Alkaline Hydrolysis of 3-Methyl-2*H*-1,3-benzothiazinium Iodides [1]

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Alkaline hydrolysis of the 3-methyl-2*H*-1,3-benzothiazinium iodide **5a** and of its 4-aryl derivatives **5b,c** in the presence of hexacyanoferrate(III) ion resulted in the formation of 2,2'-diaryloxodiphenyl disulfides **6a-c**. In contrast, the 4-benzyl derivative **5d** underwent hydrogen iodide elimination to give the enamine **7**. Mechanisms are proposed for the reactions.

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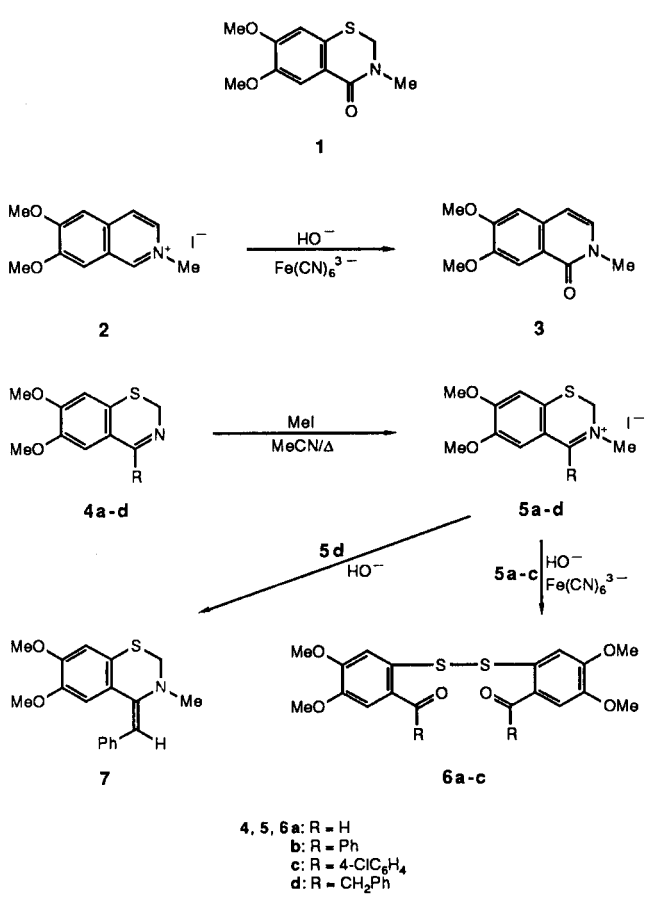
In the course of the syntheses and examination of 1,3-benzothiazine derivatives, we wished to prepare 4-oxo analogs unsubstituted at position 2 (**1**), since only the 2-substituted compounds had been reported [2].

For the synthesis of **1** we used Decker's method, developed for preparation of the 2-methyl-1-isoquinoline **3** [3]; in this procedure the 2-methylisoquinolinium iodide **2** was oxidized with hexacyanoferrate(III) ion (HCF) in the presence of alkali, to give compound **3**.

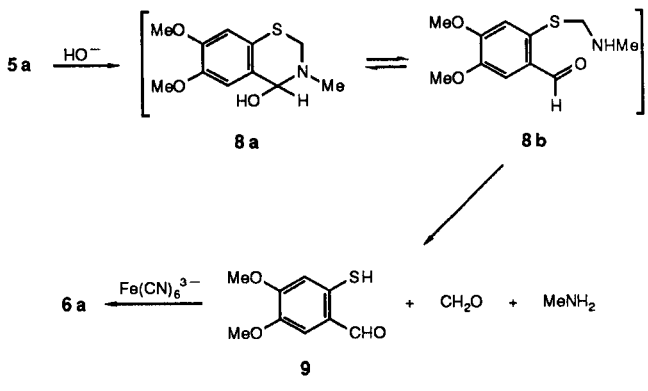
Scheme 1



However, when the quaternary salt **5a**, prepared from 6,7-dimethoxy-2*H*-1,3-benzothiazine (**4a**) and methyl iodide, was treated in aqueous solution with an equimolar amount of alkaline potassium ferricyanide solution, the product was the disulfide derivative **6a**, instead of the expected compound **1** (Scheme 1).

