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Synthesis of 4-Thia Analogues of Isoquinoline Alkaloids [1]

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Summary. (±)-4-Thiacarnegin (**3**) was synthesized by reaction of 6,7-dimethoxy-3-methyl-2*H*-1,3-benzothiazinium iodide (**2**) with methyl magnesium iodide, thereby opening a new synthetic route to 4-substituted dihydro-2*H*-1,3-benzothiazines. Compound **3** was also obtained by reduction of 6,7-dimethoxy-3,4-dimethyl-2*H*-1,3-benzothiazinium iodide (**5**). In a similar way, reduction of the quaternary salts **9a–c** afforded the (±)-4-thia analogues of cryptostilin-I, -II and -III (**10a–c**). The isomers of the former compounds (**12a–c**) were also synthesized by reduction of the 4*H*-1,3-benzothiazinium salts **11a–c**.

Keywords. 2*H*-1,3-Benzothiazines; 3,4-Dihydro-2*H*-1,3-benzothiazines; 4*H*-1,3-Benzothiazines.

Synthese von 4-Thiaanalogen von Alkaloiden mit Isochinolingerüst

Zusammenfassung. Aus 6,7-Dimethoxy-3-methyl-2*H*-1,3-benzothiaziniumjodid (**2**) wurde mit Methylmagnesiumjodid (±)-Thiacarnegin (**3**) dargestellt. Diese Reaktion bietet ein neues Verfahren für die Synthese von 4-substituierten Dihydro-2*H*-1,3-benzothiazinen. **3** wurde auch durch Reduktion von 6,7-Dimethoxy-3,4-dimethyl-2*H*-1,3-benzothiaziniumjodid (**5**) erhalten. Die Reduktion der quartären Ammoniumsalze **9a–c** ergab ebenfalls die Cryptostillin I-, II-, III-(±)-4-thiaanalogen Verbindungen (**10a–c**). Reduktion der 4*H*-1,3-Benzothiazinium-Salze **11a–c** lieferte die entsprechenden Isomeren **12a–c** der obengenannten Verbindungen.

Introduction

In our work on the preparation of thia analogues of isoquinoline alkaloids, we have previously synthesized the 4-thia analogue of 3,4-dihydropapaverine [2]. Since the 2*H*-1,3-benzothiazine derivatives are structurally related to the biologically active 3,4-dihydroisoquinolines, it seemed to be promising to synthesize 4-thia analogues of other natural isoquinoline alkaloids. In the present work we report the syntheses of 4-thiacarnegin and 4-thia analogues of the isoquinoline alkaloids of *Cryptostilis fulva,* cryptostilin-I, -II and -III [3, 4]. These syntheses represent a new route to 3,4-dihydro-1,3-benzothiazines.

Results and Discussion

Syntheses

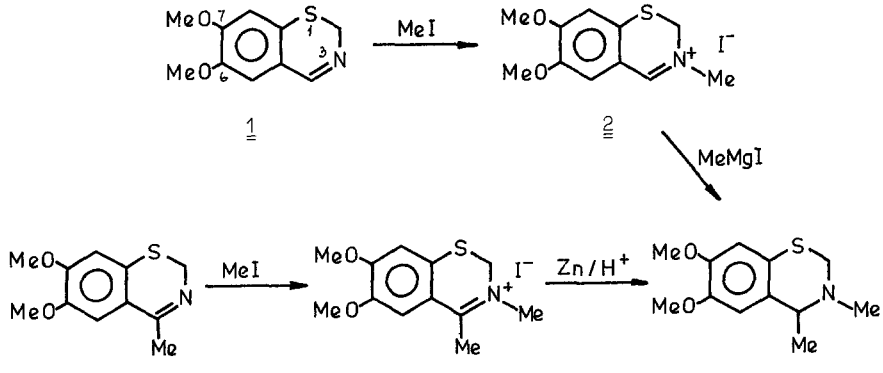
(±)-4-Thiacarnegin (**3**) was synthesized by two ways: The methoiodide **2**, obtained by quaternization of 6,7-dimethoxy-2*H*-1,3-benzothiazine with methyl iodide, reacted with methyl magnesium iodide to give the target compound **3**. Compound **3** was also synthesized by zinc/acid reduction of the quaternary compound **5**, obtained by quaternization of 6,7-dimethoxy-4-methyl-2*H*-1,3-benzothiazine (**4**) [2] with methyl iodide (Scheme 1).

