Synthesis and Structural Characterisation of 4*H*-1,3-Benzothiazine Derivatives

Lajos Fodor[a,b], Gábor Bernáth[b], Jari Sinkkonen[c] and Kalevi Pihlaja[c]*

[a]Research Group for Heterocyclic Chemistry of the Hungarian Academy of Sciences, Institute of Pharmaceutical Chemistry, University of Szeged, H-6701 Szeged, PO Box 121, Hungary
[b]Central Laboratory, County Hospital, H-5701 Gyula, PO Box 46, Hungary
[c]Structural Chemistry Group, Department of Chemistry, University of Turku, FIN-20014 Turku, Finland
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The ring-closure reactions of *N*-arylthiomethylaroylamide derivatives (**1a-g**) in the presence of phosphorus oxychloride gave 2-aryl-4*H*-1,3-benzo-thiazines (**2a-g**). 2-(3-Chlorophenyl)-6-methyl-4*H*-1,3-benzothiazine (**2b**) was reduced with Zn to obtain the corresponding 2,3-dihydro derivative (**3b**). Potassium permanganate oxidation of 2-(4-chlorophenyl)-2,3-diethoxy-4*H*- (**2e**) and 2-(2-fluorophenyl)-6,7-diethoxy-4*H*-1,3-benzo-thiazines (**2g**) gave the corresponding 4-ones (**4e**,**g**). The reactions of 2-(4-chlorophenyl)-6-methyl-4*H*-1,3-benzothiazine (**2c**) with substituted acetyl chlorides led to linearly condensed ß-lactams (**5a**,**b**). The structures of the compounds studied were confirmed by ^{1}H and ^{13}C NMR and by their characteristic mass spectrometric fragmentations.

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Introduction.

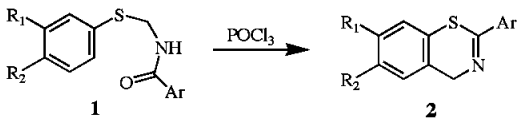
1,3-Benzothiazine derivatives were first described in 1947. However, since numerous biologically active compounds have subsequently been found among these compounds [1-7], research on the methods of synthesising this heterocyclic system has developed intensively during recent decades [2,4,5,7,8,-15]. In earlier work [13,15], we studied the ring-closure reactions of a number of *N*-arylthiomethylaroylamides in the presence of phosphorus oxychloride, leading to 4*H*-1,3-benzothiazines. It was proved that these cyclizations occur through an acid-catalysed intermolecular rearrangement. Some of the substituted 4*H*-1,3-benzothiazines prepared [1] displayed fungicidal activity. On this basis, it seemed logical to prepare and characterise various new, related 4*H*-1,3-benzothiazine derivatives.

Results and Discussion.

4-Methylphenylthioaroylamides (**1a-d**) or 3,4 diethoxyphenylthiomethyl-aroylamides (**1e-g**) were cyclized in acid medium with phosphorus oxychloride to obtain 4*H*-1,3-benzothiazine derivatives (**2a-g**) (Scheme 1).

Scheme 1

The structures of **1a-g** and **2a-g**.



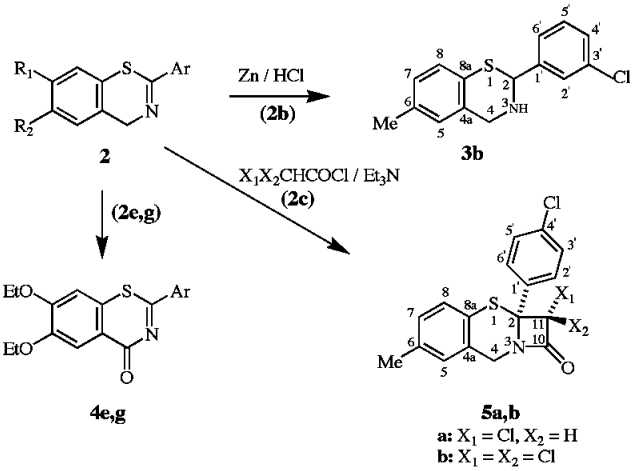
1 **2**

a: R_1 = H, R_2 = Me, Ar = 4-OMe-C_6H_4.
b: R_1 = H, R_2 = Me, Ar = 3-Cl-C_6H_4.
c: R_1 = H, R_2 = Me, Ar = 4-Cl-C_6H_4.
d: R_1 = H, R_2 = Me, Ar = 3,4-$(OMe)_2$-C_6H_3.
e: R_1 = R_2 = OEt, Ar = 4-Cl-C_6H_4.
f: R_1 = R_2 = OEt, Ar = 3,4-$(OMe)_2$-C_6H_3.
g: R_1 = R_2 = OEt, Ar = 2-F-C_6H_4.

