Synthesis of a Novel Series of 6-Chloro-1,4,2-benzodithiazine 1,1-Dioxide Derivatives with Potential Biological Activity

Z. Brzozowski and F. Sączewski

Department of Chemical Technology of Drugs, Medical University of Gdansk,
107 Gen. J. Hallera Str., 80-416 Gdansk, Poland
Received February 16, 2005

A novel series of 6-chloro-1,4,2-benzodithiazine 1,1-dioxide derivatives **2**-**19** with alkyl, aryl or heteroaryl substituents at position 3 have been synthesized by the reaction of 4-chloro-2-mercaptobenzenesulfonamides with aldehydes, aldehyde acetals or acid anhydrides. 6-Chloro-3-(2-hydroxyphenyl)-7-methyl-2,3-dihydro-1,4,2-benzodithiazine 1,1-dioxide (**7**) exhibited remarkable activity on the leukemia CCRF-CEM cell line (GI_{50}<10 nM) and moderate activity against the other 49 human tumor cell lines derived from nine different cancer type.

J. Heterocyclic Chem., **42**, 1297 (2005).

Introduction.

Compounds containing 1,4,2-benzodithiazine ring were first synthesized in our laboratories in 1984 and received considerable attention over the past years due their wide range of biological activities. Hence, 3-mercapto-1,4,2-benzodithiazine 1,1-dioxides were obtained by reacting 2-chlorobenzenesulfonamides with carbon disulfide in the presence of potassium hydroxide [1,2]. Various 3-aminobenzodithiazine derivatives of type **I** and **II** (Figure 1) have been prepared by the nucleophilc displacement of the preformed 3-methylothio-1,4,2-benzodithiazines [1-3] with the respective amines [4-6], hydrazines [4,7], guanidines [8], semicarbazides [9] or arylsulfonamides [10]. Alternatively, an access to R-3-(*N*,*N*-dimethylamino)-1,4,2-benzodithiazine 1,1-dioxides (R=H, 5-Cl, 7-Cl, 5-Me, 6-Me or 7-Me) is provided by the reactions of corresponding *S*-phenyl *N*,*N*-dimethyldithiocarbamates with chlorosulfonyl isocyanate [11]. Furthermore, 2-R-12,3-dihydro-1,4,2-benzodithiazine 1,1-dioxides (R = Me or Ph) were obtained by reacting *N*-methyl or *N*-phenylbenzene-sulfoamides with butyllithium and sulfur at – 78 °C [12].

It has been demonstrated that in mice many 1,4,2-benzodithiazine derivatives possessed low acute toxicity in rats and, depending on their structure, exhibited potential as radioprotective [1,2], hypotensive [1], diuretic [1,2], choleretic [14], anti-HIV [15] or antitumor [6.9.10,15] agents.

Recently, we have found that benzodithiazines of type **III** and **IV** (Figure 1) bearing carbon atom at the position 3 also exhibited antitumor [16] or anti-HIV [17] activity. The above findings prompted us to develop new methodologies for the syntheses of novel benzodithiazines such as **V** and **VI** depicted in Figure 1.

Results and Discussion.

The desired 3-(aryl or alkyl)-6-chloro-7-methyl-2,3-dihydro-1,4,2-benzodithiazine 1,1-dioxides (**2**-**13**) were obtained by reacting corresponding aryl aldehydes, propionaldehyde or chloroacetaldehyde dimethyl acetal with 4-chloro-2-mercapto-5-methylbenzenesulfonamide (**1a**) in boiling glacial acetic anhydride as shown in Scheme 1. An analogous reaction of aminoacetaldehyde dimethyl acetal with **1a** led to the formation of *N*-[(6-chloro-7-methyl-1,1-dioxo-2,3-dihydro-1,4,2-benzodithiazin-3-yl)methyl] acetamide (**14**) resulting from acetylation of the transiently formed 3-aminomethylbenzodithiazine (**A**) (Scheme 1).

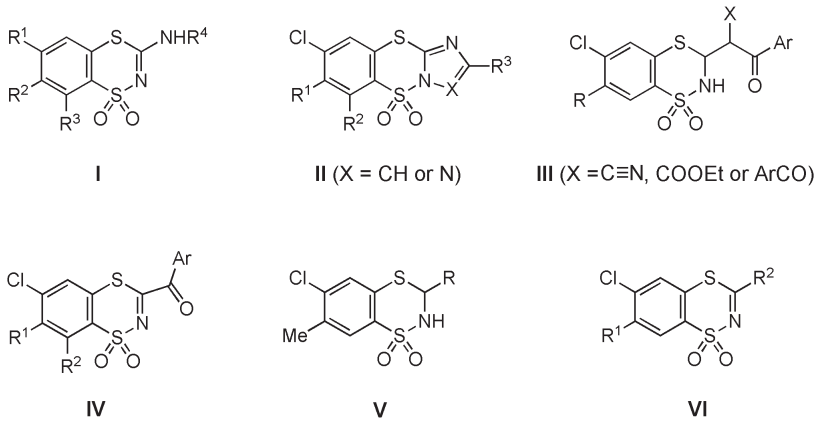
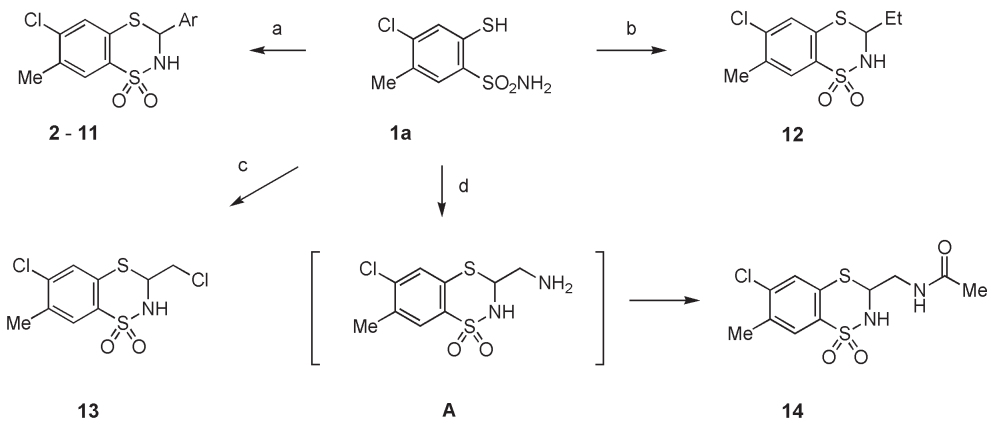
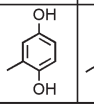
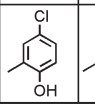
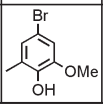
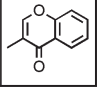