The starting material for the synthesis of 4-thia analogues of cryptostilins, the hitherto unknown carboxamide thioether **6c**, was synthesized by our earlier method [5] *via* acid-catalysed condensation of 3,4-dimethoxythiophenol and the corresponding *N*-(hydroxymethyl)-carboxamide.

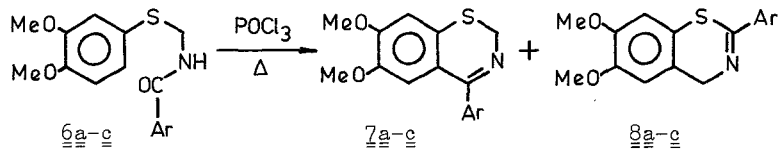
The phosphoryl chloride ring closure of carboxamide thioethers **6a–c** furnished 2*H*- and 4*H*-1,3-benzothiazine derivatives (**7a–c** and **8a–c**). Of these compounds we have already synthesized **7b** and **8a, b** on another route [6]. The separation of the isomers was easier by this method than with the previous one [7]; therefore the preparation of these compounds is included in the present paper (Scheme 2).

Through quaternization of the 2*H*-1,3-benzothiazine derivatives **7a–c** with methyl iodide and reduction of the resulting quaternary salts with zinc/hydrochloric acid, the desired (±)-4-thiacryptostilin-I, -II and -III (**10a–c**) were obtained.

The conformations of 4-aryl-3-methyl-3,4-dihydro-2*H*-1,3-benzothiazines of type **10** were earlier studied by NMR and X-ray methods [8]. In a continuation of these investigations, the 2-aryl analogues of type **12** were synthesized. The methoiodides **11a–c** were prepared from compounds **8a–c**. Reduction of **11a–c** gave the 2-aryl derivatives **12a–c** (Scheme 3).

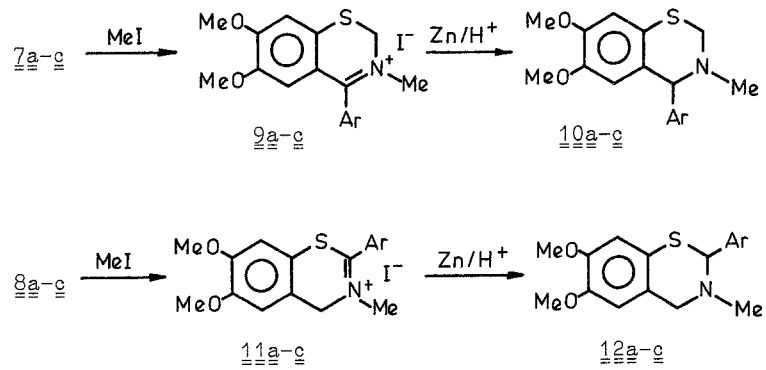


Scheme 1



a: Ar = 3,4-$(OCH_2O)C_6H_3$; b: Ar = 3,4-$(MeO)_2C_6H_3$;
c: Ar = 3,4,5-$(MeO)_3C_6H_2$

Scheme 2



a: Ar = 3,4-$(OCH_2O)C_6H_3$; b: Ar = 3,4-$(MeO)_2C_6H_3$;
c: Ar = 3,4,5-$(MeO)_3C_6H_2$

Scheme 3

The structures of all new compounds were elucidated by ^1H and ^{13}CNMR spectra (Tables 1 and 2).

Spectroscopic Studies

Since the interpretation of the spectra was straight-forward and gave unambiguous proofs for the structures, we restrict our discussion only to the more important points.

Owing to the planar thiazine ring, the methylene protons of the ring in compounds **2**, **7a**, **c**, **8c**, **9a**, **c** and **11a**, **c** are chemically equivalent in the ^1HNMR spectra. Their signals appear as singlets, whereas those of compounds **10a–c** and **12a–c** appear as AB-multiplets.

