

bath with excess acetic anhydride for 3 hr or with acetic anhydride in dioxane for 5 hr. The excess solvent and acetic acid were evaporated under reduced pressure. The solid residue was recrystallized from ethyl acetate.

**3-(5-Acetoxy-3-methyl-5-phenyl-2-pyrazolin-1-yl)-1,2-benzisothiazole 1,1-Dioxide.** Table III, 7.—3-(5-Hydroxy-3-methyl-5-phenyl-2-pyrazolin-1-yl)-1,2-benzisothiazole 1,1-dioxide (7 g) and 10 g of acetic anhydride in dioxane were heated under reflux for 12 hr. The dioxane was removed under reduced pressure and the residue was dissolved in ethyl acetate. The product was crystallized by concentrating to a small volume and cooling.

**1,2-Bis(1,2-benzisothiazol-3-yl 1,1-dioxide)hydrazine.**—I (10 g) was dissolved in 200 ml of 1 *N* HCl by warming on the steam bath until solution occurred. The insoluble solid which separated after cooling was collected, yield 2 g (22%). The product was recrystallized from a large volume of hot alcohol; mp 305° dec.

*Anal.* Calcd for  $C_{14}H_{10}N_4O_4S_2$ : C, 46.40; H, 2.78; N, 15.46. Found: C, 46.55; H, 3.08; N, 15.03.

This was identical in melting point, infrared, and titration with the material obtained as a side product in the condensation of I with 1,3-diketones in Cellosolve;  $pK_a$  (66% DMF) = 3.40, 11.43; apparent molecular weight, 385.

**3-(2-Ethoxyethoxy)-1,2-benzisothiazole 1,1-Dioxide.**—When 8 g (0.04 mole) of I was heated with 6 g (0.046 mole) of ethyl acetoacetate in 150 ml of Ethyl Cellosolve, the product, isolated by removal of the solvent under reduced pressure and crystallization of the residue from ethanol, was identified from its nmr spectra as the Cellosolve derivative, mp 109°, yield 1 g (10%).

*Anal.* Calcd for  $C_{11}H_{13}NO_4S$ : C, 51.75; H, 5.13; N, 5.49. Found: C, 51.17; H, 5.06; N, 5.41.

**Acknowledgment.**—We wish to express our thanks to our colleagues in microanalysis, physical chemistry, and pharmacology, who obtained the data referred to in this paper.

## Hypotensive 1,2-Benzisothiazole 1,1-Dioxides. II. 3-Hydrazino-1,2-benzisothiazole 1,1-Dioxides and their Hydrazone and Amide Derivatives

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3-Hydrazino-1,2-benzisothiazole 1,1-dioxides were prepared from 3-hydroxy-, 3-methoxy-, and 3-methylmercapto-1,2-benzisothiazole 1,1-dioxides. Hydrazone, carbamide, and sulfamide derivatives of the 3-hydrazino-1,2-benzisothiazole 1,1-dioxides were evaluated for their hypotensive activity in the Goldblatt rat preparation.

As an expansion of our interest in examining the biological activity of the 3-amino-1,2-benzisothiazole 1,1-dioxide structure,<sup>1</sup> 3-hydrazino-1,2-benzisothiazole 1,1-dioxide (I)<sup>2</sup> was prepared by a modification of the Schrader method. Compound I had blood pressure lowering activity exempt from ganglionic blocking or monoamine oxidase inhibition.<sup>3</sup> Hydrazone and amide derivatives of the substituted 3-hydrazino-1,2-benzisothiazole 1,1-dioxides were explored for their hypotensive activity.

The permanganate oxidation of substituted *o*-methylbenzenesulfonamides usually gave mixtures of the desired 3-hydroxy-1,2-benzisothiazole 1,1-dioxides, the *o*-sulfamoylbenzoic acids, and starting material. Attempts to cyclize the *o*-sulfamoylbenzoic acids with hot concentrated  $H_2SO_4$  were generally unsatisfactory due to incomplete cyclization and difficult recovery of material. The oxidation of 5-chloro-2-methylbenzenesulfonamide<sup>4</sup> gave entirely 4-chloro-2-sulfamoylbenzoic acid, which was alternately cyclized to 2-acetyl-6-chloro-3-keto-2H,3H-1,2-benzisothiazole 1,1-dioxide (II) with acetic anhydride (see Scheme I).

The acid hydrolysis of II yielded a mixture of 6-chloro-3-hydroxy-1,2-benzisothiazole 1,1-dioxide and 4-chloro-2-sulfamoylbenzoic acid. Mild alkaline hydrolysis yielded 2-N-acetyl-4-chlorosulfamoylbenzoic acid. More vigorous alkaline hydrolysis yielded 4-

chloro-2-sulfamoylbenzoic acid. At 125–130° hydrazine and II reacted with opening of the benzisothiazole ring and displacement of the chloro group to produce 3,6-dihydrazino-1,2-benzisothiazole 1,1-dioxide (8). When hydrazinolysis was carried out in ethanol to avoid displacement of the chloro group, a mixture of the hydrazine salt of II and 4-chloro-2-sulfamoylbenzoic acid hydrazide was obtained. An attempt to prepare 5-chloro-3,6-dihydrazino-1,2-benzisothiazole 1,1-dioxide from 5,6-dichloro-3-hydroxy-1,2-benzisothiazole 1,1-dioxide and hydrazine gave an intractable product. The reaction of hydrazine with 3-hydroxy-6-sulfamoyl-1,2-benzisothiazole 1,1-dioxide<sup>5</sup> gave a good yield of 3-hydrazino-6-sulfamoyl-1,2-benzisothiazole 1,1-dioxide.

Mixtures from the permanganate oxidations were converted directly to 3-mercapto-1,2-benzisothiazole 1,1-dioxides in yields of 30–80% by heating them with  $P_2S_5$  alone or preferably in Dowtherm (see Scheme II). 4-Chloro-2-sulfamoylbenzoic acid and  $P_2S_5$  gave the best yield of 6-chloro-3-mercapto-1,2-benzisothiazole 1,1-dioxide. The 3-mercapto-1,2-benzisothiazole 1,1-dioxides were converted to the corresponding 3-methylmercapto derivatives, which easily underwent hydrazinolysis to produce the desired substituted 3-hydrazino-1,2-benzisothiazole 1,1-dioxides.

Large quantities of pure I were obtained by the hydrazinolysis of 3-methoxy-1,2-benzisothiazole 1,1-dioxide<sup>6</sup> in methanol. The method of Meadow and Reid could not be successfully scaled up, but large

(1) C. W. Whitehead and J. J. Traverso, *J. Org. Chem.*, **25**, 413 (1960).