Figure 1

Scheme 1



Compd	2	3	4	5	6	7	8	9	10	11
Ar										

Reagents, conditions and yields: (a) ArC(=O)H (1molar equiv.), glacial acetic acid, reflux 8h, 75 - 91 %; (b) propionaldehyde (1.1 molar equiv.), 20 °C 12 h, reflux 8h, 86 %; (c) chloroacetaldehyde dimethyl acetal (1 molar equiv.), glacial acetic acid, reflux 6h, 49 %; (d) aminoacetaldehyde dimethyl acetal (1 molar equiv.), glacial acetic acid, reflux 10 h, 58 %.

We have investigated conformational preference of the 3,4-dihydrobenzodithiazine derivative **3** using density functional module (B3LYP method, 6-31G** basis set), as implemented into Titan v. 1,1 program distributed by Wavefunction Inc. The two possible low energy structures with either the sofa (**3a**) or boat (**3b**) configuration are shown in Figure 2. The computations showed that the boat conformer **3a** was favored over sofa **3b** by 3.4 kcal/mol. Thus, the limited magnitude of the energy difference between these conformers suggests that both conformers may occur in solution. The vicinal coupling constant found in ^{1}H nmr spectrum for the *H*-3 and N*H* is 12.0 Hz which corresponds to diaxial relationship between the protons.

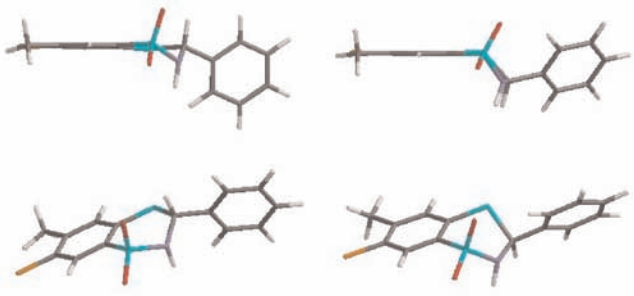


Figure 2

As shown in Scheme 2, 3-(alkyl or aryl)-6-chloro-7-methyl-1,4,2-benzodithiazine 1,1-dioxides **15**, **16** and **19** were obtained in good yields upon heating corresponding acid anhydrides for 18 h with 2-mercaptobenzenesulfonamide (**1a**) (Method A) or 2-acetylthio-benzenesulfonamide (**1b**) (Method B).

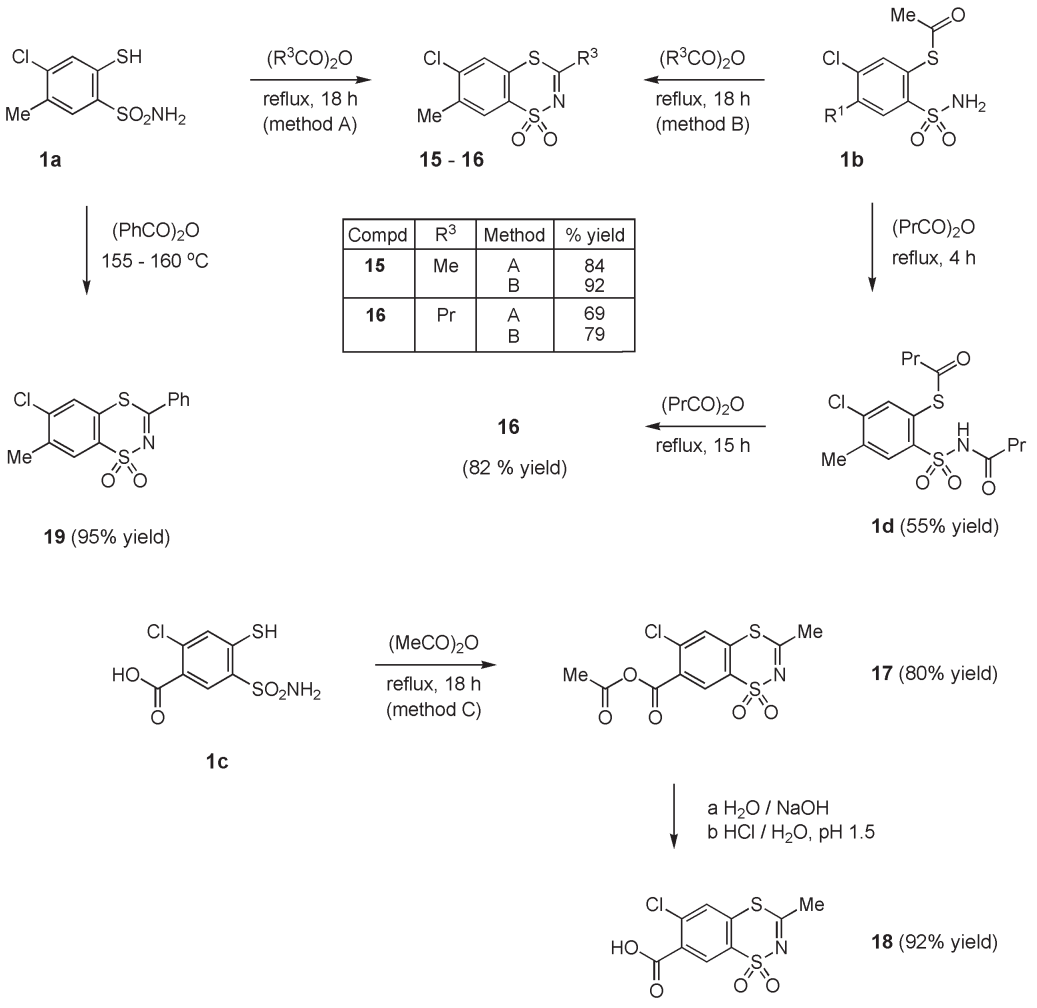
As expected, 2-chloro-4-mercapto-5-sulfamoylbenzoic acid (**1c**) heated at reflux with excess acetic anhydride gave benzodithiazine **17** containing a mixed anhydride moiety at position 7. Alkaline hydrolysis of **17** with aqueous NaOH solution carried out at room temperature for 5 h, allowed separation of corresponding carboxylic acid derivative **18** in 92% yield (Method C).

