *N*-bromosuccinimide (3.56 g, 20 mmoles) and dibenzoyl peroxide (100 mg) were added. The mixture was heated to reflux until the brown color of bromine disappeared (*ca* 1 hour). After refluxing for an additional twenty minutes the reaction mixture was allowed to cool to room temperature. The resulting succinimide was filtered and the filtrate was evaporated *in vacuo* to 20 ml to give a yellow solid which was recrystallized from carbon tetrachloride to yield 3.6 g (70%) of **7**, mp 125-127°; ir: ν 1630 (C=O) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 5.87 (s, 1H, C2-H), 7.21-7.67 (m, 4H, aromatics), 8.88 (s, 1H, NOH); ^{13}C nmr (DMSO-d_6): δ 71.6 (C-2), 115.5 (C-5), 117.3 (C-8), 123.9 (C-7), 127.1 (C-6), 128.7 (C-9), 138.5 (C-10), 158.9 (C=O); ms: m/z 259 (M^+, 49), 180 (100), 164 (18), 152 (18), 135 (17), 96 (20).

Anal. Calcd. for $C_8H_6NO_2SBr$: C, 36.94; H, 2.32; N, 5.38; S, 12.33; Br, 30.72. Found: C, 36.73; H, 2.10; N, 5.28; S, 12.05; Br, 31.01.

2,4-Dihydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one (**9**).

Method A.

4-Hydroxy-2-methoxy-2*H*-1,4-benzothiazin-3(4*H*)-one **3** (0.53 g, 2.5 mmoles) was suspended in methylene chloride (50 ml) and cooled to −78°. Boron trichloride (25 ml, 0.5 *M*) in methylene chloride was added precooled. After being warmed to room temperature the mixture was stirred for 6 hours. Water in the amount of 20 ml was added carefully and the mixture stirred vigorously for 30 minutes. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (3 x 15 ml). The combined organics were dried (sodium sulfate) and evaporated. The resulting oil was purified by column chromatography over silica gel (3 x 40 cm solumn) with ethyl acetate toluene (2:1, v/v) as eluent to give 0.14 g (26%) of **9** after recrystallization from water as mono-hydrate, mp 130-131°.

Method B.

2-Bromo-4-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one **7** (1.3 g, 5 mmoles) was stirred in 15 ml of boiling water for 15 minutes. The product crystallized after filtration of the hot reaction mixture and was recrystallized from water to yield 0.63 g (59%) **9** as the monohydrate, mp 130-131°; ir: ν 1675 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 5.44 (s, 1H, C2-H), 7.03-7.43 (m, 4H, aromatics), 10.78 (s, 1H, NOH); ^{13}C nmr (DMSO-d_6): δ 71.7 (C-2), 115.5 (C-5), 117.3 (C-8), 123.8 (C-7), 127.1 (C-6), 128.6 (C-9), 138.5 (C-10), 158.9 (C=O); ms: m/z 197 (M^+, 60), 168 (73), 151 (58), 124 (100), 109 (17).

Anal. Calcd. for $C_8H_7NO_3S \cdot H_2O$: C, 44.64; H, 4.21; N, 6.51; S, 14.89. Found: C, 44.65; H, 4.32; N, 6.69; S, 14.86.

Sublimation of an analytical sample (110°, 0.3 mm) gave **9** without water, mp 145-146°.

Anal. Calcd. for $C_8H_7NO_3S$: C, 48.72; H, 3.58; N, 7.10; S, 16.26. Found: C, 48.71; H, 3.84; N, 7.43; S, 16.76.

2-Hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one (**10**).

2-Bromo-2*H*-1,4-benzothiazin-3(4*H*)-one **8** (0.49 g, 2 mmoles) was stirred in 30 ml ethyl acetate:water (1:1, v/v) for 1 hour. The ethyl acetate layer was separated, washed with water (5 ml), dried (sodium sulfate) and evaporated *in vacuo*. The residue was recrystallized from chloroform to give 0.19 g (54%) **10**, mp 184-185°; ir: ν 1670 (C=O) cm^{-1}, 3200 (NH); ^{1}H nmr (THF-d_8): δ 5.27 (d, 1H, J = 5 Hz, C2-H), 6.69 (d, 1H, J = 5 Hz, C2-OH), 7.01-7.34 (m, 4H, aromatics), 10.50 (s, 1H, NH); ^{13}C nmr (THF-d_8): δ 72.8 (C-2), 119.1 (C-5), 119.8 (C-8), 125.0 (C-7), 128.8 (C-6), 130.6 (C-9), 139.3 (C-10), 158.9 (C=O); ms: m/z 181 (M^+, 13), 151 (100), 136 (65), 121 (24), 95 (21).

Anal. Calcd. for $C_8H_7NO_2S$: C, 53.02; H, 3.89; N, 7.73; S, 17.69. Found: C, 53.19; H, 3.80; N, 7.88; S, 17.29.

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