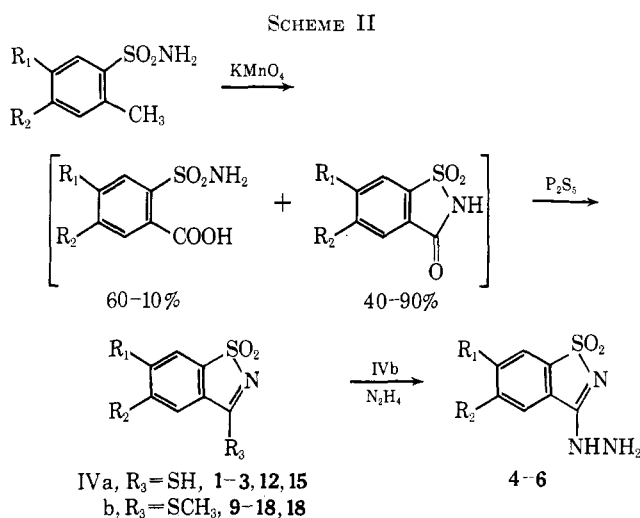
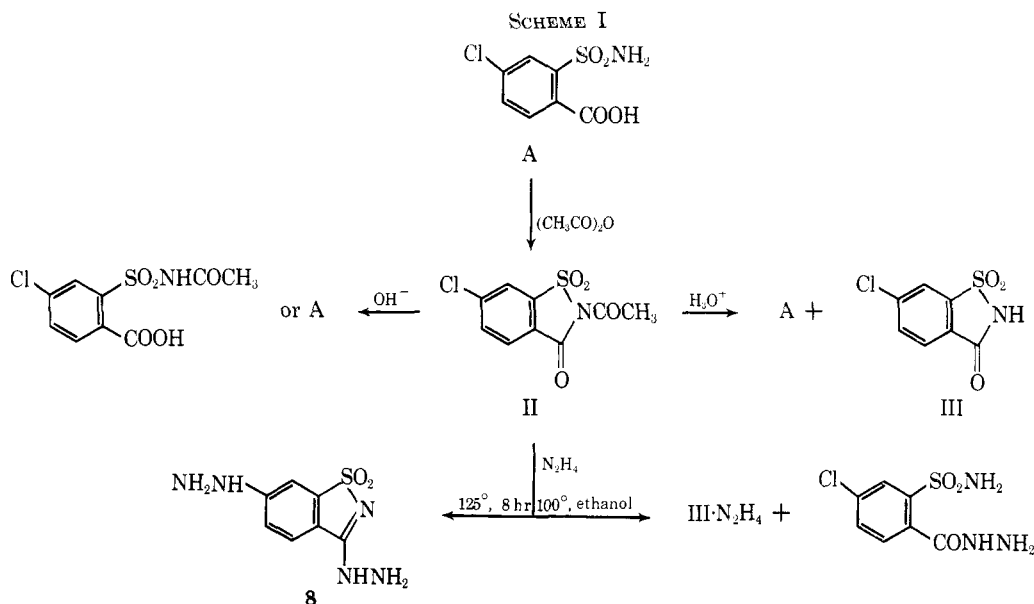
(2) E. Schrader, *J. Prakt. Chem.*, [2] **95**, 312 (1917).

(3) The pharmacology of compound I and details of the pharmacological methods are described in part III: P. W. Willard, C. W. Whitehead, and J. J. Traverso, *J. Med. Chem.*, **10**, 849 (1967).

(4) R. De Roode, *Am. Chem. J.*, **13**, 217 (1891).

(5) G. H. Hamor, *J. Pharm. Sci.*, **51**, 1109 (1962).

(6) J. R. Meadow and E. E. Reid, *J. Am. Chem. Soc.*, **65**, 457 (1943).



quantities of the pure 3-methoxybenzisothiazole 1,1-dioxide were obtained by the chlorine oxidation of 3-methylmercapto-1,2-benzisothiazole 1,1-dioxide<sup>7</sup> in methanol.

The various 3-hydrazino-1,2-benzisothiazole 1,1-dioxide derivatives were obtained by reactions with aldehydes, ketones, acid chlorides, acid anhydrides, isocyanates, and carbodiimides in inert solvents. Several of the 3-(2-arylsulfonylhydrazino)-1,2-benzisothiazole 1,1-dioxides were alkylated to give active derivatives.

**Pharmacology.**<sup>3</sup>—The compounds were tested in renal hypertensive rats. Following the control blood pressure determinations the compounds were administered by mouth to groups of three rats. Blood pressure readings were recorded hourly for 7 hr. Each figure (Table I) represents the mean change in blood pressure for three animals resulting from an oral dose of 20 mg/kg. From past experience in these laboratories with saline administration, blood pressure lowerings greater than 6% are considered to be significant.<sup>8</sup>

TABLE I

BLOOD PRESSURE RESPONSE IN RENAL HYPERTENSIVE RATS<sup>a</sup>

No.	Mean % <sup>b</sup>	Max % (hr) <sup>c</sup>	No.	Mean % <sup>b</sup>	Max % (hr) <sup>c</sup>	No.	Mean % <sup>b</sup>	Max % (hr) <sup>c</sup>
5	-21	-26 (7)	35	-8	-15 (5)	55	-5	-7 (5)
7	-3	-5 (7)	37	-10	-15 (5)	56	-6	-9 (5)
8	-9	-12 (7)	39	-8	-15 (6)	57	-2	-4 (3)
15	+2	+3 (2)	40	-9	-10 (7)	59	-9	-15 (5)
17	+1	+2 (3)	41	-7	-11 (3)	61	-13	-22 (5)
18	-5	-6 (2)	42	-4	-7 (7)	62	-5	-10 (5)
19	-8	-12 (7)	43	-9	-13 (3)	65	-4	-7 (5)
20	-13	-13 (7)	44	-2	-5 (5)	66	-6	-10 (7)
21	-11	-21 (5)	45	-9	-15 (5)	67	-14	-21 (7)
22	-11	-17 (5)	46	-10	-17 (7)	69	-12	-16 (7)
23	-3	-8 (6)	47	-5	-8 (7)	70	-6	-13 (5)
25	-4	-6 (7)	48	-11	-18 (6)	71	-5	-9 (5)
27	-3	-5 (5)	49	-10	-15 (5)	72	-1	-10 (5)
28	-14	-20 (5)	50	-13	-19 (5)	73	-10	-15 (6)
30	-11	-16 (6)	51	-6	-8 (7)	74	+2	+4 (3)
31	-9	-13 (7)	52	-15	-19 (5)	75	-5	-10 (7)
32	-1	-9 (7)	53	-6	-8 (7)	76	-5	-11 (5)
33	-1	-4 (5)	54	-8	-13 (6)	77	+1	+2 (1)

<sup>a</sup> All doses are 20 mg/kg. <sup>b</sup> Mean value for per cent decrease of blood pressure from control over a 7-hr period for three hypertensive rats. <sup>c</sup> Maximum per cent depression of blood pressure during a 7-hr period and hour at which maximum occurred.