In the compounds **9** and **10**, the *N*-methyl signals of the quaternary compounds are shifted downfield by more than 1 ppm relative to those of the corresponding saturated bases. For compounds of type **2**, and particularly type **11**, where the arylthioimino moiety is also involved in the delocalized electron system, this difference is even more pronounced: in the series **11** the chemical shift is increased by more than 1.7 ppm as compared to the analogues **12**.

The shielding of protons H-5 and H-8 in compounds **8c**, **10a–c** and **12a–c** does not differ significantly, whereas in **9a–c** the quaternary arylimmonium moiety produces significant deshielding around H-5. The analogous effect of the arylimmonium group on H-8 in compounds **11a–c** results in an even more pronounced downfield shift of the H-8 signal.

With regard to the ^{13}CNMR data it is noteworthy that in compound **8c** the signal of the $-S-C=N$ moiety appears at 161.3 ppm, in the shift region of carboxamides, indicating the highly decreased electron density around C-2.

A similarly downfield shifted signal ($\delta \approx 167$ ppm) characterizes C-4 of the conjugated imino group in compounds **7a–c**. The further decrease in electron density due to quaternization manifests itself in a further downfield shift of about 4 ppm: in the spectra of **9a**, **c** this signal appears at around 171 ppm. The corresponding shift of the thioimmonium moiety is still larger, and the C-2 signal of compounds **11a**, **c** appears at 180.6 ppm.

Table 1. ^{1}H nmr data (chemical shifts in δ, $\delta_{TMS} = 0$ ppm, coupling constants in Hz) on compounds **2**, **3**, **7a**, **c**, **8c**, **9a**, **c**, **10a–c**, **11a–c** and **12a–c** in $CDCl_3$ solution at 250 MHz[a]

Compound	O*Me* (6, 7) 2 × s (2 × 3 H)		N*Me* s (3 H)	CH_2 (2/4) s (2 H)[b]		CH (4/2) s (1 H)	*Ar*H-5,8 2 × s (2 × 1 H)		OCH_2/OCH_3 (4′) s (2/3 H)	OCH_3 (3′, 5′) s (6 H)
2	3.87[c]		4.00	5.27		9.20	7.60	7.38	–	–
3	3.83[c]		2.44	4.10	4.90	3.57[d]	6.53[c]		1.42[f]	–
7a	3.74	3.94	–	4.65		–	6.85	6.90	6.01	–
7c	3.75	3.96	–	4.69		–	6.88	6.92	3.90	3.86
8c	3.89[c]	3.94[e]	–	4.72		–	6.85	6.89	3.94[e]	3.89[c]
9a	3.98	4.04	3.68	5.51		–	7.07	6.59	6.20	–
9c	3.98[c]	4.05	3.66	5.53		–	7.07	6.57	3.98[c]	3.94
10a	3.76	3.87	2.60	3.88	4.53	4.66	6.63	6.70[c]	5.93	–
10b	3.75	3.86	2.60	3.88	4.52	4.71	6.50[c]	6.64	3.83	3.84[g]
10c	3.78[c]	3.89[h]	2.61	3.90	4.55	4.69	6.51	6.65	3.83[h]	3.78[c]
11a	3.93	4.00	4.13	5.56		–	6.97	7.49	6.16	–
11b	3.98[h]	4.05	4.12	5.50		–	7.07	7.46	3.99[h]	3.98[g, h]
11c	3.94	4.00[h]	4.13	5.61		–	7.02	7.47	3.99[h]	3.97
12a	3.82	3.86	2.38	3.80	4.04	5.06	6.52	6.61	5.92	–
12b	3.83[h]	3.86[h]	2.38	3.82	4.10	5.74	6.53	6.63	3.88[h]	3.90[g, h]
12c	3.84[h]	3.85[c, h]	2.39	~3.85[c]	4.11	5.73	6.54	6.63	3.87[h]	3.88[h]