Subsequently, certain chemical reactions of the new benzothiazines were investigated. The reduction of **2b** with Zn afforded the 2,3-dihydro derivative (**3b**) (Scheme 2). Potassium permanganate oxidation of **2e**,**g** in acetone solution furnished the corresponding 4-oxo derivatives **4e**,**g** in good yields. Analogously to the cycloaddition reactions of imines with acid chlorides, **2c** reacted with chloroacetyl chloride or dichloroacetyl chloride to give the linearly condensed ß-lactam derivatives **5a**,**b** (Scheme 2).

Scheme 2

Synthetic routes and structures of **3b**, **4e**,**g** and **5a**,**b** including the numbering system of studied compounds.



2 **3b** **4e,g** **5a,b**

a: X_1 = Cl, X_2 = H
b: X_1 = X_2 = Cl

^{1}H and ^{13}C NMR Spectra.

The ^{1}H NMR chemical shifts of **2e-g, 3b, 4e,g** and **5a,b** are shown in Table 3. They are consistent with the proposed structures of the prepared compounds. Only **3b** and **5a,b** exhibit a resolved doublet for the protons on C4 (J_{44} ~ −17 Hz), in agreement with their non-symmetric structures. As expected, **3b** also gives a signal for the proton on C2 (5.64 ppm).

Table 1

Physical and Analytical Data on Compounds **1a-g**.

Compound	Yield %	M.p. °C	Formula M.w.	Analysis (%) Calcd/Found C	H	N	S
1a	91	106-107	$C_{16}H_{17}NO_2S$	66.87	5.96	4.87	11.16
			287.38	66.71	5.87	4.98	11.28
1b	88	111-112	$C_{15}H_{14}ClNOS$	61.74	4.84	4.80	10.99
			291.80	61.85	4.76	4.86	10.84
1c	92	108-109	$C_{15}H_{14}ClNOS$	61.74	4.84	4.80	10.99
			291.80	61.68	4.76	4.73	11.06
1d	84	119-120	$C_{17}H_{19}NO_3S$	64.33	6.03	4.41	10.10
			317.40	64.22	6.11	4.50	10.01
1e	93	131-132	$C_{18}H_{20}ClNO_3S$	59.09	5.51	3.83	8.76
			365.88	59.16	5.42	3.90	8.61
1f	86	140-141	$C_{20}H_{25}NO_5S$	61.36	6.44	3.58	8.19
			391.48	61.43	6.32	3.67	8.07
1g	92	119-120	$C_{18}H_{20}FNO_3S$	61.87	5.77	4.01	9.18
			349.42	61.99	5.66	4.08	9.29

Table 2

Physical and Analytical Data on Compounds **2a-g**, **4e**,**g** and **5a**,**b**

