Cycloaddition Reactions of Benzothiete with Azomethines

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A new synthetic route to 3,4-dihydro-2*H*-1,3-benzothiazines **5** has been developed by the regiospecific cycloaddition of Schiff bases **4** and benzothiete **1**, which is primarily opened by heating to the corresponding *o*-quinoidal form **2**.

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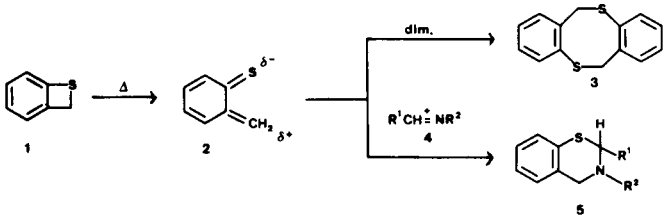
In continuation of our earlier studies on addition and cycloaddition reactions of benzothietes [1,2], we have investigated the reactivity towards Schiff bases. A convenient route for the synthesis of 2*H*-1,3-benzothiazine derivatives was elaborated. This class of heterocyclic Compounds is of special pharmacological interest, since psychotropic [3], antidepressant [4,5] and antitubercular activity [6] has been found for various systems of this type. Additionally an inhibition of serine proteinases [7] and phenylethanolamine *N*-methyltransferase [8] has been detected.

Opening of the four-membered ring **1**→**2** by heating is the most characteristic chemical property of the easily accessible benzothietes [9-13]. The *o*-quinoidal form is stabilized by dimerization and oligomerization reactions. In the presence of an excess amount of azomethines **4** the dimerization is extensively suppressed in favour of the formation of 3,4-dihydro-2*H*-1,3-benzothiazines **5**. The orientation in this [4π + 2π] cycloaddition corresponds to the polarity of both components. In the open form **2** of the benzothiete the sulfur atom has a partial negative charge and the methylene carbon atom a partial positive charge. Besides ~70% of **5** about 10% of 1,5-dibenzo[*b*,*f*]dithiocin (**3**) can be isolated:



4,5	R¹	R²	% 5	% 3
a	C_6H_5	C_6H_5	69	9
b	C_6H_5	4-OCH_3-C_6H_4	71	12
c	C_6H_5	4-Cl-C_6H_4	72	12
d	4-CH_3-C_6H_4	4-Cl-C_6H_4	71	8

The 2*H*-1,3-benzothiazine derivatives **5** are colourless solid compouds, which have been characterized carefully by high-field nmr spectroscopy. The ^{1}H- and ^{13}C-chemical shifts are summarized in Tables 1 and 2, respectively.

EXPERIMENTAL

Melting points were determined on a Büchi melting point apparatus and are uncorrected. The ir spectra were taken on a Beckmann Acculab 4 spectrometer as potassium bromide pellets. The ^{1}H- and ^{13}C-nmr spectra were recorded on a Bruker AM 400 specrometer. Mass spectra were obtained on a Varian 711 A double focusing machine. Elemental analyses were performed in the microanalytical laboratory of the institute.

Preparation of 2,3-Diaryl-3,4-dihydro-2*H*-1,3-benzothiazines **5**.

Benzothiete **1** (0.366 g, 3 mmoles) [1,12] and 5 mmoles of Schiff base **4a-d** are refluxed for 2-2 1/2 hours in dry toluene. After evaporation under vacuum the reaction mixture is separated by chromatography on silica gel (column 3 × 80 cm). Elution with petrol ether (50-70°) furnishes 1,5-dibenzo[*b*,*f*]dithiocin **3**, colourless needles, mp 170°, yield 8-12% (compare theoretical part). Further elution using a mixture of petrol ether (50-70°) and toluene (1:1) affords the corresponding 2,3-diaryl-3,4-dihydro-2*H*-1,3-benzothiazine **5a-d** which is recrystallized from dichloromethane/petrol ether (1:5).

3,4-Dihydro-2,3-diphenyl-2*H*-1,3-benzothiazine (**5a**).

This compound was obtained as colourless needles, mp 87°, yield 69%; ir (potassium bromide): 3050, 1590, 1490, 1440, 1365, 1260, 1210, 1140, 1120, 1030, 950, 750, 720, 690 cm^{-1}; ms: (70 eV): m/e = 303 (M^+, 78%), 270 (M-SH^+, 19), 226 (M-$C_6H_5^+$, 26), 212 (42); 211 (38), 181 (65), 180 (90), 121 (36), 92 (43), 91 (85), 77 (100).

Anal. Calcd. for $C_{20}H_{17}NS$: C, 79.21; H, 5.61; N, 4.62. Found: C, 78.94; H, 5.54; N, 4.52.