[a] In the case of **2**, in *DMSO-d_6* solution at 80 MHz. Signals of the aromatic hydrogens in the aryl group (pos. 2/4): *Ar*H-2′, d ($J \cong 2$ Hz, 1 H): 7.08 (**7a**), 7.29[e] (**9a**), 6.47 (**10a**), 6.85 (**10b**), 7.56 (**11a**), 7.81 (**11b**), 7.06[c] (**12a**), 7.10[c] (**12b**); *Ar*H-2′,6′, s (2 H): 6.78 (**7c**), 7.28 (**8c**), 7.12 (**9c**), 6.38 (**10c**), 7.42 (**11c**), 6.84 (**12c**); *Ar*H-5′, d ($J \cong 8$ Hz, 1 H): 6.83 (**7a**), 7.02 (**9a**), 6.72[c] (**10a**), 6.74 (**10b**), 7.03 (**11a**), 7.05 (**11b**), 6.78 (**12a**), 6.84 (**12b**); *Ar*H-6′, dd (1 H): 7.03 (**7a**), ~ 7.32[e] (**9a**), 6.55 (**10a**), 6.48[c] (**10b**), 7.75 (**11a**), 7.66 (**11b**), 7.04[c] (**12a**), 7.08[c] (**12b**)

[b] AB-type multiplet (2 × d, 2 × 1 H) for compounds **3**, **10a–c** and **12a–c**, J(A, B): 12.1 ± 0.1 Hz (**3**, **10a–c**) and 16.5 Hz (**12a–c**)

[c, e] Two overlapping signals

[d] qa

[f] Methyl group (pos. 4), d ($J = 7$ Hz)

[g] Methoxy group (pos. 3′), (3 H)

[h] Reversed assignments are also possible

Table 2. ^{13}C nmr chemical shifts ($\delta_{TMS} = 0$ ppm) of compounds **2**, **3**, **7a**, **c**, **8c**, **9a**, **c**, **10a–c**, **11b**, **c** and **12a–c** in $CDCl_3$ solution at 20 MHz[a]

Compound	C-2	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	OCH_3 (6, 7)		NCH_3	C-1′	C-2′	C-6′	C-3′	C-5′	C-4′
2	49.7[b]	163.5	131.8	117.6	148.3	157.6	110.3	118.0	56.5	57.1	47.4[b]	–	–	–	–	–	–
3	51.6	57.7	124.5	113.1	146.5[b]	148.3[b]	110.7	122.6	55.9	56.3	40.3	–	–	–	–	–	–
7a	49.1	167.0	133.3	114.3	146.8	151.7	110.6	121.5	56.1	56.3	–	131.2	109.8	124.0	147.6	107.6	149.1
7b	49.1	167.5	134.3	114.4	146.9	152.0	110.8	121.5	56.3	56.5[c]	–	131.5	107.6		153.1		140.4
8c	161.3	56.5[d]	123.8[b]	110.9[e]	149.2[f]	149.5[f]	110.4[e]	122.1[b]	56.5[d]		–	132.5	105.8		153.3		141.4
9a	55.2	171.0	136.3	118.3	148.1[b]	157.1	111.3	121.8	56.6	57.2	47.2	127.6	109.9[e]	123.6	148.5[b]	109.0[e]	152.1
9c	54.9	171.6	136.0	118.5	148.2	157.3	109.9	121.6	56.6	57.2	47.6	124.9	109.4		153.8		142.4
10a	51.3	66.1	124.3	114.4	146.4	148.7	110.3	119.9	55.8	56.1	40.9	136.7	109.3	122.4	147.7[b]	107.6	146.7[b]
10b	47.8	67.0	123.1	113.9	147.9[b]	150.2[b]	109.1	118.7	55.6	55.9[c]	39.0	126.3	111.1	119.7	149.8[b]	113.7	149.3[b]
10c	51.6	66.4	124.4	114.5	146.3	148.7	110.3	119.8	55.8	56.1[c]	40.9	137.7	106.8		153.0		138.7
11b	180.6	60.1	120.8[b]	111.7	150.3[e]	151.4[e]	111.6[f]	117.0	56.3	56.7	48.3	121.2[b]	108.7	126.0	149.8[e]	114.2[f]	155.2
11c	180.7	60.0	120.4	111.6	150.2[e]	151.4[e]	108.5	116.4	56.6	56.8	48.5	123.1	109.2		153.5		143.9
12a	70.8	54.7	123.6[b]	112.1	146.6[e]	148.2[e]	110.4	119.4	55.8	56.0	37.2	133.3	108.4	121.3[b]	147.5[e]	107.6	147.1[e]
12b	71.0	55.1	123.9[b]	112.2	146.7[e]	148.3[e]	110.5[f]	119.6	55.9[g]	56.1	37.1	132.0	111.2[f]	120.4[b]	149.0[c,e]	111.9[f]	149.0[c,e]
12c	71.6	55.5	123.9	112.4	147.0[b]	148.6[b]	110.8	119.8	56.1	56.4[c]	37.5	134.9	106.0		153.3		138.4