Twenty-five (or 45%) of the 54 compounds reported in Table I have better than minimal activity. Two hydrazine compounds (5, 8), seven alkylaldehyde derivatives (19-22, 28, 30, 31), two ketone derivatives (35, 37), ten benzaldehyde derivatives (39-41, 43, 45, 46, 48-50, 52), and four amide derivatives (61, 67, 69, 73) have significant blood pressure lowering activity. Thirteen per cent of the compounds (5, 14, 20, 50, 52, 61, 67) show a very good blood pressure lowering ranging from 13 to 21% decrease.

### Experimental Section<sup>9</sup>

**Permanganate Oxidation of *o*-Methylbenzenesulfonamides.**—The appropriate *o*-methylbenzenesulfonamide (0.30 mole) was

(7) J. R. Meadow and J. C. Cavagnol, *J. Org. Chem.*, **16**, 1582 (1951).

(8) P. W. Willard, C. E. Powell, and F. G. Henderson, *Proc. Soc. Exptl. Biol. Med.*, **115**, 785 (1964).

(9) The melting points are corrected. All melting points were determined on hot stage apparatus (Mel-Temp and Culatti) which were calibrated against standard reference samples of specified melting ranges in accordance with the U. S. Pharmacopeia.

TABLE II  
 3-SUBSTITUTED 1,2-BENZISOTHIAZOLE 1,1-DIOXIDES


No.	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	Mp, °C	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
							Calcd	Found	Calcd	Found	Calcd	Found
1	Cl	Cl	SH	198	40	C <sub>7</sub> H <sub>3</sub> Cl <sub>2</sub> NO <sub>2</sub> S <sub>2</sub>					5.22	4.81
2	H	Cl	SH	210	68	C <sub>7</sub> H <sub>4</sub> ClNO <sub>2</sub> S <sub>2</sub>	35.97	35.62	1.72	1.75		
3	Cl	H	SH	198	61	C <sub>7</sub> H <sub>3</sub> ClNO <sub>2</sub> S <sub>2</sub>		36.02		1.81	5.99	5.74
4	Cl	Cl	NHNH <sub>2</sub>	275 dec	40	C <sub>7</sub> H <sub>3</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub> S	31.57	31.50	1.89	2.09	15.79	15.66
5	Cl	H	NHNH <sub>2</sub>	278	75	C <sub>7</sub> H <sub>4</sub> ClN <sub>3</sub> O <sub>2</sub> S	36.29	36.52	2.61	2.76	18.14	17.90
6	H	Cl	NHNH <sub>2</sub>	256	70	C <sub>7</sub> H <sub>4</sub> ClN <sub>3</sub> O <sub>2</sub> S		36.10		2.69		17.81
7	SO <sub>2</sub> NH <sub>2</sub>	H	NHNH <sub>2</sub>	270 dec	60	C <sub>7</sub> H <sub>3</sub> N <sub>4</sub> O <sub>4</sub> S <sub>2</sub>	30.43	30.71	2.92	3.06	20.28	20.57
8	NHNH <sub>2</sub>	H	NHNH <sub>2</sub>	285	44	C <sub>7</sub> H <sub>3</sub> N <sub>4</sub> O <sub>2</sub> S	37.43	37.26	3.99	4.17	30.81	30.77
9	Cl	H	CH <sub>3</sub> S	242	95	C <sub>8</sub> H <sub>4</sub> ClNO <sub>2</sub> S <sub>2</sub>	39.05	39.46	2.16	2.77	5.68	5.59
10	H	Cl	CH <sub>3</sub> S	195	70	C <sub>8</sub> H <sub>4</sub> ClNO <sub>2</sub> S <sub>2</sub>		38.96		2.71		5.48
11	H	CH <sub>3</sub> O	SH	168	60	C <sub>8</sub> H <sub>7</sub> NO <sub>2</sub> S <sub>2</sub>	41.90	42.06	3.07	3.06	6.11	6.21
12	CH <sub>3</sub> O	CH <sub>3</sub> O	Cl	85	60	C <sub>9</sub> H <sub>7</sub> ClNO <sub>2</sub> S	41.30	41.43	3.08	3.31	5.35	5.33
13	H	C <sub>2</sub> H <sub>5</sub> O	OH	243	68	C <sub>9</sub> H <sub>9</sub> NO <sub>2</sub> S	47.97	47.62	3.99	3.89	6.16	6.19
14	CH <sub>3</sub> O	CH <sub>3</sub> O	SH	246	40	C <sub>9</sub> H <sub>9</sub> NO <sub>2</sub> S <sub>2</sub>	41.68	41.26	3.50	3.45	5.40	5.50
15	H	H	NHN(CH <sub>3</sub> ) <sub>2</sub>	238 dec	90	C <sub>9</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> S	47.98	48.17	4.92	5.05	18.65	18.81
16	CH <sub>3</sub> O	CH <sub>3</sub> O	CH <sub>3</sub> S	312	64	C <sub>10</sub> H <sub>12</sub> NO <sub>2</sub> S <sub>2</sub>	43.78	43.61	4.40	4.11	5.11	5.05
17	H	H	NHNH-2,5-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	265 dec	23	C <sub>12</sub> H <sub>5</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub> S	45.62	45.83	2.65	2.81	12.28	12.54
18	H	H	NHNHC <sub>6</sub> H <sub>5</sub>	227 dec	62	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> S·H <sub>2</sub> O	53.59	53.77	4.50	4.61	14.42	14.40

dissolved in 1.2 l. of water containing 36 g of NaOH. The stirred solution was heated to 90°. A saturated aqueous solution of 106 g (0.6 mole) of KMnO<sub>4</sub> was added dropwise over a period of 4 hr. The hot solution was filtered, and the filtrate was acidified (H<sub>2</sub>SO<sub>4</sub>). First-crop material was obtained by allowing the solution to stand overnight. The oxidation product was collected, and the filtrate was evaporated to dryness under reduced pressure. The residue was extracted with hot ethanol, and the material obtained by concentration of the ethanol filtrate was added to the first crop. The oxidation products usually consisted of mixtures of 60–10% of the substituted 3-hydroxy-1,2-benzisothiazole 1,1-dioxides and 40–90% of the corresponding 2-sulfamoylbenzoic acid. The relative amounts were determined by titration. The 3-hydroxy-1,2-benzisothiazole 1,1-dioxides are strong acids with pK<sub>a</sub>'s below 3, and the 2-sulfamoylbenzoic acids have pK<sub>a</sub>'s at 4–6 for the carboxyl group and another at about 13 for the sulfonamide group. Yields of 35–50% were obtained from 5-nitro- and 4,5-dimethoxy-2-methylbenzenesulfonamides and 50–80% yields from the chloro- and methoxy-substituted 2-methylbenzenesulfonamides.