In order to gain a closer insight into the mechanism of the reaction of **1a** with acid anhydrides, we attempted to isolate intermediates formed in the course of the reaction. Indeed, when the reaction of **1a** with butyric acid anhydride was stopped after 4 h, the *S*,*N*-diacyl derivative **1d** could be separated from the reaction mixture in 55% yield (Scheme 2). This compound was then transformed into cyclic product **16** by further heating in boiling anhydride for 15 h.

From the above results one can infer that the reaction of **1a** with acid anhydride leads to the formation of **1d**, *via* initial formation of **B**. Subsequent addition of the amide NH group to the carbonyl group of **B** gives rise to the formation of cyclic hemiaminal **C** which, upon elimination of corresponding carboxylic acid, gives the final products **15**-**19**, as depicted in Scheme 3.

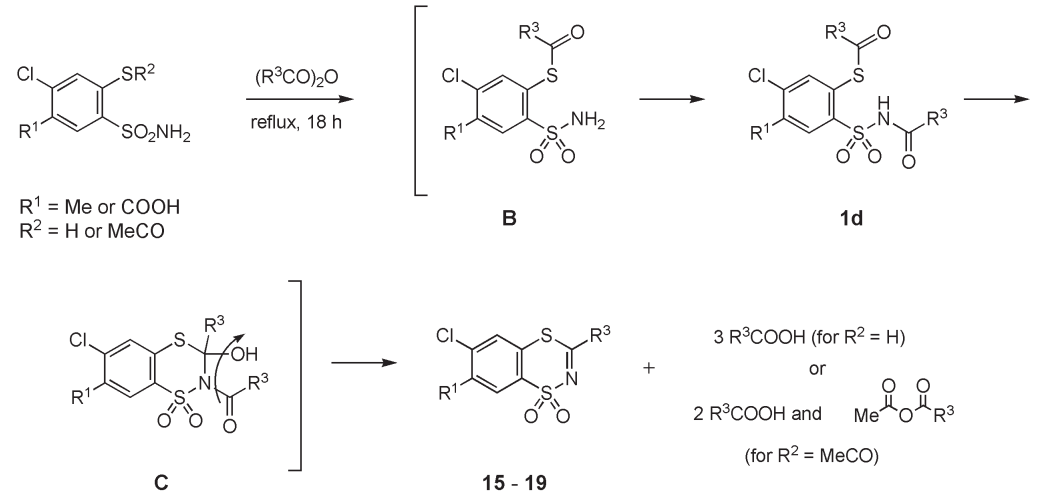
One of the synthesized compound (**7**) has been tested by the National Cancer Institute (Bethesda, USA) employing

Scheme 2



Compd	R^3	Method	% yield
15	Me	A	84
		B	92
16	Pr	A	69
		B	79

Scheme 3



Proposed mechanism of the formation of benzodithiazines **15** - **19**.

Table 1

In Vitro Tumor Growth Inhibition Data with 2-(6-Chloro-7-methyl-1,1-dioxo-2,3-dihydro-1,4,2-benzodithiazin-3-yl)phenol (**7**)[a]

Tumor/Cell Line	GI_{50} (μM)[b]	Tumor /Cell Line	GI_{50} (μM)[b]
Leukemia		**Melanoma**	
CCRF-CEM	< 0.01	LOX IMVI	43.7
HLC-60TB	59.6	MALME-3M	24.4
K-562	27.6	M14	52.0
MOLT-4	12.5	SK-MEL-2	87.3
RPMI-8226	20.7	SK-MEL-28	49.4
SR	10.4	SK-MEL-5	42.6
		UACC-257	53.5
Non Small Cell Lung Cancer		UACC-62	29.1
HOP-62	*		
HOP-92	54.1	**Ovarian Cancer**	
EKVX-A549/ATCC	56.9	IGROV1	42.4
NCI-H226	86.4	OVCAR-3	21.7
NCI-H23	70.7	OVCAR-4	63.6
NCI-H322M	*	OVCAR-5	40.1
NCI-H460	91.2	OVCAR-8	*
NCI-H522	48.8	SK-OV-3	*
		Renal Cancer	
Colon Cancer		786-0	34.1
COLO 205	20.8	A498	*
HCC-2998	31.0	ACHN	52.9
HCT-116	27.5	CAKI-1	50.5
HCT-115	19.4	RXF 393	53.4
HT29	45.4	SN12C	41.1
KM12	94.0	TK-10	*
SW-620	19.2	UO-31	63.2
CNS Cancer			
SF-268	91.4	**Breast Cancer**	
SF-295	*	MCF7	36.9
SF-539	48.7	NCI/ADR-RES	30.1
SNB-19	81.3	MDA-MB-231/ATCC	32.4
SNB-75	*	HS 578T	38.4
U251	73.0	MDA-MB-435	45.7
Prostate Cancer		BT-549	47.2
PC-3	68.6	T-47D	6.9
DU-145	33.9		

[a] Data obtained from the National Cancer Institute (Bethesda, USA); [b] Molar concentration of the compound that inhibits 50% net cell growth; * - not active, GI_{50}>100μM.

in vitro disease-oriented primary anticancer drug program [19-21] on a panel of 58 cell lines at five concentrations at 10-fold dilution. A 48 h continuous drug exposure protocol was used and sulforhodamine B (SRB) protein was applied to estimate cell growth. The GI_{50} values obtained (Table 1) indicated, that the compound **7** exhibited weak (GI_{50} = 50-94μM), moderate or fairly high activity (GI_{50} = 6.9-49.4 μM) against 49 tumor cell lines, and showed a selective high activity against leukemia CCRF-CEM cell line (GI_{50} = 0.01 μM and Δ = 3.62). It is pertinent to note that further evaluations concerning biological activity of benzodithiazines of type **V** and **VI** are in progress.