Compound	Yield %	M.p. °C	Formula M.w.	Analysis (%) Calcd/Found C	H	N	S
2a	9.2	123-124	$C_{16}H_{15}NOS$	71.34	5.61	5.20	11.90
			269.36	71.43	5.70	5.09	11.79
2b	8.1	134-135	$C_{15}H_{12}ClNS$	65.80	4.42	5.12	11.71
			273.78	65.69	4.49	5.21	11.60
2c	10.3	137-138	$C_{15}H_{12}ClNS$	65.80	4.42	5.12	11.71
			273.78	65.92	4.37	5.02	11.87
2d	8.7	143-144	$C_{17}H_{17}NO_2S$	68.20	5.72	4.68	10.71
			299.39	68.31	5.83	4.59	10.79
2e	41.4	152-153	$C_{18}H_{18}ClNO_2S$	62.15	5.22	4.03	9.22
			347.86	62.24	5.17	4.11	9.34
2f	36.3	146-147	$C_{20}H_{23}NO_4S$	64.32	6.21	3.75	8.59
			373.47	64.21	6.30	3.68	8.70
2g	38.7	130-131	$C_{18}H_{18}FNO_2S$	62.24	5.47	4.23	9.68
			331.41	62.33	5.38	4.30	9.77
3b	69.0	92- 93	$C_{15}H_{14}ClNS$	65.32	5.12	5.08	11.63
			275.80	65.46	5.03	5.19	11.49
4e	79.1	183-184	$C_{18}H_{16}ClNO_3S$	59.75	4.46	3.87	8.86
			361.84	59.67	4,52	3.80	8.97
4g	74.3	192-193	$C_{18}H_{16}FNO_3S$	62.59	4.67	4.06	9.28
			345.39	62.67	4.58	4.12	9.40
5a	87.2	165-166	$C_{17}H_{13}Cl_2NOS$	58.29	3.74	4.00	9.15
			350.26	58.37	3.62	4.11	9.02
5b	91.3	145-146	$C_{17}H_{12}Cl_3NOS$	53.07	3.14	3.64	8.34
			384.71	53.18	3.07	3.72	8.44

The ^{13}C spectra of the compounds studied were likewise found to correspond to their expected structures (Table 4). Compounds **2g** and **4g** yield typical (and similar) CF coupling patterns, and **3b** and **5a**,**b** furnish the typical signals of CH and CH_2 groups for C2 and C4, respectively. For **4e,g** the C4 chemical shifts are typical for C=O carbons, again as expected.

It is interesting to note that for compounds **2a-2d**, which differ from each other only in respect of the substituent(s) on the aryl ring, the C-2, C-4a, C-8a and C-1' chemical shifts, despite the relatively small ranges, show very good linear correlations to Hammett σ^+ parameters [16] the correlation coefficients being 0.995, 0.989, 0.9997, and 0.974, respectively. This shows that a certain amount of conjugation is exerted also through C-S-C-moiety.

Mass Spectra.

The mass spectra of the compounds studied also nicely confirmed the proposed structures. The stabilities of the molecular ions of all compounds (Table 5) are relatively close to each other, except for **3b**, in which the saturation of the C-N bond makes it appreciably more stable. The fragmentation of all compounds leads first to the base

Scheme 3

Mass spectrometric fragmentation of **2a-g**, **3b**, **4e**,**g** and **5a**,**b**.