It may be assumed that in this reaction the quaternary base, formed from the quaternary salt **5a** on the action of hydroxide ions, is converted to the pseudobase **8a**. The open formyl tautomer **8b** of the pseudobase can then undergo splitting with the loss of formaldehyde and methylamine, to give 6-mercaptoveratraldehyde (**9**), which is oxidized by the HCF ion to the disulfide **6a** (Scheme 2).

Scheme 2



It is known that the acid hydrolysis of 4-aryl-2*H*-1,3-benzothiazine derivatives also results in the formation of 2-mercaptobenzophenone derivatives [4,5]. Earlier, we studied [6] the alkaline hydrolysis of quaternary 2-aryl-4*H*-1,3-benzothiazines. For the purpose of comparison, we have now carried out the alkaline hydrolysis of the 2*H*-isomers.

The 2*H*-1,3-benzothiazine derivatives **4c,d** [7] were converted with methyl iodide to the methiodides **5c,d**, and the alkaline hydrolysis of these compounds and also that of **5b**, prepared earlier [8], was studied.

Table 1

^{1}H NMR Data (Chemical Shifts in δ, δ_{TMS} = 0 ppm, and Coupling Constants in Hz) of Compounds **5a-d, 6a-c** and **7** at 250 MHz [a]

Compound	CH_2 (2) s (2H)	OCH_3 (6,7) 2 × s (2 × 3H)		NCH_3 s (3H)	ArH-5,8 2 × s (2 × 1H)		ArH(4) 1-3m (4 or 5H) [b]
5a	5.17	3.82	3.95	3.78	7.33	7.50	—
5b	5.63	4.00	3.95	3.58	6.43	7.12	7.6-7.85
5c	5.63	3.95	4.05	3.62	6.42	7.17	7.62 and 7.84 [c]
5d	5.20	3.91	3.94	3.79	7.35	7.64	7.15 [c] and 7.2-7.4
6a	—	3.76	3.84	—	7.29	7.49	—
6b	—	3.65	3.71	—	7.00	7.27	7.51 and 7.64 [c]
6c	—	3.79	3.80	—	6.90	7.37	7.43 and 7.65 [c]
7	4.42	3.78	3.81	2.60	6.81	7.27	7.12, 7.31 [d] and 7.64 [c]

[a] Solvent: DMSO-d_6 (**5a,d, 6a,b** and **7**) or deuteriochloroform (**5b,c** and **6c**); further signals: H-4 (**5a**): 8.99 s (1H), CH_2 (benzyl, **5d**): 5.21 s (2H), CHO (**6a**): 10.03 s (1H), =CH (Pos. 4, **7**): 6.20 s (1H); ir ν C=O band (in potassium bromide, cm^{-1}): 1670 (**6a**), 1640 and 1630 (split bands) (**6b**), 1631 (**6c**). [b] **5b**: m (5H); **5c** and **6c**: AA'BB'-type spectrum 2 × m, (2 × 2H), J (A,B): 8.5 Hz; **5d** and **6b**: 2 × m (2 + 3H); **7**: 3 × m (1 + 2 + 2H). [c] H-2',6'. [d] H-3',5'.

Table 2

^{13}C NMR Chemical Shifts (δ_{TMS} = 0 ppm) of Compounds **5a-d, 6a-c** and **7** at 20 MHz [a]

Compound	C-2	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	NCH_3	OCH_3 (Positions 6,7)		C-1'	C-2',6'	C-3',5'	C-4'
5a	57.7	165.3	133.0	118.8	149.7	158.8	112.2	119.5	48.8	57.9	58.7	—	—	—	—
5b	54.0	170.8	135.3	117.0	147.1	156.3	109.4	120.7	46.5	55.5	56.9	132.3	129.8	128.4	129.6
5c	54.0	169.6	138.7	116.8	147.3	156.5	109.5	120.5	46.5	55.6	56.9	127.9	131.7	128.8	135.6
5d [b]	55.1	175.0	135.7 [c]	116.9	149.6	157.2	112.1	122.2	46.7	58.3	58.6	135.7 [c]	130.9	129.8	129.1
6a	—	191.8 [d]	133.8 [e]	114.6 [f]	150.6	155.5	115.8 [f]	129.9 [e]	—	57.2 [c]		—	—	—	—
6b	—	196.1 [d]	132.8 [e]	114.6 [f]	149.5	153.2	115.3 [f]	131.0 [e]	—	57.3	57.6	138.9	131.3	130.3	134.8 [e]
6c	—	193.8 [d]	131.6 [e]	113.3 [f]	148.1	152.3	113.7 [f]	130.7 [e]	—	56.2	56.4	136.4	131.3	128.9	139.4
7	58.4	145.1	127.3 [e]	112.5 [f]	148.9	150.8	113.7 [f]	124.3 [e]	41.6	57.5	57.6	139.7	130.2	129.9	129.4 [e]