[a] In *DMSO-d_6* solution for **2**, and at 63 MHz for **9c** and **11b**. In the case of **10b**, the data measured for the HCl salt are given. Further signals: CH_3 (pos. 4): 22.7 (**3**); OCH_2O (aryl): 101.3 (**7a**), 102.6 (**9a**), 100.8 (**10a**), 100.9 (**12a**), OCH_3 (aryl), pos. 3′,4′: 55.9[c], 56.2 (**10b**), 56.9, 57.6 (**11b**), 55.9[g] (**12b**), pos. 3′,5′: 56.5[c] (**7c**), 56.5[d] (**8c**), 57.7 (**9c**), 56.1[c] (**10c**), 57.2 (**11c**), 56.4[c] (**12c**); pos. 4′: 60.9 (**7c**, **8c**), 61.0 (**9c**), 60.5 (**10c**), 60.7 (**11c**, **12c**)

[b,e,f] Reversed assignments may also be possible

[c,d,g] Two, four, three overlapping lines

In the case of **7 a–c** the electron density-decreasing effect of the conjugation is responsible for the downfield shifts of the C-4 and C-7 signals. This is further increased in the quaternary analogues **2** and **9 a, c**, where the C-5 signal is also shifted downfield.

In analogy to the ^{1}H NMR data, in the quaternary compounds **2**, **9 a, c** and **11 b, c** the carbon signals of the *N*-methyl group exhibit considerably higher chemical shifts (47–48.5 ppm) than those of the basic counterparts (37–41 ppm).

Experimental

The NMR spectra were recorded in $CDCl_3$ or *DMSO-d_6* solution in 5 or 10 mm tubes at room temperature on Bruker WM-250 or WP-80-SY FT-spectrometers controlled by an Aspect 2000 computer at 250 or 80 (^{1}H) and at 63 or 20 MHz (^{13}C), respectively, with the deuterium signal of the solvent as the lock and *TMS* as internal standard. Lorentzian exponential multiplication for signal-to-noise enhancement was applied; line width: 0.7 or 0.5 (^{1}H) and 22 or 1 Hz (^{13}C). The most important measuring parameters of the spectra were as follows: ^{1}H NMR: sweep width 5 or 0.9 kHz, pulse width 1 μs (~ 20° flip angle), acquisition time 1.64 or 4.56 s, number of scans 8, 16 or 32, computer memory 16 or 8 K.

^{13}C NMR: sweep width, 15 or 5 kHz, pulse width 7.5 or 3.5 μs (~ 30° flip angle), computer memory 32, or 16 K, acquisition time 0.5 or 1.64 s, number of scans: 1–32 K, complete proton noise decoupling with ~ 1 or ~ 3 W power, repetition rate 2 s.

The melting points are uncorrected.

6,7-Dimethoxy-3-methyl-2H-1,3-benzothiazinium Iodide (**2**)

Add 2 ml of methyl iodide to a solution of 2.45 g (10 mmol) of 6,7-dimethoxy-2*H*-1,3-benzothiazine in 10 ml of acetonitrile and reflux for 1 h. Filter off the precipitated yellow crystals (2.50 g, 71.2%). Crystallized from acetonitrile, m.p. 191–192°C (dec.).

Anal. calcd. for $C_{11}H_{14}INO_2S$: C 37.62, H 4.02, N 3.99. Found C 37.90, H 4.28, N 3.96.