**2-Acetyl-6-chloro-3-keto-2H,3H-1,2-benzisothiazole 1,1-Dioxide.**—A 176-g mixture of 60% 6-chloro-3-hydroxy-1,2-benzisothiazole 1,1-dioxide and 40% 4-chloro-2-sulfamoylbenzoic acid was heated under reflux in 1 l. of acetic anhydride for 4 hr. The mixture was cooled and the crystalline product was collected and crystallized from ethyl acetate; yield 125 g (60%), mp 245°.

*Anal.* Calcd for C<sub>9</sub>H<sub>5</sub>ClNO<sub>2</sub>S: C, 41.63; H, 2.33; N, 5.39. Found: C, 41.75; H, 2.42; N, 5.42.

**Hydrolysis of 2-Acetyl-6-chloro-3-keto-2H,3H-1,2-benzisothiazole 1,1-Dioxide.**—2-Acetyl-6-chloro-3-keto-2H,3H-1,2-benzisothiazole 1,1-dioxide (1.5 g) in 10 ml of H<sub>2</sub>SO<sub>4</sub> was heated on the steam bath for 4 hr. The cooled solution was poured onto ice and 1 g of product was collected. It was shown by titration to be a mixture of 6-chloro-3-hydroxy-1,2-benzisothiazole 1,1-dioxide and 4-chloro-2-sulfamoylbenzoic acid.

2-Acetyl-6-chloro-3-keto-2H,3H-1,2-benzisothiazole 1,1-dioxide (3.0 g) was heated in a 50:50 solution of 1 N NaOH and ethanol until solution occurred. The ethanol was removed under reduced pressure, and the aqueous residue was acidified with HCl. N-Acetyl-4-chloro-2-sulfamoylbenzoic acid (2 g) was obtained, pK<sub>a</sub> = 4.80 and 7.65.

2-Acetyl-6-chloro-3-keto-2H,3H-1,2-benzisothiazole 1,1-dioxide (3.0 g) was heated at 100° for 5 hr in 1 N NaOH. Upon acidification with HCl, 1.5 g of 4-chloro-2-sulfamoylbenzoic acid, pK<sub>a</sub> = 4.40 and 13.40, was obtained.

**Reaction of Hydrazine with 2-Acetyl-6-chloro-3-keto-2H,3H-1,2-benzisothiazole 1,1-Dioxide.**—2-Acetyl-6-chloro-3-keto-2H,3H-1,2-benzisothiazole 1,1-dioxide (13.5 g) and 27.0 g of anhydrous hydrazine were heated at 130° for 8 hr in a sealed tube. The excess hydrazine was removed from the cooled mixture under reduced pressure, and the residue was neutralized with acetic

acid. The product which separated was collected and recrystallized from dilute ethanol to yield 3,6-dihydrazino-1,2-benzisothiazole 1,1-dioxide (Table I, 8).

2-Acetyl-6-chloro-3-keto-2H,3H-1,2-benzisothiazole 1,1-dioxide (70 g), 35 g of anhydrous hydrazine, and 175 ml of ethanol were heated at 100° for 8 hr in a sealed bomb. The ethanol was removed under reduced pressure from the cooled mixture, and the residue was neutralized with acetic acid to yield 42.6 g of solid. Crystallization from ethanol gave 25 g of 6-chloro-3-hydroxy-1,2-benzisothiazole 1,1-dioxide hydrazine salt, mp 190° dec, pK<sub>a</sub> = 8.3.

*Anal.* Calcd for C<sub>9</sub>H<sub>5</sub>ClN<sub>3</sub>O<sub>2</sub>S: C, 33.67; H, 3.22; N, 16.83. Found: C, 33.96; H, 3.53; N, 16.74.

The filtrate from above was concentrated to yield a solid. The solid was washed with water; yield 13 g of 4-chloro-2-sulfamoylbenzoic acid hydrazide, mp 194°, pK<sub>a</sub> = 11.45.

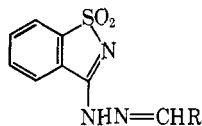
*Anal.* Calcd for C<sub>9</sub>H<sub>5</sub>ClN<sub>3</sub>O<sub>2</sub>S: C, 33.67; H, 3.22; N, 16.83. Found: C, 33.94; H, 3.40; N, 17.12.

**3-Mercapto-1,2-benzisothiazole 1,1-Dioxides (Table II, 1–3, 12, 15).**—The appropriate 3-hydroxy-1,2-benzisothiazole 1,1-dioxide (20–40 g) or its mixture with the benzoic acid and an equal molar amount of P<sub>2</sub>S<sub>5</sub> were heated in an oil bath at 165°. The solids were stirred as they gradually melted, and their color changed to dark orange. In some cases the exothermic reaction could not be controlled and decomposition occurred. When sand was added in a quantity of two times the weight of the combined reactants, the reaction was moderated. Better control was achieved by using 200–400 ml of Dowtherm (tetralin) as a solvent. The cooled, dry reaction mixtures were extracted five to seven times (CHCl<sub>3</sub>). The CHCl<sub>3</sub> was concentrated to yield the product. The Dowtherm reactions were cooled and the product was separated and purified by crystallization from benzene.

**3-Methylmercapto-1,2-benzisothiazole 1,1-Dioxides (Table II, 9, 10, 18).**—The appropriate 3-mercapto-1,2-benzisothiazole 1,1-dioxide (0.10 mole) was suspended in 250 ml of water containing 12 g (0.30 mole) of NaOH. The stirred mixture was heated to 45° and 28 g (0.20 mole) of CHI<sub>3</sub> was added dropwise over a period of 2 hr. The product was collected from the cooled mixture and purified by crystallization from benzene.