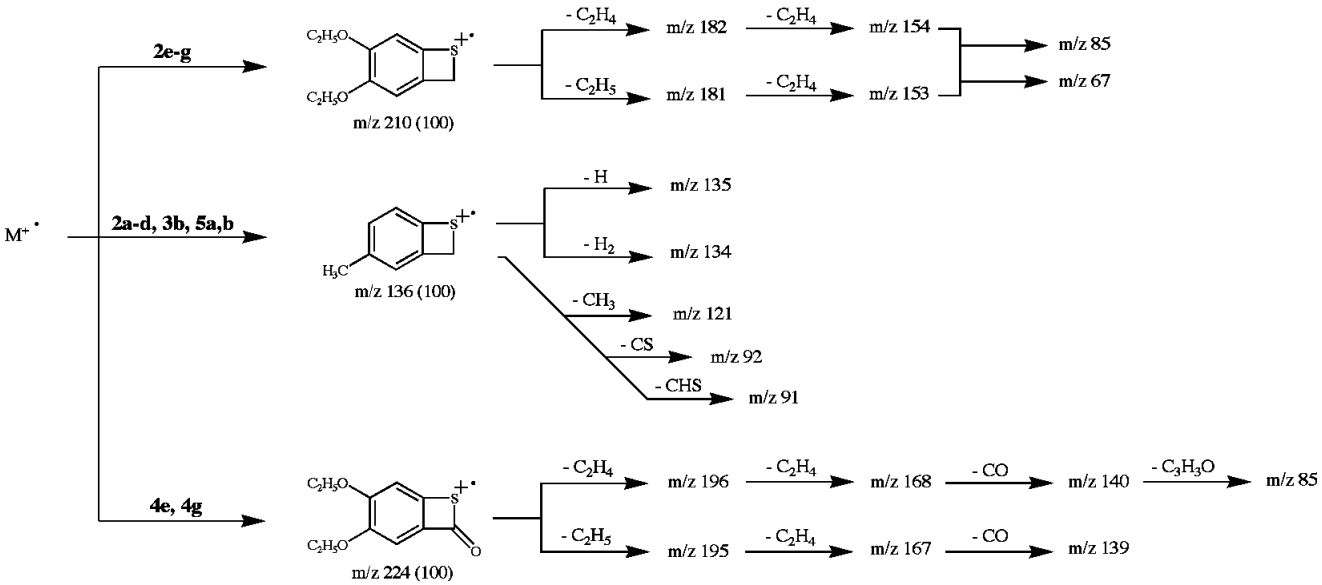


Table 3

^{1}H Chemical Shifts (ppm from TMS) of **2a-g**, **3b**, **4e**,**g** and **5a**,**b**

Compound	H4	H5	H7	H8	CH_3 on C6	H2'	H3'	H4'	H5'	H6'	OR
2a	4.72	7.15	7.10	7.26	2.37	7.95	6.92	-	6.92	7.95	CH_3O 3.86 at C4'
2b	4.75	7.15	7.11	7.25	2.36	7.99	-	7.43	7.34	7.87	-
2c	4.74	7.15	7.11	7.25	2.36	7.93	7.39	-	7.39	7.93	-
2d	4.72	7.13	7.09	7.26	2.35	7.57	-	-	6.87	7.62	CH_3O 3.95 at C3', CH_3O 3.91 at C4'
2e	4.70	6.85	-	6.87	-	7.93	7.39	-	7.39	7.93	CH_2O 4.09 & 4.10, CH_3CH$_2$ 1.46 at C6/7
2f	4.69	6.85	-	6.89	-	7.57	-	-	6.89	7.62	CH_2O 4.09 & 4.10, CH_3CH$_2$ 1.45 at C6/7, CH_3O 3.93 at C3', CH_3O 3.96 at C4'
2g	4.74	6.85	-	6.83	-	-	7.13	7.40	7.15	7.69	CH_2O 4.07 & 4.11, CH_3CH$_2$ 1.45/6 at C6/7
3b[a]	4.13 4.20	6.88	6.96	7.00	2.29	7.51	-	7.30	7.31	7.38	-
4e	-	7.95	-	6.88	-	8.13	7.49	-	7.49	8.13	CH_2O 4.20 & 4.24, CH_3CH$_2$ 1.52/5 at C6/7
4g	-	7.97	-	6.89	-	-	7.22	7.55	7.30	8.18	CH_2O 4.20 & 4.25, CH_3CH$_2$ 1.52/4 at C6/7
5a[b]	4.28 4.94	7.005	6.995	7.10	2.28	7.375	7.355	-	7.355	7.375	-
5b[c]	4.22 4.90	7.06	7.04	7.18	2.31	7.38	7.37	-	7.37	7.38	-

[a] H2 5.64; J_{44} −16.9 Hz; [b] H11 5.11; J_{44} −16.5 Hz; [c] J_{44} −16.1Hz.

Table 4

^{13}C Chemical Shifts (ppm from TMS) of **2a-g**, **3b**, **4e**,**g** and **5a**,**b**