3,4-Dihydro-3-(4-methoxyphenyl)-2-phenyl-2*H*-1,3-benzothiazine (**5b**).

This compound was obtained as colourless needles, mp 112-113°, yield 71%; ir (potassium bromide): 3050, 2935, 1580, 1500, 1430, 1350, 1240, 1020, 820, 740 cm^{-1}; ms: (70 eV) m/e = 333 (M^+, 92%), 300 (M-SH^+, 12), 242 (23), 227 (24), 211 (100), 210 (25), 197 (52), 196 (81), 91 (25).

Anal. Calcd. for $C_{21}H_{19}NOS$: C, 75.67; H, 5.71; N, 4.20. Found: C, 75.49; H, 5.94; N, 3.91.

3-(4-Chlorophenyl)-3,4-dihydro-2-phenyl-2*H*-1,3-benzothiazine (**5c**).

This compound was obtained as colourless needles, mp 111°, yield 72%; ir (potassium bromide) 3050, 2900, 1580, 1485, 1440, 1420, 1365, 1260, 1230, 1210, 945, 815, 745 cm^{-1}; ms: (70 eV) m/e = 339/337 (M^+, 34/88%), 306/304 (M-SH^+, 6/21), 248/246 (16/43), 226 (34), 217 (30), 216 (45), 215 (93), 214 (100), 211 (44), 197 (55), 121 (44), 111 (66), 91 (42).

Anal. Calcd. for $C_{20}H_{16}$ ClNS: C, 71.79; H, 5.13; N, 4.00. Found: C, 71.59; H. 5.17; N, 4.13.

3-(4-Chlorophenyl)-3,4-dihydro-2-(4-methylphenyl)-2*H*-1,3-benzothiazine (**5d**).

This compound was obtained as colourless needles, mp 139°, yield 71%; ir (potassium bromide): 3040, 1585, 1490, 1470, 1430, 1350, 1255, 1200, 1105, 945, 930, 830, 810, 745 cm^{-1}; ms: (70 eV) m/e = 353/351 (M^+, 34/86%), 320/318 (M-SH^+, 6/17), 248/246 (28/80), 231 (30), 230 (42), 229 (74), 228 (100), 225 (44), 197 (43), 121 (32), 111 (61), 105 (66), 91 (72).

Anal. Calcd. for $C_{21}H_{18}$ ClNS: C, 71.11; H, 4.74; N, 4.14. Found: C, 71.10; N, 4.97; N, 4.21.

Table 1

^{1}H-NMR-Data of 2,3-Diaryl-3,4-dihydro-2*H*-1,3-benzothiazines **5** (δ-Values in Deuteriochloroform, TMS Internal)

Compound	2-H	4-H		5,6,7,8-H	2-aryl				3-aryl			
	s	AB	2J	A B C D	H_o	H_m	H_p	CH_3(s)	H_o	H_m	H_p	OCH_3 (s)
5a	6.29	4.27 4.40	16.5 Hz	7.03-7.18	7.63	7.37	7.30	—	7.05	7.23	6.89	—
5b	6.15	4.23 4.28	17.0 Hz	7.03-7.18	7.65	7.37	7.30	—	7.00	6.78	—	3.72
5c	6.20	4.28 4.34	16.5 Hz	7.04-7.18	7.60	7.36	7.30	—	6.96	7.17	—	—
5d	6.18	4.28 4.33	16.0 Hz	7.04-7.18	7.48	7.17	—	2.35	6.95	7.16	—	—

Table 2

^{13}C-NMR-Data of 2,3-Diaryl-3,4-dihydro-2*H*-1,3-benzothiazines **5** (δ-Values in Deuteriochloroform, TMS Internal)

Compound	C-2	C-4	C-4a, 8a	C-5,6,7,8	2-Aryl					3-Aryl				
					C_q	C_o	C_m	C_p	CH_3	C_q	C_o	C_m	C_p	OCH_3
5a	67.2	47.3	131.8 133.0	124.9 127.2 127.5 127.9	141.0	127.9	128.6	127.9	—	149.0	117.4	129.2	120.7	—
5b	68.9	48.5	130.9 133.1	124.6 127.0 127.4 127.7	140.8	128.2	128.5	127.9	—	142.9 154.7	120.5	114.5		55.5
5c	67.2	47.8	131.4 132.9	125.1 127.4 127.6 128.1	140.6	127.9	128.7	127.9	—	147.6 125.8	118.9	129.2	—	—
5d	67.1	47.7	131.4 133.0	125.0 127.4 127.5 127.9	137.6 137.9	127.8	129.4		21.0	147.6 125.7	118.9	129.1	—	—

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