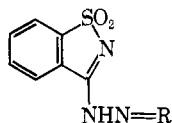
**3-Hydrazino-1,2-benzisothiazole 1,1-Dioxides (Tables II, 4–6).**—The 3-methylmercapto-1,2-benzisothiazole 1,1-dioxide (0.1 mole) and 14.7 g (0.25 mole) of 85% hydrazine hydrate in 200 ml of ethanol were heated under reflux for 1 hr. The mixture was cooled in an ice bath and the product was collected. Second-crop material was obtained by concentrating the filtrate. The products were purified by crystallization from either large volumes of ethanol or ethanol–DMF.

**3-Methoxy-1,2-benzisothiazole 1,1-Dioxide by Chlorinolysis in Methanol.**—Chlorine gas was passed through, at a moderate rate, a stirred suspension of 40 g (0.19 mole) of 3-methylmercapto-1,2-benzisothiazole 1,1-dioxide in 600 ml of methanol. The

TABLE III  
 3-[2-(SUBSTITUTED ALKYLIDENE)HYDRAZINO]-1,2-BENZISOTHIAZOLE 1,1-DIOXIDES


No.	R	Mp, °C	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
					Calcd	Found	Calcd	Found	Calcd	Found
19	CH <sub>2</sub> =C(CH <sub>3</sub> )	223 dec	51	C <sub>11</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> S	52.99	53.32	4.44	4.72	16.85	17.10
20	CH <sub>3</sub> CH=CH	196 dec	55	C <sub>11</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> S		52.79		4.75		16.83
21	CH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub>	100	40	C <sub>11</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S · H <sub>2</sub> O					15.60	15.24
22	2-Thienyl	279	96	C <sub>12</sub> H <sub>9</sub> N <sub>3</sub> O <sub>2</sub> S <sub>2</sub>	49.47	49.62	3.11	3.15	14.42	14.23
23	2-Furyl	260	80	C <sub>12</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub> S	52.35	52.36	3.29	3.26	15.26	15.22
24	CH <sub>3</sub> CH=C(CH <sub>3</sub> )	265	50	C <sub>12</sub> H <sub>12</sub> ClN <sub>3</sub> O <sub>2</sub> S <sup>a</sup>	48.40	48.43	4.06	4.28	14.11	13.99
25	4-Pyridyl	260 dec	87	C <sub>13</sub> H <sub>10</sub> N <sub>4</sub> O <sub>2</sub> S	53.76	53.53	4.01	3.82	18.58	18.57
26	2-Furyl-CH=CH	254	60	C <sub>14</sub> H <sub>11</sub> N <sub>3</sub> O <sub>3</sub> S	55.80	55.50	3.67	3.80	13.95	13.81
27	6-Methyl-2-pyridyl	265 dec	75	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub> S	55.98	56.19	4.03	4.23	18.65	18.63
28	Δ <sup>3</sup> -Cyclohexenyl	220	83	C <sub>14</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	58.11	58.10	5.22	5.33	14.52	14.26
29	CH <sub>3</sub> CH=C(CH <sub>3</sub> )	250	23	C <sub>14</sub> H <sub>17</sub> N <sub>3</sub> O <sub>4</sub> S <sup>b</sup>	52.00	51.84	5.30	5.44	13.00	12.74
30	5-Norbornen-2-yl	155	81	C <sub>15</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	59.78	59.97	5.01	5.30	13.94	13.85
31	3-Indolyl	327	70	C <sub>16</sub> H <sub>12</sub> N <sub>4</sub> O <sub>2</sub> S	59.24	59.19	3.73	3.92	17.27	17.04
32	C <sub>6</sub> H <sub>5</sub> CH=CH	259	65	C <sub>16</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> S	61.72	61.43	4.20	4.17	13.50	13.43

<sup>a</sup> 6-Chloro. <sup>b</sup> 5,6-Dimethoxy.

 TABLE IV  
 KETONE DERIVATIVES OF 3-HYDRAZINO-1,2-BENZISOTHIAZOLE 1,1-DIOXIDES


No.	R	Mp, °C	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
					Calcd	Found	Calcd	Found	Calcd	Found
33	Isopropylidene	215	58	C <sub>10</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> S	50.61	50.41	4.67	4.77	17.71	17.49
34	Cyclopentylidene	230 dec	75	C <sub>12</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> S	54.73	54.43	4.97	5.28		
35	Cyclohexylidene	178	70	C <sub>13</sub> H <sub>15</sub> N <sub>3</sub> O <sub>2</sub> S	56.29	55.96	5.45	5.68	15.15	14.79
36	=C(CH <sub>3</sub> )CH <sub>2</sub> CO <sub>2</sub> C <sub>2</sub> H <sub>5</sub>	228 dec	55	C <sub>13</sub> H <sub>15</sub> N <sub>3</sub> O <sub>4</sub> S	50.47	50.57	4.88	4.97	13.58	13.28
37	C <sub>6</sub> H <sub>5</sub> NO <sub>2</sub> <sup>a</sup>	232	75	C <sub>15</sub> H <sub>13</sub> N <sub>4</sub> O <sub>3</sub> S	49.58	49.76	4.16	4.04	15.42	15.62
38	C <sub>6</sub> H <sub>13</sub> O <sup>b</sup>	270	71	C <sub>15</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub> S	56.41	56.21	5.36	5.64	13.15	12.92

<sup>a</sup> 4-Ethoxycarbonyl-2-oxo-3-piperidylidene. <sup>b</sup> 5,5-Dimethyl-3-oxocyclohexylidene.

temperature rose to 60°, and gentle reflux of the methanol occurred while HCl was given off. The passage of Cl<sub>2</sub> was continued until the yellow color of both the solid and the solution was discharged. The reaction flask was cooled in an ice bath while air was passed through the mixture to expel excess Cl<sub>2</sub>. The solid was collected and the methanol filtrate was concentrated to yield 32 g (85%) of product, mp 180° (lit.<sup>6</sup> 182°). A mixture melting point with an authentic sample was not depressed. The ir and nmr spectra were identical with those of an authentic reference sample.

**3-Hydrazino-1,2-benzisothiazole 1,1-Dioxide (I).**—Thirty grams (0.5 mole) of 85% hydrazine hydrate was added dropwise with stirring to 98 g (0.50 mole) of 3-methoxy-1,2-benzisothiazole 1,1-dioxide in 2 l. of methanol under reflux. The reflux was continued for 1 hr after completion of the hydrazine addition. The mixture was cooled, and the product was collected by filtration. The yield of first crop material was 75% or better in subsequent runs. Some second-crop material was obtained by concentrating the filtrate. Purification was effected by crystallization from hot water (1 g/100 ml) after treatment with carbon, mp 249° dec (lit.<sup>2</sup> 257° dec), p*K*<sub>a</sub> (66% DMF) = 7.8.