Compound	C2	C4	C4a	C5	C6	C7	C8	C8a	C1'	C2'	C3'	C4'	C5'	C6'	6-CH$_3$
2a[a]	161.3	56.6	131.67	127.5	137.4	128.2	126.4	127.7	127.8	129.4	113.8	162.0	113.8	129.4	21.06
2b	160.7	56.8	130.95	127.6	137.7	128.4	126.4	127.0	138.8	127.8	134.6	131.0	129.7	125.8	21.06
2c	160.8	56.8	131.1	127.6	137.7	128.4	126.4	127.1	135.5	129.0	128.7	137.2	128.7	129.0	21.06
2d[b]	161.4	56.6	131.7	127.5	137.4	128.2	126.3	127.6	129.9	110.0	148.9	151.6	110.3	121.4	21.05
2e[a]	160.9	56.5	123.3	112.2	148.8	148.5	111.6	121.3	135.5	129.0	128.7	137.2	128.7	129.0	-
2f[c]	161.5	56.4	124.0	112.3	148.6	148.4	111.7	121.9	129.9	110.0	148.9	151.6	110.3	121.4	-
2g[d,e]	158.1	56.6	122.7	112.2	148.7	148.5	111.3	121.8	126.2	160.2	116.2	131.7	124.1	129.9	-
3b	64.4	49.4	130.1	127.8	134.4	128.0	127.5	130.0	142.1	127.0	134.6	128.5	130.0	124.9	20.90
4e[f]	170.7	169.0	115.5	111.9	150.7	153.4	107.7	128.2	135.3	128.7	129.3	139.7	129.3	128.7	-
4g[f,g]	168.1	168.6	115.6	111.7	150.8	153.4	107.4	129.3	125.0	160.9	116.7	134.0	124.7	130.3	-
5a[h]	70.9	43.3	129.4	128.9	137.2	129.2	129.6	125.7	135.3	128.4	128.7	135.0	128.7	128.4	21.00
5b[i]	81.8	44.3	132.05	129.0	137.5	129.7	129.9	126.85	136.2	129.0	127.15	135.3	127.15	129.0	21.05

[a] *C*H$_3$O 55.4; [b] 2*C*H$_3$O 55.9; [c] 2*C*H$_3$O 56.0; 2CH$_3$*C*H$_2$O 64.9; 2*C*H$_3$CH$_2$O 14.8. [d] 2CH$_3$*C*H$_2$O 64.9; 2*C*H$_3$CH$_2$O 14.8; [e] $J_{C2,F}$ 3.6 Hz, $J_{C8a,F}$ 2.3 Hz, $J_{C1',F}$ 11.4 Hz, $J_{C2',F}$ 252.9 Hz, $J_{C3',F}$ 21.9 Hz, $J_{C4',F}$ 8.8 Hz, $J_{C5',F}$ 3.6 Hz, $J_{C8a',F}$ 2.3 Hz; [f] CH$_3$**C**H$_2$O 65.1 (C6) & 64.9 (C7); 2**C**H$_3$CH$_2$O 14.5; [g] $J_{C2,F}$ 5.0 Hz, $J_{C8a,F}$ 5.9 Hz, $J_{C1',F}$ 10.5 Hz, $J_{C2',F}$ 255.3 Hz, $J_{C3',F}$ 22.4 Hz, $J_{C4',F}$ 9.1 Hz, $J_{C5',F}$ 3.7 Hz, $J_{C6',F}$ 1.3 Hz; [h] C10 164.3; C11 68.3; [i] C10 163.0; C11 89.7.

peak, that of ion $A^{+\cdot}$, at *m/z* 136 (Scheme 3); for **2a-d**, **3b** and **5a**,**b**, this leads further to the ions $[A\text{-}H]^+$, *m/z* 136, and $[A\text{-}H_2]^{+\cdot}$, *m/z* 135 (Table 5). The ions with *m/z* 121, 92 and 91 correspond to the loss of methyl, CS and CHS, respectively, from $[A\text{-}H]^+$ (Scheme 3). In contrast, **2e-g** and **4e**,**g** (Table 5) lose C_2H_4, C_2H_5, $2xC_2H_4$ and (C_2H_4 + C_2H_5), respectively, from ion $A^{+\cdot}$ (*m/z* 210 for **2e-g** and *m/z* 224 for **4e**,**g**) (Scheme 3). Compounds **4e**,**g** further lose CO from $[A\text{-}2C_2H_4]^{+\cdot}$, *m/z* 168, and $[A\text{-}C_2H_4\text{-}C_2H_5]^+$, *m/z* 167, leading to the ions with *m/z* 140 and 139, respectively (Table 5). Finally, the ions with *m/z* 154/153 (**2e-g**) and 168 (**4e**,**g**) give the ion with *m/z* 85, and the former also the ion with *m/z* 67 (Table 5 and Scheme 3).