EXPERIMENTAL

The following instruments and parameters were used: melting points: Büchi 535 apparatus; ir spectra: KBr pellets, 400-4000 cm^{-1} Perkin Elmer 1600 FTIR spectrometer; ^1H and ^{13}C nmr: Varian Gemini 200 apparatus at 200 and 50 MHz, respectively; chemical shifts are expressed as δ values relative to tetramethylsilane as standard. Mass spectra were recorded on a Finigan MAT 95 spectrometer at 70 eV.

The starting 4-chloro-2-mercapto-5-methylbenzenesulfonamides **1a-c** were obtained according to the methods described previously: **1a** [2], **1b** [18], **1c** [1].

General Procedure for the Preparation of 3-Aryl-6-chloro-7-methyl-2,3-dihydro-1,4,2-benzodithiazine 1,1-Dioxides (**2-11**).

A solution of 4-chloro-2-mercapto-5-methylbenzenesulfonamide (**1a**, 2.38 g, 0.01 mol) and the appropriate aldehyde (0.01 mol) in glacial acetic acid (1.5 ml) was refluxed with stirring for 18 h. The small amount of insoluble side products was filtered off when hot and the filtrate was left overnight. The precipitate thus obtained was collected by filtration, washed successively with acetic acid ((2 x 1ml) then toluene (4 x 3 ml), and dried.

In this manner the following benzodithiazines were obtained:

6-Chloro-7 methyl-3-(2-naphthyl)-2,3-dihydro-1,4,2-benzodithiazine 1,1-Dioxide (**2**).

Starting from 2-naphthalenecarbaldehyde (1.56 g) the title compound **2** was obtained (3.2 g, 85%): mp 200-201°; ir: 3235 (NH), 1325, 1165 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.38 (s, 3H,

C*H*$_3$), 6.66 (d, *J* = 11.8 Hz, 1H, *H*-3, bemzodithiazine), 7.57-7.63 (m, 3H, arom.), 7.78-7.83 (m, 1H, H-1, naphthyl), 7.95-8.05 (m, 4H, arom.), 8.22 (s, 1H, *H*-8, benzodithiazine), 9.27 (d, *J* = 11.8 Hz, 1H, N*H*) ppm.

Anal. Calcd. for $C_{18}H_{14}ClNO_2S_2$: C, 57.51; H, 3.75; N, 3.73. Found: C, 57.73; H, 3.86; N, 3.80.

6-Chloro-7-methyl-3-phenyl-2,3-dihydro-1,4,2-benzodithiazine 1,1-Dioxide (**3**).

Starting from benzaldehyde (1.06 g) the title compound **3** was obtained (2.7 g, 83%): mp 145-147°; ir: 3225 (NH), 1325, 1160 (SO_2) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.37 (s, 1H, C*H*$_3$), 6.47 (d, *J* = 12.0 Hz, 1H, *H*-3, benzodithiazine), 7.42-7.50 (m, 3H, Ph), 7.57 (s, 1H, *H*-5, benzodithiazine), 7.63-7.70 (m, 2H, Ph), 7.98 (s, 1H, *H*-8, benzodithiazine), 9.12 (d, *J* = 12.0 Hz, 1H, N*H*) ppm.

Anal. Calcd. for $C_{14}H_{12}ClN_2S_2$: C, 51.60; H, 3.71; N, 4.29. Found: C, 51.58, H, 3.90, N, 4.51.

6-Chloro-7-methyl-3-(4-methylphenyl)-2,3-dihydro-1,4,2-benzodithiazine 1,1-Dioxide (**4**).

Starting from 4-methylbenzaldehyde (1.2 g) the title compound **4** was obtained (3.1 g, 91%): mp 208-210°; ir: 3280 (NH), 1330, 1170, (SO_2) cm^{-1}; ^{1}H nmr: (DMSO-d$_6$) δ 2.33 (s, 3H, 4-CH_3Ph), 2.37 (s, 3H, C*H*$_3$-7, benzodithiazine), 6.41(d, *J* = 12.1 Hz, 1*H*, H-3 benzodithiazine), 7.27 (d, *J* = 8.0 Hz, 2H, 4-CH_3Ph), 7.53 (s, 1H, *H*-5, benzodithiazine) 7.60 (d, *J* = 8.0 Hz, 2H, 4-CH_3-Ph), 7.98 (s, 1H, *H*-8), 9.07 (d, *J* = 12.1 Hz, 1H, N*H*) ppm.

Anal. Calcd. for $C_{15}H_{14}ClNO_2S_2$: C, 53.01; H, 4.15, N, 4.12. Found: C, 53.21, H, 4.21; N, 4.42%).

3-(4-Bromophenyl)-6-chloro-7-methyl-2,3-dihydro-1,4,2-benzodithiazine 1,1-Dioxide (**5**).

Starting from 4-bromobenzaldehyde (1.85 g) the title compound **5** was obtained (3.1 g, 76%): mp 203-205°; ir: 3285 (NH), 1335, 1170 (SO_2) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.37 (s, 3H, C*H*$_3$), 6.52 (d, *J* = 11.9 Hz, 1H, *H*-3 benzodithiazine), 7.58-7.73 (m, 4H, phenyl-*H* + 1H, *H*-5 benzodithiazine), 7.99 (s, 1H, *H*-8). 9.16 (d, *J* = 11.9 Hz, 1H, N*H*) ppm.

Anal. Calcd. for $C_{14}H_{11}BrClNO_2S_2$: C, 41.54, H, 2.74; N, 3.46. Found: C, 41.40; H, 3.01, N, 3.60.

6-Chloro-3-(4-chlorophenyl)-7methyl-2,3-dihydro-1,4,2-benzodithiazine 1,1-Dioxide (**6**).