(±)-6,7-Dimethoxy-3,4-dimethyl-2H-1,3-benzothiazine (**3**)

Add methyl magnesium iodide prepared from 0.71 g (5 mmol) of methyl iodide in 10 ml of ether to a suspension of 1.76 g (5 mmol) of compound **2** in 30 ml of ether under constant stirring. Continue stirring for an additional 30 min, then add 20 ml of water, extract with ether, dry (Na_2SO_4) and evaporate to dryness. The residue is dissolved in 5 ml of ethanol, and the picrate is obtained with saturated ethanolic picric acid solution. Yellow crystals from ethanol, m.p. 182–183°C (dec.).

Anal. calcd. for $C_{18}H_{20}N_4O_9S$: C 46.15, H 4.30, N 11.36. Found C 45.45, H 4.43, N 11.78.

The base liberated from the crude picrate (0.45 g; 37.6%) is purified by chromatography on a preparative silica gel plate, using benzene – ethanol (9 : 1) as developing mixture. A pale-yellow oil is obtained.

Anal. calcd. for $C_{12}H_{17}NO_2S$: C 60.22, H 7.16, N 5.85. Found C 60.54, H 7.39, N 5.74.

6,7-Dimethoxy-3,4-dimethyl-2H-1,3-benzothiazinium Iodide (**5**)

Add 1 ml of methyl iodide to a solution of 1.12 g (5 mmol) of 6,7-dimethoxy-4-methyl-2*H*-1,3-benzothiazine (**4**) in 10 ml of acetonitrile, and reflux for 1 h. Evaporate the reaction mixture to dryness, dissolve the residue in 2 ml of chloroform, then add 80 ml of ether in portions to precipitate the product (1.14 g; 62.5%), m.p. 162–164°C (dec.).

Anal. calcd. for $C_{12}H_{16}INO_2S$: C 39.47, H 4.41, N 3.84. Found C 38.95, H 4.72, N 4.00.

Table 3. Physical and analytical data on compounds **7a–c**, **8a–c**, **9a**, **c**, **10a–c**, **11a–c** and **12a–c**

Compound	Yield %	M.p. °C	Formula	Mol. wt.	Analysis %, Calculated/Found					
					C		H		N	
7a	1.7	186–187	$C_{17}H_{15}NO_4S$	329.36	61.99	61.67	4.59	4.79	4.25	4.06
7b[a]	1.7	152–153	$C_{18}H_{18}NO_4S$	344.39	62.77	62.80	5.27	5.40	4.07	4.17
7c	3.1	190–191	$C_{19}H_{21}NO_5S$	375.43	60.78	61.00	5.64	5.75	3.73	3.90
8a[a]	36	174–176	$C_{17}H_{15}NO_4S$	329.36	61.99	61.70	4.59	4.65	4.25	4.42
8b[a]	39.7	133–134	$C_{18}H_{18}NO_4S$	344.39	62.77	62.88	5.27	5.35	4.07	4.30
8c	45	141–142	$C_{19}H_{21}NO_5S$	375.43	60.78	60.92	5.64	5.80	3.73	3.85
9a	93	186–188[b]	$C_{18}H_{18}INO_4S$	471.30	45.87	46.14	3.85	4.09	2.97	3.15
9c	88.3	189–190[b]	$C_{20}H_{24}INO_5S$	517.37	46.43	46.18	4.68	4.88	2.71	2.80
10a	77.3	137–138	$C_{18}H_{19}NO_4S$	345.40	62.59	62.70	5.54	5.57	4.06	4.24
10b	52	100–103	$C_{19}H_{23}NO_4S$	361.44	63.13	62.84	6.41	6.50	3.88	4.10
10c	97	91– 92	$C_{20}H_{25}NO_5S$	391.47	61.36	61.70	6.44	6.64	3.58	3.72
11a	83.9	214–215[b]	$C_{18}H_{18}INO_4S$	471.30	45.87	46.10	3.85	4.15	2.97	3.20
11b	86.3	218–219[b]	$C_{19}H_{22}INO_4S$	487.35	46.82	46.90	4.55	4.75	2.87	3.10
11c	70	200–202[b]	$C_{20}H_{24}INO_5S$	517.37	46.43	46.38	4.68	4.97	2.71	2.55
12a	61.6	132–133	$C_{18}H_{19}NO_4S$	345.40	62.59	62.30	5.54	5.81	4.06	3.96
12b	54	153–154	$C_{19}H_{23}NO_4S$	361.44	63.13	62.95	6.41	6.63	3.88	3.79
12c	57.8	143–144	$C_{20}H_{25}NO_5S$	391.47	61.36	61.39	6.44	6.62	3.58	3.70