*Anal.* Calcd for C<sub>7</sub>H<sub>7</sub>N<sub>3</sub>O<sub>2</sub>S: C, 42.63; H, 3.58; N, 21.31. Found: C, 42.37; H, 3.50; N, 21.35.

Compounds **16**, **19**, and **20** (Table I) were prepared by a modification of this method. Benzene was used as a solvent with the appropriately substituted hydrazine.

**Hydrazones of 3-Hydrazino-1,2-benzisothiazole 1,1-Dioxides (Tables III-V).**—The 3-hydrazino-1,2-benzisothiazole 1,1-dioxide (0.1 mole) and 0.1 mole of the appropriate aldehyde or ketone were heated under reflux in dioxane for 2 hr. The dioxane was removed under reduced pressure. The residue was taken up in hot ethanol or ethyl acetate and the product was obtained by

concentration of the solvent. The hydrazones were recrystallized from ethanol or ethyl acetate.

**3-[1-Acetyl-2-(2-methyl-2-butylidene)hydrazino]-1,2-benzisothiazole 1,1-Dioxide.**—3-[2-(2-Methyl-2-butylidene)hydrazino]-1,2-benzisothiazole 1,1-dioxide (5 g, 0.02 mole) 1.6 g (0.02 mole) of pyridine, and excess acetic anhydride were allowed to stand at room temperature for 2 days. The acetic anhydride was removed under reduced pressure and ethanol was added to the resulting syrup. The ethanol solution was treated with carbon, filtered, and concentrated to give the product; yield 55%, mp 159°.

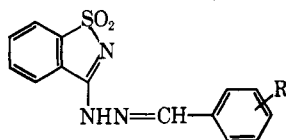
*Anal.* Calcd for C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>S: C, 55.06; H, 4.95; N, 13.76. Found: C, 55.41; H, 5.24; N, 13.57.

**Amides of 3-Hydrazino-1,2-benzisothiazole 1,1-Dioxide (Table VI).**—Compound I (10 g, 0.05 mole) was added to excess formic acid, excess acetic anhydride, or 0.05 mole of the appropriate acid anhydride in dioxane. The mixture was heated under reflux for 2 hr.

I (10 g, 0.05 mole) was dissolved in dioxane with 5 g (0.05 mole) of triethylamine. The appropriate acid chloride, alkylsulfonyl chloride, or ethyl chloroformate was added with stirring. The mixture was warmed on the steam bath for 2 hr. Alternately, I (10 g, 0.05 mole) was dissolved in water containing 2 g (0.05 mole) of NaOH. The arylsulfonyl chloride was added with stirring and the mixture was warmed on the steam bath for 2 hr. The solutions were evaporated under reduced pressure and the residual products crystallized from ethanol. The arylsulfonyl derivatives were collected from the aqueous solutions and crystallized from ethanol.

**Alkylation of 3-(2-Arylsulfonylhydrazino)-1,2-benzisothiazole 1,1-Dioxide.**—The 3-(2-arylsulfonylhydrazino)-1,2-benzisothiazole 1,1-dioxide (0.05 mole) was dissolved in water containing 2-4 g (0.05-0.10 mole) of NaOH. Allyl bromide (12 g, 0.1 mole),

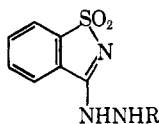
TABLE V  
3-[2-(SUBSTITUTED BENZYLIDENO)HYDRAZINO]-1,2-BENZISOTHIAZOLE 1,1-DIOXIDES



No.	R	Mp, °C	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
					Calcd	Found	Calcd	Found	Calcd	Found
33	3,4-Cl <sub>2</sub>	327	71	C <sub>14</sub> H <sub>9</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>2</sub> S	47.47	47.63	2.56	2.85	11.86	11.75
40	2-Cl	290	75	C <sub>14</sub> H <sub>10</sub> ClN <sub>3</sub> O <sub>2</sub> S	52.58	52.70	3.15	3.22	13.14	12.53
41	3-Cl	307	89	C <sub>14</sub> H <sub>10</sub> ClN <sub>3</sub> O <sub>2</sub> S		52.71		3.40		13.09
42	4-Cl	315	80	C <sub>14</sub> H <sub>10</sub> ClN <sub>3</sub> O <sub>2</sub> S		52.59		3.32		12.85
43	2-F	297	92	C <sub>14</sub> H <sub>10</sub> FN <sub>3</sub> O <sub>2</sub> S	55.44	55.54	3.32	3.54	13.85	14.09
44	3-F	319	87	C <sub>14</sub> H <sub>10</sub> FN <sub>3</sub> O <sub>2</sub> S		55.61		3.51		13.60
45	4-F	301	93	C <sub>14</sub> H <sub>10</sub> FN <sub>3</sub> O <sub>2</sub> S		55.74		3.64		13.96
46	H	290 dec <sup>a</sup>	80	C <sub>14</sub> H <sub>11</sub> N <sub>3</sub> O <sub>2</sub> S	58.93	58.76	3.88	3.96	14.73	14.99
47	2-OH	358	85	C <sub>14</sub> H <sub>11</sub> N <sub>3</sub> O <sub>3</sub> S	55.80	55.70	3.67	3.81	13.95	13.80
48	3-OH	300 dec	69	C <sub>14</sub> H <sub>11</sub> N <sub>3</sub> O <sub>3</sub> S		55.98		3.81		13.86
49	4-CH <sub>3</sub>	295	79	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> O <sub>2</sub> S	60.18	60.03	4.38	4.75	14.04	13.94
50	3-OCH <sub>3</sub>	264	92	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S	57.13	57.28	4.15	4.23	13.33	13.05
51	4-OCH <sub>3</sub>	285 <sup>b</sup>	78	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S		57.14		4.17		13.04
52	2,3-(OCH <sub>3</sub> ) <sub>2</sub>	274	85	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O <sub>4</sub> S	55.64	55.60	4.37	4.67	12.16	12.08
53	2,4-(OCH <sub>3</sub> ) <sub>2</sub>	280	98	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O <sub>4</sub> S	55.64	55.82	4.37	4.50	12.16	12.03
54	2,5-(OCH <sub>3</sub> ) <sub>2</sub>	275	71	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O <sub>4</sub> S		55.48		4.41		11.91
55	3,4-(OCH <sub>3</sub> ) <sub>2</sub>	269	89	C <sub>16</sub> H <sub>15</sub> N <sub>3</sub> O <sub>4</sub> S		55.53		4.36		12.06
56	3,4,5-(OCH <sub>3</sub> ) <sub>3</sub>	311	75	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> O <sub>5</sub> S	54.39	54.42	4.56	4.56	11.19	10.99

<sup>a</sup> Lit.<sup>2</sup> 287°. <sup>b</sup> Lit.<sup>2</sup> 270°.