EXPERIMENTAL

General Procedure for Preparing **1a-g.**

A solution of 3,4-dimethoxythiophenol (0.1 mol) and the *N*-hydroxymethyl-substituted acid amide in 30 mL of ethanol was treated with 10 mL of a saturated solution of HCl in ethanol. The mixture was kept at room temperature for 3 hours, after which the crystalline product was separated by filtration and recrystallized

Table 5

Electron Ionisation Mass Spectra of **2a-g**, **3b**, **4e**,**g** and **5a**,**b** at 70 eV

Compound	Ion *m/z* (% R. A.)								
	$M^{+\cdot}$	$A^{+\cdot}$	$[A-H]^+$	$[A-H_2]^{+\cdot}$	$C_7H_5S^+$	$C_7H_8^{+\cdot}$		$C_7H_7^+$	
2a	269(31)	136(100)	135(32)	134(7)	121(4)	92(7)		91(14)	
2b	273(22) 275(8)	136(100)	135(34)	134(5)	121(5)	92(8)		91(16)	
2c	273(21) 275(8)	136(100)	135(33)	134(4)	121(4)	92(7)		91(14)	
2d[a]	299(34)	136(100)	135(28)	134(3.5)	121(3)	92(7)		91(10.5)	
3b[b]	275(94.5)	136(100)	135(55)	134(7)	121(8)	92(13)		91(30)	
5a[c]	349(17) 351(12	136(100)	135(30)	134(5)	121(4)	92(6)		91(13)	
5b[d]	383(16) 385(16) 387(6)	136(100)	135(32)	134(4)	121(5)	92(7)		91(15)	
			$[A-C_2H_4]^{+\bullet}$	$[A-C_2H_5]^+$	$[A-2C_2H_4]^{+\bullet}$	$[A-C_2H_4-C_2H_5]^+$		C_3HOS^+	$C_4H_3O^+$
2e	347(19) 349(7)	210(100)	182(14)	181(26)	154(14)	153(63)		85(9)	67(12)
2f	373(24)	210(100)	182(12)	181(23)	154(12)	153(51)		85(6)	67(9)
2g	331(24)	210(100)	182(15)	181(27)	154(15)	153(71)		85(11)	67(14)
							$C_6H_4O_2S^{+\bullet}$	$C_6H_3O_2S^+$	$C_3H_3OS^+$
4e[e]	361(12)	224(100)	196(15)	195(7)	168(21)	167(25)	140(7)[f]	139(4)[g]	85(17)
4g[e]	345(15)	224(100)	196(15.5)	195(8)	168(25)	167(30)	140(6)[f]	139(3.5)[g]	85(14)

[a] $[M-A]^+$: 163(2.5); [b] $[M-CH_3]^+$: 260(6.5); $[M-HS]^+$: 242(14); $[M-C_6H_4Cl]^+$: 164(6); $[M-C_7H_6Cl]^+$: 150(56); $C_7H_6Cl^+$: 125(7); $C_8H_7^+$: 103(6); $C_8H_6^{+\cdot}$: 102(6); $C_7H_5^+$: 89(10); 77(11.5); 65(6); 63(5); 51(6); CHS^+: 45(16); [c] $[M-H]^+$: 350(6), 348(4); $[M-Cl]^+$: 316(11),314(28); $[M-HCl]^{+\cdot}$: 315(7), 313(6); $[M-2Cl]^{+\cdot}$: 279(6); $[M-C_2HOCl]^+$: 273(5); $[M-C_2H_2OCl]$: 272(4); $C_8H_8NS^+$: 150 (6); [d] $[M-Cl]^+$: 352(3), 350(14), 348(20.5); $[M-HCl]^{+\cdot}$: 351(4), 349(13), 347(13); $[M-2Cl]^{+\cdot}$ 315(4), 313(9); $[M-C_6H_5Cl]^+$274(6), 272(15); $C_8H_8NS^+$: 150 (5); [e] $C_5H_3OS^+$: 111(4); [f] $[A-2C_2H_4-CO]^{+\cdot}$; [g]$[A-C_2H_4-C_2H_5-CO]^+$.

from ethanol. The physical constants and analytical data are given in Table 1.

General Procedure for Preparing **2a-g**.

A mixture of **1** (0.1 mol) and phosphorus oxychloride (30 mL) was heated on a boiling water bath for 1 hour. It was then cooled to room temperature and ice was added to decompose the excess phosphorus oxychloride. The solution was neutralized with Na_2CO_3 and extracted with benzene. The extract was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness, and the residue was crystallized from ethanol. The physical constants and analytical and spectral data are given in Tables 2-5.