Starting from 4-chlorobenzaldehyde (1.4 g) the title compound **6** was obtained (2.9 g, 80%): mp 194-195°; ir: 3285 (NH) 1330, 1165 (SO_2) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.39 (s, 3H, CH_3), 6.54 (d, *J* = 12.0 Hz, 1H, *H*-3, benzodithiazine), 7.56 (d, *J* = 8.7 Hz, 2H, 4-ClPh); 7.60 (s, 1H, *H*-5, benzodithiazine), 7.73 (d, *J* = 8.7 Hz, 2H, 4-ClPh), 8.00 (s, 1H, H-8), 9.17 (d, *J* = 12.0 Hz, 1H, N*H*) ppm; ^{13}C nmr (DMSO-d$_6$): δ 19.21, 60.57, 127.07, 127.74, 129.27, 129.47, 130.19, 132,16, 134.08, 134.39, 135.04, 137.88 ppm.

Anal. Calcd. for $C_{14}H_{11}Cl_2NO_2S_2$: C, 46.67; H, 3.08; N, 3.89. Found C, 46.45; H, 4.01; N, 4.07.

2-(6-Chloro-7-methyl-1,1-dioxo-2,3-dihydro-1,4,2-benzodithiazin-3-yl)phenol (**7**).

Starting from salicylaldehyde (1.22 g) the title compound **7** was obtained (2.7 g, 79%): mp 215-217°; ir: 3395 (OH), 3275 (NH), 1345, 1160 (SO_2) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.37 (s, 3H, CH_3), 6.67 (d, *J* = 12.2 Hz, 1H, *H*-3, benzodithiazin), 6.88-6.95, (m, 2H, 2-HOPh), 7.21-7.30 (m, 1H, 2-HOPh), 7.54 (s, 1H, *H*-5, benzodithiazine) 7.64-7.69 (m, 1H, 2-HOPh), 7.96 (s, 1H, *H*-8), 9.00 (d, *J* = 12.2 Hz, 1H, N*H*), 10.26 (s, 1H, O*H*) ppm.

Anal. Calcd. for $C_{14}H_{12}ClNO_3S_2$: C, 49.19; H, 3.53; N, 4.10. Found: C, 49.29; H, 3.80; N, 4.27.

2-(6-Chloro-7-methyl-1,1-dioxo-2,3-dihydro-1,4,2-benzodithiazin-3-yl)benzene-1,4-diol (**8**).

Starting from 2,5-dihydroxybenzaldehyde (1.39 g) the title compound **8** was obtained (2.7 g, 75%): mp 216-217°; ir: 3520, 3465 (OH + OH), 3240 (NH), 1340, 1325, 1165 (SO_2) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.36 (s, 3H, C*H*$_3$), 6.60 (d, *J* = 12.1 Hz, 1H, *H*-3, benzodithiazin), 6.66-6.76 (m, 2H, Ph), 7.07 (s, 1H, *H*-6, Ph), 7.54 (s, 1H, *H*-5, benzodithiazine), 7.94 (s, 1H, *H*-8, benzodithiazine), 8.96 (d, *J* = 12.1 Hz, 1H, N*H*), 9.00 (s, 1H, O*H*), 9.50 (s, 1H, O*H*) ppm.

Anal. Calcd. For $C_{14}H_{12}ClNO_4S_2$: C, 46.99; H, 3.38; N, 3.91. Found: C, 47.20; H, 3.49, N, 3.88.

4-Chloro-2-(6-chloro-7-methyl-1,1-dioxo-2,3-dihydro-1,4,2-benzodithiazin-3-yl)phenol (**9**).

Starting from 5-chloro-2-hydroxybenzaldehyde (1.57 g) the title compound **9** was obtained (2.9 g, 77%): mp 215-216°; ir: 3440 (OH),3215 (NH), 1340, 1155 (SO_2) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.37 (s, 3H, CH3), 6.60 (d, *J* = 12.2 Hz, *H*-3, benzodithiazin), 6.95 (d, J_{ortho} = 8.8 Hz, 1H, *H*-3, Ph), 7.31 (dd, J_{ortho} = 8.8 Hz, J_{meta} = 2.5 Hz, 1H, *H*-4, Ph), 7.56 (s, 1H, *H*-5, benzodithiazine), 7.74 (d, J_{meta} = 2.5 Hz, 1H, *H*-6, Ph), 7.97 (s, 1H, *H*-8, benzodithiazine), 9.05 (d, *J* = 12.2 Hz, 1H, N*H*), 10.66 (s, 1H, O*H*) ppm; ms: m/z 377 (M$^+$+2, 31.9), 375 (M$^+$, 47.1), 222 (17.1), 220 (37.2), 157 (45.8), 155 (100).

Anal. Calcd for $C_{14}H_{11}Cl_2NO_3S_2$: C, 44.68; H, 2.95; N, 3.72. Found: C, 44.74; H, 3.13; N, 3.84.

4-Bromo-2-(6-chloro-7-methyl-1,1-dioxo-2,3-dihydro-1,4,2-benzodithiazin-3-yl)-6-methoxyphenol (**10**).

Starting from 5-bromo-2-hydroxy-3-methoxybenzaldehyde (2.31 g) the title compound **10** was obtained (3.6 g, 80%): mp 254-255°; ir: 3515 (OH), 3240 (NH), 1345, 1335, 1165 (SO_2) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.37 (s, 3H, C*H*$_3$), 3.86 (s, 3H, C*H*$_3$O), 6,64 (d, *J* = 12.3 Hz, 1H, *H*-3, benzodithiazine), 7.20 (d, *J* = 2.2 Hz , 1H, Ph), 7.49 (d, *J* = 2.2 Hz, 1H, Ph), 7.56 (s, 1H, *H*-5, benzodithiazine), 7.97 (s, 1H, *H*-8, benzodithiazine), 9.02 (d, *J* = 12.3 Hz, 1H, N*H*), 9.87 (s, 1H, O*H*) ppm.

Anal. Calcd. for $C_{15}H_{13}BrClNO_4S_2$: C, 39.96; H, 2.90; N, 3.11. Found: C, 40.11; H, 3.08; N, 3.28.

3-(6-Chloro-7-methyl-1,1-dioxo-2,3-dihydro-1,4,2-benzodithiazin-3-yl)-4*H*-chromen-4-one (**11**).