[a] Measuring frequency for **5a**: 63 MHz; Solvent: DMSO-d_6; for **5b,c** and **6c**: deuteriochloroform. [b] Assignments were proved by DEPT measurement. [c] Two overlapping lines. [d] Aldehyde (**6a**) or ketone (**6b,c**) carbonyl. [e,f] Assignments may also be interchanged. [g] =CH (Position 4): 111.3.

Table 3

Physical and Analytical Data for Compounds **5a,c,d, 6a-c** and **7**

Compound	Yield (%)	Mp (°C) solvent	Molecular formula MW	Analysis (Calculated/Found) C (%)	H (%)	N (%)	S (%)
5a	85	183-184	$C_{11}H_{14}INO_2S$	37.02	4.02	3.99	—
		methyl cyanide	351.20	37.44	3.97	3.70	—
5c	94	133-134	$C_{17}H_{17}ClINO_2S$	44.22	3.71	3.03	—
		methyl cyanide	461.75	44.06	3.96	3.25	—
5d	65	158-159	$C_{18}H_{20}INO_2S$	48.99	4.57	3.17	—
		methyl cyanide-diethyl ether	441.32	49.06	4.72	3.30	—
6a	40	182-183	$C_{18}H_{18}O_6S_2$	54.81	4.60	—	16.25
		methanol	394.45	54.74	4.67	—	16.40
6b	82	147-148	$C_{30}H_{26}O_6S_2$	65.91	4.80	—	11.73
		ethyl-acetate	546.64	66.09	4.88	—	12.03
6c	85	187-188	$C_{30}H_{24}Cl_2O_6S_2$	58.53	3.93	—	10.42
		dioxane-ethanol	615.53	58.41	3.82	—	10.70
7	69	153-154	$C_{18}H_{19}NO_2S$	68.98	6.11	4.47	10.23
		ethyl acetate	313.40	69.13	6.32	4.52	10.40

In light of the experience obtained in the hydrolysis of **4a**, the reaction was performed in the presence of HCF ions to avoid other, undesired transformations of the mercapto derivatives. The quaternary 4-aryl compounds gave **6b,c** in high yields, formed analogously to **6a**. However, the action of hydroxide ions on the 4-benzyl derivative **5d** resulted in hydrogen iodide elimination and the product was the enamine derivative **7**.

The alkaline hydrolysis of the quaternary salts **5a-c** in the presence of HCF ions, and also the alkaline hydrolysis of **5d**, are new reactions of 2*H*-1,3-benzothiazines. The structures of the products were confirmed by ir, ^{1}H and ^{13}C nmr spectroscopy (Tables 1 and 2).

Of the spectral data relating to **5b,c**, interest is attached to the very large upfield shift (0.9 ppm) of the singlet due to H-5, as compared with the values measured for the analogs **5a,d**. A similar but small diamagnetic shift (0.2 ppm) was observed in the *N*-methyl signal, indicating that in the preferred conformation the 4-aryl group is perpendicular to the fused skeleton. In this conformation, increased shielding of H-5 and the *N*-methyl group, situated "above" and "below" the plane of the C-4 benzene ring, is caused due to the anisotropic effect of the π-electron sextet [9a]. This arrangement can also be expected, owing to the strong steric hindrance that would arise between the *N*-methyl group and the C-4 aryl group if they were coplanar. The very high shift difference can not be solvent effect. The ^{1}H nmr spectra of **5a,d** were recorded in dimethyl-d_6 sulfoxide, and those of **5b,c** in chloroform-d. The analogous shifts for **6a,b** in dimethyl-d_6 sulfoxide were only 0.4 and 0.1 ppm greater, respectively, than the shift observed for **6c** in chloroform-d.