Preparation of 2-(3-Chlorophenyl)-6-methyl-2,3-dihydro-4*H*-1,3-benzothiazine (**3b**).

2-(3-Chlorophenyl)-6-methyl-4*H*-1,3-benzothiazine (**2b**) (0.54 g, 2 mmol) was dissolved in 20 mL of ethanol, and 1 mL of conc. HCl and 0.3 g of Zn were added to the ice-cooled solution. The mixture was shaken until it became colourless, the excess Zn was immediately removed by filtration, and the filtrate was transferred to ice-cold K_2CO_3 solution. The resulting mixture, containing a precipitate, was extracted with benzene, and the benzene layer was washed with water and dried over anhydrous Na_2SO_4, followed by removal of the solvent by distillation. The residue was crystallized from ethanol, to give 0.38 g (69%) of colourless needles. The physical constants and analytical and spectral data are given in Tables 2-5.

$KMnO_4$ Oxidation of **2e,g**.

$KMnO_4$ (4.24 g) was dissolved in acetone (200 mL) and a solution of **2e** or **2g** (10 mmol) in acetone (50 mL) was added, with stirring and cooling in ice water. Stirring was continued for 3 hours. Thereafter, $CHCl_3$ (100 mL) was added, and the precipitated MnO_2 removed by filtration with suction, and washed with $CHCl_3$. The solvent was evaporated off and the residue was crystallized from ethanol, to give light-yellow crystals of **4e** or **4g**. The physical constants and analytical and spectral data are given in Tables 2-5.

Preparation of **5a,b**.

Compound **2c** (10 mmol) and chloroacetyl chloride or dichloroacetyl chloride (10 mmol) were dissolved in benzene, and triethylamine (10 mmol) was added dropwise, with stirring during 1 hour. The crystalline $Et_3N{\bullet}HCl$ formed was removed by filtration, the benzene solution was evaporated to dryness and the residue was crystallized from ethanol, to yield colourless crystals of **5a** or **5b**. The physical constants and analytical and spectral data are given in Tables 2-5.

^1H and ^{13}C NMR Spectra.

NMR spectra were acquired by using a JEOL JNM-A-500 spectrometer operating at 500.16 MHz for ^1H, and at 125.78 MHz for ^{13}C, or a JEOL JNM-L-400 spectrometer operating at 399.78 MHz for ^1H, and 100.54 MHz for ^{13}C. All spectra were recorded at 25 °C in $CDCl_3$. Proton and carbon spectra were referenced internally to the tetramethylsilane (TMS) signal at 0.00 ppm.

1D proton spectra were acquired with normal single-pulse excitation, 45° flip-angle consisting of 32K data points. 1D carbon spectra were acquired with normal single-pulse excitation, broadband proton decoupling, 45° flip-angle and with spectral widths of 30 kHz consisting of 65K data points and with 0.3–0.5 Hz exponential weighting applied prior to Fourier transformation. 2D het-

eronuclear one-bond correlation experiments were acquired using carbon detected CH-shift correlation with partial homonuclear decoupling in the f1 dimension. Long-range heteronuclear correlation experiments included either carbon detected COLOC or proton detected HMBC with gradient selection. One-bond coupling constant was 145 Hz and the long-range coupling constants were 5−12 Hz in proton-carbon correlation spectra. 2D homonuclear H,H-correlation experiments were acquired using phase-sensitive double quantum filtered COSY. The spectral widths of 2D spectra were optimised from 1D spectra.

Mass Spectra.

The electron ionisation mass spectra (*cf*. Table 5 and Scheme 3) of **2a**-**g**, **3b**, **4e**,**g** and **5a**,**b** were recorded at 70 eV on an MM 7070E mass spectrometer (VG Analytical Ltd, Manchester, UK) equipped with an OPUS data system. The samples were introduced into the mass spectrometer through the solid-inlet system at ambient temperature (~323 K) for low-resolution (R = 1000), accurate mass (peak matching method in HR mode) and metastable (B/E) measurements.

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* Correspondence to: Prof. Kalevi Pihlaja, Department of Chemistry, University of Turku, Vatselankatu 2, FIN-20014 Turku, Finland, email: kpihlaja@utu.fi, phone: 358-(2)-3336767, fax:358-(2)-3336750.

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