Starting from 3-chromonecarbaldehyde (1.75 g) the title compound **11** was obtained (3.3 g, 83%): mp 270-272°; ir: 3200 (NH), 1640 (C=O), 1345, 1330, 1170 (SO_2) cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.37 (s, 3H, CH_3), 6.55 (s, 1H, *H*-3, benzodithiazine), 7.52-7.74 (m, 2H, *H*-arom. + 1H, *H*-5, benzodithiazine.), 7.84-7.93 (m, 1H arom.) 7.98 (s, 1H, *H*-8, benzodithiazine), 8.09-8.14 (m, 1H, arom.), 8.71 (s, 1H, *H*-2, chromone), 9.04 (s, 1H, N*H*) ppm., ^{13}C nmr (DMSO-d$_6$) δ 19.21, 53.01, 118.93, 120.25, 123.11, 125.55, 126.52, 127.23, 127.64, 131.84, 134.13, 134.32, 135.31, 138.02, 155.91, 157.51, 174.03 ppm; ms: m/z 394 (M$^+$, 100), 174 (3.7).

Anal. Calcd. $C_{17}H_{12}ClNO_4S_2$: C, 51.83; H, 3.07; N, 3.55. Found: C, 51.98, H, 3.22; N, 3.71.

6-Chloro-3-ethyl-7methyl-2,3-dihydro-1,4,2-benzodithiazine 1,1-Dioxide (**12**).

To a solution of propionaldehyde (0.64 g, 0.01 mol) in glacial acetic acid (12 ml) was added 4-chloro-2-mercapto-5-methylbenzenosulfonamide **1a** (2.38, 0.01 mol). The reaction mixture was stirred at room temperature for 12 h, followed by reflux for 8 h. The small amount of insoluble side products was filtered of when hot. Water (8 ml) was added portionwise to the filtrate, and stirring was continued at room temperature for 8 h. The title compound thus obtained was collected by filtration, washed thoroughly with water, and dried initially at room temperature then at 98°. Yield 2.4 g (86%), mp 120-121°; ir: 3225 (NH), 1345, 1330, 1164 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.04 (t, *J* = 7.3Hz, 3H, CH_2CH_3), 1.81-2.01 (m, 2H, **C***H*$_2$CH$_3$), 2.34 (s, 3H, C*H*$_3$-7), 5.20 (q, *J* = 7.3Hz, 1H, *H*-3), 7.53(s, 1H, *H*-5), 7.89 (s, 1H, H-8), 8.52 (d, *J* = 11.5 Hz, 1H, N*H*) ppm.

Anal. Calcd. for $C_{10}H_{12}ClNO_2S_2$: C, 43.23; H, 4.35, N, 5.04. Found: C, 43.32; H, 4.52, N, 5.27.

6-Chloro-3-chloromethyl-7-methyl-2,3-dihydro-1,4,2-benzodithiazine 1,1-Dioxide (**13**).

To a solution of chloroacetaldehyde dimethyl acetal (1.87 g, 0.015 mol) in glacial acetic acid (12 ml), 4-chloro-2-mercapto-5-methylbenzenesulfonamide (**1a**, 3.56 g, 0.015 mol) was added. The reaction mixture was stirred at reflux for 6 h and left to stand at room temperature overnight. The small amount of insoluble side products was filtered off and the filtrate was poured into water-crushed ice mixture (250 g). After vigorous stirring for 1 h, the precipitate was collected by filtration, washed with water and dried, then purified by crystallization from 2-propanol to afford **13** as white crystals. Yield 2.2g (49%), mp 119-121°; ir: 3220 (NH), 1340, 1330, 1170 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.34 (s, 3H, C*H*$_3$), 4.25 (m, 2H, C*H*$_2$), 5.3-5.52 (m, 1H, *H*-3), 7.60 (s, 1H, *H*-5), 7.91 (s, 1H, *H*-8), 8.77 (d, *J* = 9.8 Hz, 1H, N*H*) ppm.

Anal. Calcd. for $C_9H_9Cl_2NO_2S_2$: C, 36.25; H, 3.04; N, 4.69. Found: C, 36.20; H, 3.26; N, 4.76.

N-[(6-Chloro-7-methyl-1,1-dioxo-2,3-dihydro-1,4,2-benzodithiazin-3-yl)methyl]acetamide (**14**).

The 4-chloro-2-mercapto-5-methylbenzenesulfonamide **1a** (3.56 g, 0.015 mol) was added portionwise to a solution of aminoacetaldehyde dimethyl acetal (1.6 g, 0.015 mol) in glacial acetic acid (20 ml). Stirring was continued at room temperature for 1h followed by reflux for 10 h, then left to stand at room temperature overnight. The precipitate of side products (0.5-0.7 g) was filtered off, and the filtrate was evaporated to dryness under reduced pressure. The crude product thus obtained was recrystallized from ethanol to give **13** as white crystals. Yield 2.9 g (58%), mp 187-189°. ir: 3390 (NH), 1650 (C=O), 1340, 1330, 1170, (SO_2) cm^{-1}, ^1H nmr (DMSO-d_6): δ 1.87 (s, 3H, C*H*$_3$CO), 2.34 (s, 3H, C*H*$_3$-7), 3.52 (t, *J* = 6.2 Hz, 2H, C*H*$_2$), 5.31-5.45 (m, 1H, *H*-3), 7.55 (s, 1H, *H*-5), 7.88 (s, 1H, *H*-8), 8.32 (t, *J* = 6.2 Hz, 1H, C*H*$_2$NHCO), 8.60 (s, 1H, N*H*) ppm., ^{13}C nmr (DMSO-d_6): δ 19.15, 22.74, 42,64, 58.97, 127.49, 127.62, 131.89, 133.63, 134.04, 137.79, 170.32 ppm.

Anal. Calcd. for $C_{11}H_{13}ClN_2O_3S_2$: C, 41.18; H, 4.08; N, 8.73. Found: C, 41.31, H, 4.17; N, 8.71.

Procedure for the Preparation of 3-Alkyl-6-chloro-1,4,2-benzodithiazine 1,1-Dioxides **15**-**17** (Mthods A, B and C).