TABLE VI  
3-(2-SUBSTITUTED HYDRAZINO)-1,2-BENZISOTHIAZOLE 1,1-DIOXIDES



No.	R	Mp, °C	Yield, %	Formula	Carbon, %		Hydrogen, %		Nitrogen, %	
					Calcd	Found	Calcd	Found	Calcd	Found
57	CHO	211 dec	25	C <sub>8</sub> H <sub>7</sub> N <sub>3</sub> O <sub>3</sub> S	42.66	42.38	3.15	3.52	18.66	18.68
58	CH <sub>3</sub> SO <sub>2</sub>	270	23	C <sub>8</sub> H <sub>8</sub> ClN <sub>3</sub> O <sub>4</sub> S <sub>2</sub> <sup>a</sup>	31.02	31.71	2.60	2.98	13.56	13.21
59	CH <sub>3</sub> SO <sub>2</sub>	272	29	C <sub>8</sub> H <sub>9</sub> N <sub>3</sub> O <sub>4</sub> S <sub>2</sub>	34.91	34.90	3.29	3.35	15.26	15.40
60	CH <sub>3</sub> CO	274	51	C <sub>9</sub> H <sub>9</sub> ClN <sub>3</sub> O <sub>3</sub> S <sup>a</sup>	39.49	39.81	2.94	3.27	15.35	14.95
61	CH <sub>3</sub> CO	265 dec	82	C <sub>9</sub> H <sub>9</sub> N <sub>3</sub> O <sub>3</sub> S	45.18	45.20	3.79	4.12	17.56	17.24
62	C <sub>2</sub> H <sub>5</sub> CO	211	67	C <sub>10</sub> H <sub>11</sub> N <sub>3</sub> O <sub>3</sub> S	47.42	47.08	4.37	4.84	16.59	16.55
63	C <sub>2</sub> H <sub>5</sub> OCO	207	27	C <sub>10</sub> H <sub>11</sub> N <sub>3</sub> O <sub>4</sub> S	44.60	44.97	4.11	4.22	15.60	15.60
64	C <sub>3</sub> H <sub>7</sub> CO <sup>b</sup>	206	95	C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S	49.80	50.02	4.17	4.26	15.84	15.76
65	<i>n</i> -C <sub>8</sub> H <sub>17</sub> CO	110	45	C <sub>11</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S	49.42	49.63	4.90	5.19	15.72	15.99
66	3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> SO <sub>2</sub>	222	58	C <sub>13</sub> H <sub>9</sub> Cl <sub>2</sub> N <sub>3</sub> O <sub>4</sub> S <sub>2</sub>	38.43	38.85	2.23	2.21	10.34	10.73
67	<i>p</i> -BrC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>	210	85	C <sub>13</sub> H <sub>10</sub> BrN <sub>3</sub> O <sub>4</sub> S <sub>2</sub>	37.51	37.68	2.42	2.52	10.09	9.70
68	C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub>	125	90	C <sub>13</sub> H <sub>10</sub> ClN <sub>3</sub> O <sub>4</sub> S <sub>2</sub> <sup>a</sup>	41.99	41.45	2.71	2.99	11.30	11.04
69	<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>	237 dec	71	C <sub>13</sub> H <sub>10</sub> N <sub>4</sub> O <sub>6</sub> S <sub>2</sub>	40.83	41.19	2.63	2.82	14.65	14.78
70	C <sub>6</sub> H <sub>5</sub> SO <sub>2</sub>	134	92	C <sub>13</sub> H <sub>11</sub> N <sub>3</sub> O <sub>4</sub> S <sub>2</sub> · H <sub>2</sub> O	44.00	44.12	3.69	3.75	11.84	11.89
71	C <sub>6</sub> H <sub>5</sub> CO	285 <sup>c</sup>	54	C <sub>14</sub> H <sub>11</sub> N <sub>3</sub> O <sub>3</sub> S	55.80	56.19	3.67	4.03	13.95	13.69
72	C <sub>6</sub> H <sub>5</sub> NHCO	164	69	C <sub>14</sub> H <sub>12</sub> N <sub>4</sub> O <sub>3</sub> S	53.15	53.07	3.82	4.02	17.71	17.88
73	<i>p</i> -CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub>	178	71	C <sub>14</sub> H <sub>13</sub> N <sub>3</sub> O <sub>4</sub> S <sub>2</sub>	47.83	47.60	3.72	3.75	11.96	11.81
74	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> CO	232	76	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S					13.32	13.04
75	C <sub>6</sub> H <sub>5</sub> OCH <sub>2</sub> CO	239	30	C <sub>15</sub> H <sub>13</sub> N <sub>3</sub> O <sub>4</sub> S	54.37	54.25	3.95	4.20	12.68	12.33
76	C <sub>10</sub> H <sub>7</sub> SO <sub>2</sub> <sup>d</sup>	211	67	C <sub>17</sub> H <sub>13</sub> N <sub>3</sub> O <sub>4</sub> S <sub>2</sub>	52.70	52.78	3.38	3.69	10.85	11.12
77	3,4,5-(CH <sub>3</sub> O) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> CO	223	49	C <sub>17</sub> H <sub>17</sub> N <sub>3</sub> O <sub>5</sub> S	52.16	52.37	4.51	4.70		

<sup>a</sup> 6-Chloro. <sup>b</sup> Cyclopropyl. <sup>c</sup> Lit.<sup>2</sup> 287°. <sup>d</sup> Naphthyl.

methyl iodide (14.2 g, 0.10 mole), or dimethyl sulfate (6.3 g, 0.05 mole) was added dropwise to the stirred mixture. The mixture was heated to 60° when the alkyl halides were used, and the dimethyl sulfate alkylation was run at room temperature. After 2 hr the following products were collected and crystallized from ethanol.

3-[2-(2-Methylbenzenesulfonyl)hydrazino]-1,2-benzisothiazole 1,1-dioxide, yield 91.5%, mp 188°. *Anal.* Calcd for C<sub>14</sub>H<sub>13</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub>: C, 47.85; H, 3.72; N, 11.96. Found: C, 47.60; H, 3.75; N, 11.81.

3-[2-(Methyltosyl)hydrazino]-1,2-benzisothiazole 1,1-dioxide, yield 68.5%, mp 211°. *Anal.* Calcd for C<sub>15</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub>: C, 49.30; H, 4.14; N, 11.50. Found: C, 49.46; H, 4.44; N, 11.71.