[a] All physical and chemical properties are identical with those of the described compounds [6]

[b] With decomposition

Preparation of (±)-6,7-Dimethoxy-3,4-dimethyl-2H-1,3-benzothiazine (**3**) *From Compound* **5**

Suspend 1.83 g (5 mmol) of **5** in 40 ml of ethanol, then add 10 ml of 10% hydrochloric acid under stirring and cooling in an ice–water bath, then 1 g of zinc powder, and continue stirring until decolouring of the reaction mixture (ca. 2 min). Then add immediately an aqueous solution of sodium carbonate in excess to make the solution alkaline and extract with benzene. Dry the benzene solution (Na_2SO_4), evaporate, dissolve the residue in ethanol and form its picrate salt (0.43 g; 18.0%). Purify the base liberated from the picrate salt by chromatography on a silica gel plate to obtain a pale-yellow oil. Its picrate salt is crystallized from ethanol to give yellow crystals, m.p. 182–183°C, identical with **5** prepared by another route [6].

N-(3,4-Dimethoxyphenylthiomethyl)-3',4',5'-trimethoxybenzamide (**6 a**)

Dissolve 17 g (100 mmol) of 3,4-dimethoxythiophenol and 24.12 g (100 mmol) of *N*-hydroxymethyl-3,4,5-trimethoxybenzamide in 50 ml of ethanol, add 20 ml of saturated ethanolic hydrochloric acid, and allow to stand for 1 h. Filter off the precipitated crystals (33.8 g; 86.0%), and crystallize from ethanol to obtain colourless crystals, m.p. 107–109°C.

Anal. calcd. for $C_{19}H_{23}NO_6S$: C 58.00, H 5.89, N 3.56. Found C 58.04, H 6.20, N 3.68.

Procedure for Preparation of 1,3-Benzothiazine Derivatives **7 a–c** *and* **8 a–c**

Heat 50 mmol of compound **6 a–c** with 20 ml of phosphoryl chloride for 1 h on a hot water bath, then decompose the reaction mixture with ice-water, neutralize with sodium carbonate and extract with benzene. Stir the benzene phase with 100 ml of 10% hydrochloric acid for 10 min at ambient temperature then allow to stand for 1 h. Filter off the precipitated yellow crystals, wash with benzene and with 10% hydrochloric acid, then suspend in water, and neutralize with sodium carbonate and extract with benzene. After drying (Na_2SO_4) and evaporation, recrystallize the residue from ethanol. Compounds **8 a–c** are colourless crystals.

Heat the hydrochloric acid phase on a hot water bath for 1 h, treat with charcoal, filter, then neutralize with sodium carbonate and extract with benzene. After drying (Na_2SO_4) and evaporation, recrystallize the product from ethanol to obtain pale-yellow crystalline compounds **7 a–c** (cf. Table 3).

Procedure for Preparation of Compounds **9 a**, **c** *and* **11 a–c**

Dissolve 50 mmol of compound **7 a**, **c** or **8 a–c** in 10 ml of acetonitrile, add 1 ml methyl iodide, reflux for 2 h, then evaporate and crystallize from acetonitrile. Pale-yellow crystals (cf. Table 3).

Procedure for Preparation of Compounds **10 a–c** *and* **12 a–c**

Dissolve 25 mmol of compound **9 a–c** or **11 a–c** in a mixture of 50 ml of ethanol and 10 ml of 10% hydrochloric acid, add 1 g of zinc powder under cooling and stirring until decolouring (ca. 2 min), then immediately make alkaline with sodium carbonate solution and extract with benzene. After drying (Na_2SO_4) and evaporation, crystallize the residue from ethanol (cf. Table 3).

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