A mixture of the corresponding 2-mercaptobenzenesulfonamide **1a** (Method A), **1b** (Method B) or **1c** (Method C) (0.01 mol) and an appropriate acid anhydride was refluxed with stirring for 18 h. After cooling to room temperature the suspension obtained was left overnight. The precipitate was collected by filtration, washed successively with acetic acid (2 x 1 ml) then toluene (3 x 1 ml), and dried. Crude products **15** and **16** were further purified by recrystallization from 2-propanol.

In this manner the following benzodithiazines were obtained:

6-Chloro-3,7-dimethyl-1,4,2-benzodithiazine 1,1-Dioxide (**15**).

Starting from 6-chloro-2-mercapto-7-methylbenzesulfonamide (**1a**, 2.38 g) or 2-acetylthio-6-chloro-7-methylbenzenesulfonamide (**1b**, 2.8 g) and acetic anhydride (12 ml) the title compound **15** was obtained (2.2 g, 84% from **1a** or 2.4 g, 92% from **1b**): mp 176-177° (dec); ir: 1635 (C=N), 1335, 1165 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.49 (s, 3H, C*H*$_3$-7), 2.64 (s, 3H, C*H*$_3$-3), 7.39 (s, 1H, *H*-5), 8.04 (s, 1H, *H*-8) ppm; ^{13}C nmr (deuteriochloroform): δ 20.44, 29.60, 125.67, 126.57, 128.17, 128.71, 139.58, 139.98, 174.92, ppm.

Anal. Calcd. for $C_9H_8ClNO_2S_2$: C, 41.30, H, 3.08, N, 5.35. Found: C, 41.31; H, 3.17; N, 5.39.

6-Chloro-7-methyl-3-propyl-1,4,2-benzodithiazine 1,1-Dioxide (**16**).

Starting from 6-chloro-2-mercapto-7-methylbenzenesulfonamide (**1a**, 2.8 g) or 2-acetylthio-6-chloro-7-methylbenzenesulfonamide (**1b**, 2.8 g) and butyric anhydride (16 ml), the title compound **16** was obtained (2.0 g 69% from **1a** or 2.3g, 79% from **1b**): mp 108-109°; ir: 1575 (C=N), 1340, 1320, 1170 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.03 (t, *J* = 7.3 Hz, 3H, CH_2CH_3), 1.87 (m, 2H, $CH_2CH_2CH_3$), 2.47 (s, 3H, C*H*$_3$-7), 2.77 (t, *J* = 7.3Hz, 2H, **C***H*$_2$CH$_2$), 7.38 (s, 1H, *H*-5), 8.03 (s, 1H, *H*-8) ppm.

Anal. Calcd. for $C_{11}H_{12}ClNO_2S_2$: C, 45.59; H, 4.17; N, 4.83. Found: C, 45.40; H, 4.33; N, 5.04.

Acetic 6-chloro-3-methyl-1,1-dioxo-1,4,2-benzodithiazine-7-carboxylic Anhydride (**17**).

Starting from 2-chloro-4-mercapto-5-sulfamoylbenzoic acid (**1c**, 2.68 g) and acetic anhydride (18 ml), the title compound **17** was obtained (2.7 g, 80%): mp 261-262°; ir: 1820 (ArC=O), 1725, (CH_3C=O), 1635 (C=N), 1350, 1325, 1175 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.89 (s, 3H, C*H*$_3$-3), 3,35 (s, 3H, C*H*$_3$CO), 8.18 (s, 1H, *H*-5), 8.39 (s, 1H, *H*-8) ppm.

Anal. Calcd. for $C_{11}H_8ClNO_5S_2$: C, 39.58; H, 2.41; N, 4.19. Found: C, 39.67; H, 2.61; N, 4.30.

Synthesis of 6-Chloro-3-methyl-1,4,2-benzodithiazine-7-carboxylic Acid 1,1-Dioxide (**18**) from Mixed Anhydride (**17**).

To a stirred solution of NaOH (1 g, 0.025 mol) in water (90 ml) was added anhydride **17** (3.34 g, 0.01 mol). Stirring was continued at room temperature for 5 h. The resulting solution (pH~11) was acidified to pH 6 with 0.5 % hydrochloric acid, filtered with charcoal, and the filtrate was slowly acidified to pH 1.5 with 0.5% hydrochloric acid. The title product which precipitated was collected by filtration, washed thoroughly with water and dried at temperature gradually rising to 105 °C. Yield 3.1 g (92%), mp 261-262° (dec). ir: 3510, 3235, 2865, 2715, 2570 (OH carboxylic), 1720 (C=O), 1350, 1160 (SO_2) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.02 (s, 3H, C*H*$_3$), 8.31 (s, 1H, *H*-5), 8.39 (s, 1H, *H*-8), 12.9 (br.s, 1H, COO*H*) ppm.

Anal. Calcd. for $C_9H_6ClNO_4S_2$: C, 37.04; H, 2.07; N, 4.80. Found: C, 37.17; H, 2.18, N, 4.77.

Synthesis of 6-chloro-7-methyl-3-phenyl-1,4,2-benzodithiazine 1,1-Dioxide (**19**).

A mixture of 4-chloro-2-mercapto-5-methylbenzenesulfonamide **1a** (2.38 g, 0.01 mol) and benzoic acid anhydride (12.2 g, 0.1 mol) was stirred at 155-160 °C for 12 h. After cooling to room temperature, a solution of $KHCO_3$ (10 g, 0,1 mol) in water (120 ml) was added and stirring was continued at room temperature for 6 h. The precipitate was collected by filtration, washed thoroughly with water and dried. The crude product was purified by recrystallization from acetone to afford **19** as white crystals. Yield 3.1 g (95%), mp 194-195°; ir: 1345, 1330 (SO_2) cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.50 (s, 3H, C*H*$_3$-7), 7.52-7.70 (m, 5H, Ph), 8.08 (s, 1H, *H*-5), 8.13 (s, 1H, *H*-8) ppm.

Anal. Calcd. for $C_{14}H_{10}ClNO_2S_2$: C, 51.92; H, 3.11; N, 4.32. Found: C, 52.11; H, 3.29; N, 4.43.

Synthesis of 5-{2-[(Butyrylamino)sulfonyl]-5-chloro-4-methylphenyl}butanethioate (**1d**) from 2-Acetylthio-4-chloro-5-methylbenzenesulfonamide (**1b**).