3-[2-(2-Allylbenzenesulfonyl)hydrazino]-1,2-benzisothiazole 1,1-dioxide, yield 45%, mp 122–126°. *Anal.* Calcd for C<sub>16</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>S<sub>2</sub> · C<sub>2</sub>H<sub>5</sub>OH: C, 51.04; H, 5.00; N, 9.92; S, 15.14. Found: C, 50.97; H, 5.00; N, 9.82; S, 15.08.

3-[3,4-Di(*p*-dimethylaminophenyl)-2-iminosemicarbazido]-1,2-benzisothiazole 1,1-Dioxide.—Compound I (3 g, 0.015 mole) was suspended in dioxane with 1.5 g (0.015 mole) of bis(*p*-dimethyl-

aminophenyl)carbodiimide and heated for 2 hr. The dioxane was removed under reduced pressure. The residue was crystallized from dilute ethanol; yield 850 mg (38%), mp 242° dec.

*Anal.* Calcd for  $C_{24}H_{27}N_7O_2S$ : C, 60.35; H, 5.69. Found: C, 60.62; H, 5.95.

**3-(3,4-Dicyclohexyliminosemicarbazido)-1,2-benzisothiazole 1,1-dioxide** was prepared by the procedure above; yield 46%, mp 238°.

*Anal.* Calcd for  $C_{20}H_{23}N_5O_2S$ : C, 59.52; H, 7.21; N, 17.35. Found: C, 60.21; H, 7.71; N, 16.79.

**Acknowledgment.**—We wish to express our thanks to our colleagues in microanalysis, physical chemistry, and pharmacology, who obtained the data referred to in this paper.

## Hypotensive 1,2-Benzisothiazole 1,1-Dioxides. III. 3-[2-(2-Methyl-2-butyldene)hydrazino]-1,2-benzisothiazole 1,1-Dioxide and Related Analogs

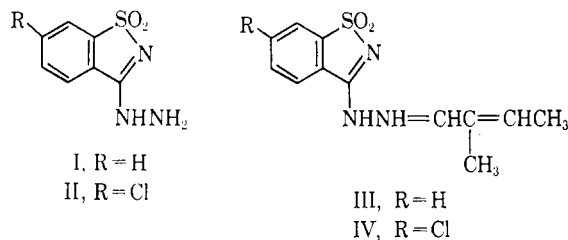
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A series of 1,2-benzisothiazole 1,1-dioxides have been prepared, some of which produce significant hypotensive activity. One of the members of this series, 3-[2-(2-methyl-2-butyldene)hydrazino]-1,2-benzisothiazole 1,1-dioxide (III), produces significant hypotensive activity in unanesthetized animals. A consistent observation for active members of the series has been the erratic hypotensive activity in renal hypertensive rats. *In vivo* and *in vitro* activity indicates a mechanism of action other than a direct effect on the nervous systems or the vascular smooth muscle.

In the preceding papers a series of 1,2-benzisothiazole 1,1-dioxides has been reported.<sup>1,2</sup> Many of the compounds in the series exhibited significant hypotensive activity; however, 3-[2-(2-methyl-2-butyldene)hydrazino]-1,2-benzisothiazole 1,1-dioxide (III) was given preference for extensive pharmacological study primarily because of its potent and relatively reproducible activity in a large number of pharmacological test preparations.



### Experimental Section

**Pharmacological Methods. Hypertensive Rats.**—Compound III was administered orally (20 mg/kg) to groups of three renal<sup>3</sup> and three steroid (DOCA)<sup>4</sup> hypertensive rats. Blood pressures were determined during the day by the method of Friedman and Freed<sup>5</sup> before and at 1, 2, 3, 5, 6, and 7 hr following drug administration. Because of the increased activity of III with daily administration, the drug was given, and blood pressures were determined, on at least 5 consecutive days. The hypotensive response to III was also measured during 19 days of continuous administration of the drug. The blood pressures from the three rats in each group were averaged at each hour and over the 7-hr interval. The results were expressed as a per cent decrease from control at the hour of maximum decrease and for the 7-hr period. Other compounds from the series evaluated in the same animal preparation include 3-hydrazino-1,2-benzisothiazole 1,1-dioxide (I), which is the starting material for preparation of III, 6-chloro-3-hydrazino-1,2-benzisothiazole 1,1-dioxide (II), and 6-chloro-3-[2-(2-methyl-2-butyldene)hydrazino]-1,2-benzisothiazole 1,1-dioxide (IV).

**Hypertensive Dogs.**—Two dogs were selected from a colony of renal hypertensive dogs made hypertensive by a modification of the methods of Goldblatt, *et al.*,<sup>6</sup> and Page.<sup>7</sup> In dog ZH-114 the left kidney was removed and the right kidney was wrapped in silk. About six months later the right renal artery was constricted by a Goldblatt clamp. In dog ZH-124 both renal arteries were partially occluded with a Goldblatt clamp. These clamps were tightened eight months following the initial surgery. Following femoral arterial puncture blood pressure observations were made before and at 1, 3, and 6 hr after oral drug administration. Each dog received 10 mg/kg of III for 5 consecutive days followed by a rest period of 9 days at the end of which time medication was resumed at a dose of 20 mg/kg for 5 days. Postmedication pressures were taken to measure the extent of delayed activity.

**Hemodynamic Studies.**—Two normotensive dogs were anesthetized with sodium phenobarbital (150 mg/kg) intravenously. The trachea was intubated for artificial respiration and the thoracic cavity was opened for exposure of the ascending aorta. A probe from an electromagnetic blood flow meter was positioned on the aorta for cardiac output measurement. The carotid artery was cannulated and pressure was determined by transducer measurement. Lead II of the electrocardiogram was monitored for heart rate. Stroke volume was calculated from the cardiac output and heart rate. Peripheral vascular resistance (PVR) was derived by the following formula. These values were

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$$\text{Total PVR} = \frac{\text{arterial blood pressure (mm)} \times 100}{\text{cardiac output (ml/min)}}$$

measured and calculated before and at 30-min intervals following intravenous administration of 10 mg/kg of III.

**Sympathetic Postganglionic Nerve Stimulation.**—In three normotensive phenobarbital-anesthetized (150 mg/kg) dogs the thoracic cavity was opened and the cardiac-accelerator nerve originating from the stellate ganglion was dissected free. Control stimulation (14 v, 20 cps with a 0.5-msec duration for 30 sec) of the sympathetic postganglionic nerve fibers produced cardiac acceleration that was compared to postdrug neural-induced tachycardia.<sup>8</sup> In addition, the per cent change in heart rate was

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