In the ^{13}C nmr spectrum of **5a-d**, the downfield shift of the C-7 line, as compared with one of the similar C-6, is worthy of note. This can be explained by the polarization of the π-electron system by the elecron-attracting substituent at C-4a, since the chemical shift is inversely proportional to the electron density around the carbon [9b]. The electron deficiency around C-7 is the greatest in **5a-d**, owing to the effect of the $C=N^+$ group (the shift difference of C-6 and C-7 is about 9 ppm). The electron deficit is also considerable (about 4.5 ppm) for the carbonyl derivatives **6a-c**, whereas in **7** the downfield shift caused by the conjugated C=C bond, is only to 2 ppm.

EXPERIMENTAL

Melting points are uncorrected.

The ir spectra were run in potassium bromide discs on a Bruker IFS-113v FT spectrometer equipped with an Aspect 2000 computer. The ^{1}H and ^{13}C nmr spectra were recorded at room temperature in 5 mm tubes, on Bruker WM-250 and WP-80 SY FT spectrometers controlled by an Aspect 2000 computer, at 250.13 (^{1}H) and 20.14 (^{13}C) MHz, respectively, with the deuterium signal of the solvent as the lock and TMS as internal standard.

DEPT [10] spectra were run in a standard way [11], using only the $\theta = 135°$ pulse to separate CH/CH_3 and CH_2 lines phased "up and down", respectively.

General Procedure for Synthesis of Compounds **5a,c,d**.

Compound **4a,c,d** (10 mmoles) was dissolved in acetonitrile (20 ml). Methyl iodide (20 mmoles) was added, and the mixture was refluxed for 2 hours. After evaporation of the solvent, the residue was crystallized (*cf.* Table 3).

General Procedure for Synthesis of Compounds **6a-c** and **7**.

Compounds **5a-d** (2 mmoles) was dissolved in water (40 ml) and, with stirring, a solution of sodium hydroxide (2 mmoles) and potassium hexacyanoferrate(III) (2 mmoles) in water (15 ml) was added in small portions. Stirring was continued for 1 hour. The mixture was then extracted with benzene, the extract was dried over sodium sulfate, the solvent was evaporated off, and the residue was crystallized (*cf.* Table 3).

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REFERENCES AND NOTES

[1] Saturated Heterocycles, Part **154**, Part **153**: Gy. Dombi, S. Szalma, J. Szabó, and G. Bernáth, *Monatsh Chem.*, accepted for publication.

[2] R. C. Moreau and E. Dolacous, *Bull. Soc. Chim. France*, 502 (1962).

[3] H. Decker, *J. Prakt Chem.*, **47**, 37 (1983).

[4] J. Szabó, L. Fodor, I. Varga and P. Sohár, *Acta Chim. Acad. Sci. Hung.*, **88**, 149 (1976).

[5] P. Gruber, L. Müller and W. Steglich, *Chem. Ber.*, **106**, 2863 (1973).

[6] J. Szabó, I. Varga, E. Vinkler and É Bartos, *Acta Chim. Acad. Sci. Hung.*, **70**, 71 (1971).

[7] J. Szabó, L. Fodor, I. Varga, E. Vinkler and P. Sohár, *Acta Chim. Acad. Sci. Hung.*, **92**, 317 (1977).

[8] A. Kálmán, Gy. Argay, P. Sohár, J. Szabó, L. Fodor and G. Bernáth, *J. Mol. Struct.*, **145**, 341 (1986).

[9] P. Sohár, "Nuclear Magnetic Resonance Spectroscopy", CRC Press, Boca Raton, Florida, 1983; [a] Vol **1**, pp 35-38; [b] Vol **2**, pp 152-153.

[10] D. T. Pegg, D. M. Doddrell and M. R. Bendall, *J. Chem. Phys.*, **77**, 2745 (1982).

[11] M. R. Bendall, D. M. Doddrell, D. T. Pegg and W. E. Hull, "High Resolution Multiplets NMR Spectrum", Editing and DEPT. Bruker, Karlsruhe, 1982.