A solution of **1b** (2.8 g, 0.01 mol) in butyric acid anhydride (7.9 g, 0.05 mol) was heated under reflux for 4 h. Excess of anhydride was removed by evaporation under reduced pressure. To the oily residue thus obtained a solution of $KHCO_3$ (5 g, 0.05 mol) in water (80 ml) was added. After 30 min. the insoluble material was filtered off and pH of the filtrate was adjusted to 2 with 1% hydrochloric acid. The crystalline **1d** that precipitated was collected by filtration, washed with water, and dried initially at room temperature, then at 80 °C. Yield 2.1 g (55%), mp 110-112°; ir: 3240 (NH), 1730 (ArSC=O), 1705 (NHC=O), 1345, 1175 (SO_2) cm^{-1}. ^1H nmr (deuteriochloroform): δ 0.68 (t, *J* = 7.3Hz, 3H, $CH_2\mathbf{C}H_3$), 1.00 (t, *J* = 7.3 Hz, 3H, $CH_2\mathbf{C}H_3$), 1.57 (m, 2H, $CH_2\mathbf{C}H_2CH_3$), 1.75 (m, 2H, $CH_2\mathbf{C}H_2CH_3$), 2.17 (t, *J* = 7.3 Hz, 2H, $\mathbf{C}H_2CH_2$), 2.50 (s, 3H, CH_3Ph), 2.75 (t, *J* = 7.3 Hz, 2H, ($\mathbf{C}H_2CH_2$), 7.57 (s, 1H, ClC-C*H*=CS), 8.23 (s, 1H, CH_3-C-C*H*=CSO_2), 9.29 (s, 1H, N*H*) ppm.

Anal. Calcd. for $C_{15}H_{20}ClNO_4S_2$: C, 47.67; H, 5.33; N, 3.70. Found: C, 47.60; H, 5.53; N, 3.82.

Synthesis of 6-Chloro-7-methyl-3-propyl-1,4,2-benzodithiazine 1,1-Dioxide (**16**) from 5-{2-[(Butyrylamino)sulfonyl]-5-chloro-4-methylphenyl}butanethioate (**1d**).

A mixture of **1d** (3.78 g, 0.01 mol) and butyric acid anhydride(15.8 g, 0.1 mol) was refluxed with stirring for 15 h. After cooling to room temperature the suspension was left overnight. The solid product was collected by filtration, washed successively with acetic acid (2 x 1 ml) then toluene, dried and purified by recrystallization from 2-proponol. Yield 2.4 g (82%), mp 108-109°; ir and ^1H nmr data were accordance with those reported above for the authentic sample of **16**.

Acknowledgments.

Authors thank the Ministry of Science and Informatization, Poland, for financial support (Grant No 2P05F 03527).

REFERENCES AND NOTES

[1] Z. Brzozowski.and J. Sławiński, *Acta Polon. Pharm*., **41**, 5 (1984).

[2] Z. Brzozowski and J. Sławiński, *Acta Polon. Pharm*., **41**, 133 (1984).

[3] Z. Brzozowski, F. Gajewski, J. Sławiński and E. Pomarnacka, *Acta Polon. Pharm. Drug Res*., **50**, 199 (1993).

[4] Z. Brzozowski, *Acta Polon. Pharm., Drug Res*., **55**, 473 (1998).

[5] Z. Brzozowski and F. Saczewski, *Eur. J. Med. Chem*., **37**, 285 (2002).

[6] Z. Brzozowski and F. Saczewski, *J. Med. Chem*., **45**, 430 (2002).

[7] E. Pomarnacka, *Acta Polon. Pharm. Drug Res*., **55**, 481 (1998).

[8] Z. Brzozowski, *Acta Polon. Pharm. Drug Res*., **52**, 91 (1995).

[9] E. Pomarnacka and M.Gdaniec, *Bioorg. Med. Chem*., **11**, 1259 (2003).

[10] Z. Brzozowski, F. Sączewski and M. Gdaniec, *Bioorg. Med.Chem*., **11**, 3673 (2003).

[11] T. Iwokawa, H. Tamura, A. Murabayashi and Y. Hayase, *Chem. Pharm. Bull*., **39**, 1939 (1991).

[12] S.W. Wright, *J. Heterocyclic Chem*., **38**, 723 (2001).

[13] Z. Brzozowski, J. Sławiński, F. Gajewski, S. Angielski and A. Hoppe, *Acta Polon. Pharm*. **42**, 413 (1985).

[14] Z. Brzozowski, J. Sławiński, W. Janiec, U. Cegła, L. Śliwiński and I., Sedlak, *Acta Polon. Pharm. Drug. Res*., **49**, 75 (1992).

[15] Z. Brzozowski, *Acta Polon. Pharm., Drug Res*.**,** **54**, 293 (1997).

[16] Z. Brzozowski, F. Sączewski and M. Gdaniec, *Eur. J. Med. Chem*., **38**, 991 (2003).

[17] Z. Brzozowski, F. Saczewski, T. Sanchez, L. Ch. Kuo, M Gdaniec and N. Neamati., *Bioorg. Med. Chem*., **12**, 3663 (2004).

[18] Z. Brzozowski, *Acta Polon. Pharm*., **44**, 486 (1987).

[19] M. R. Boyd, *Am. Assoc. Cancer Res*., **30**, 652 (1989).

[20] A. Monks, D. Scudiero, P. Skehan, R. Shoemaker, K. Poull, D. Vistica, C. Hose, J. Langley, P. Cronise, A. Vaigro-Wolff, M. Gray-Goodrich, H. Combell, J. Mayo and M. Boyd, *J. Natl. Cancer Inst*., **83**, 757 (1991).

[21] I. N. Weinstein, T. G. Myers, P. M. O'Conner, S. H. Friend, A. J. Jr Fornance, K. W. Kohn, T. Fojo, S. E. Bates, L. V. Robinstein, J. K. Buolamwini, W. W. van Osdol, A. P. Monks, D. A. Scudiero, E. A. Sausiville, D. Zaharevitz, B. Bunow, V. N. Viswanadhan, G. S. Johnson, R. E. Wittes and K. D. Paull, *Science* **275**, 343 (1997).