Anal. Calcd for $C_{11}H_8ClN$: C, 70.41; H, 3.22; N, 7.47. Found: C, 70.51; H, 3.13; N, 7.66.

4-Chloro-1-naphthalenemethylamine.—Reduction of 47 g (0.25 mole) of 4-chloro-1-naphthonitrile was accomplished with $LiAlH_4$. The nitrile was dissolved in 1.0 l. of 1:1 ether–THF and added to 9.5 g (0.25 mole) of the hydride in 500 ml of ether. Two distillations of the product gave 17.6 g (37%) of yellow oil, bp 113–115° (0.2 mm) $n^{25}D$ 1.6446.

Anal. Calcd for $C_{11}H_{10}ClN$: C, 68.92; H, 5.26; N, 7.31. Found: C, 69.17; H, 5.54; N, 7.13.

Acknowledgments.—The microanalyses were provided by Mr. Orville Kolsto and Mr. Victor Rauschel and staff of the Abbott Microanalytical Laboratory. The catalytic hydrogenations and other pressure reactions were carried out by Mr. Morris Freifelder and Mr. Daniel Dunnigan. Certain intermediate compounds were prepared by Mr. Walter J. Ramus, Jr., Mr. C. Wayne Ours, and Miss Elizabeth Kurella. Mr. William Washburn and his associates provided the infrared spectra. The nmr spectra were provided by Dr. Milton Levenberg and Ruth Stanaszek. We also wish to thank Messrs. Harold Brondyk, Charles Shannon, William Watrous, and Leo Wiemeler for assisting with the pharmacological studies.

Hypotensive 1,2-Benzisothiazole 1,1-Dioxides. I. Pyrazole and Pyrazoline Derivatives

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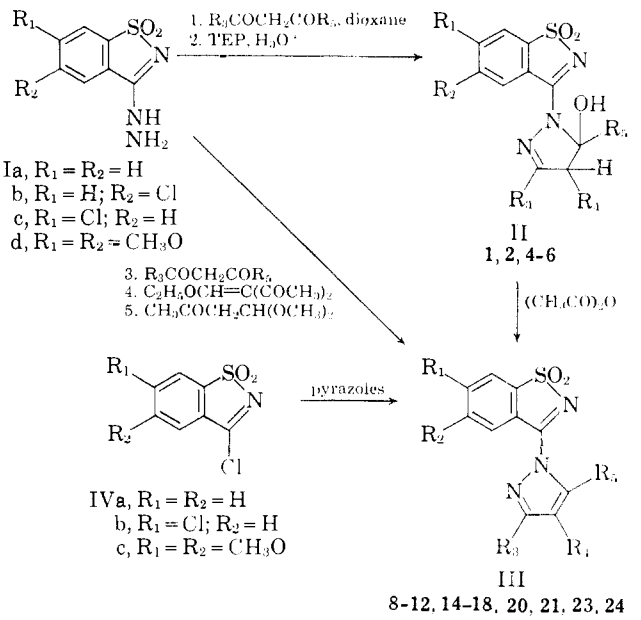
Pyrazolyl- and pyrazolinyl-1,2-benzisothiazole 1,1-dioxides were prepared by the condensation of 3-hydrazinobenzisothiazole 1,1-dioxides with 1,3-diketones, keto esters, ketoacetaldehyde acetals, diacetals, and unsaturated ketones. Hydroxypyrazolines were obtained under certain conditions and these were dehydrated to pyrazoles. The hypotensive activities were determined in the Goldblatt rat preparation.

In our search for hypotensive agents 3-(3,5-dimethylpyrazol-1-yl)-1,2-benzisothiazole 1,1-dioxide was prepared and subsequently was found to lower blood pressure in the Goldblatt rat preparation. Additional substituted pyrazolyl and pyrazolinyl derivatives were synthesized and studied to confirm the hypotensive activity of this series. Condensation of 1,3-diketones with 3-hydrazino-1,2-benzisothiazole 1,1-dioxide[1] (I) in refluxing Ethyl Cellosolve yielded 3-(3,5-disubstituted pyrazol-1-yl)-1,2-benzisothiazol 1,1-dioxides (Scheme I). The corresponding 3-(3,5-disubstituted 5-hydroxypyrazolin-1-yl)-1,2-benzisothiazole 1,1-dioxides were obtained when the reaction was carried out in dioxane. This indicates that hydroxypyrazolines are intermediates in the Cellosolve reaction and undergo dehydration to the pyrazoles *in situ* at the boiling temperature of the solvent.

Dehydration of the hydroxypyrazolines was also accomplished with acetic anhydride. Acylation of the hydroxy group occurred in the case of 3-(5-hydroxy-3-methyl-5-phenyl-2-pyrazolin-1-yl)-1,2-benzisothiazole 1,1-dioxide. Dehydration of the 3,5-dialkyl-5-hydroxypyrazolines always occurred under the mildest conditions required for reaction with acetic anhydride. An alternate method was used when substituted 3-hydrazino-1,2-benzisothiazole 1,1-dioxides were not easily accessible. Pyrazole, 4-chloropyrazole, and 3,5-dimethylpyrazole were fused with substituted 3-chloro-1,2-benzisothiazole 1,1-dioxides[2] to yield the corresponding substituted 3-pyrazolyl-1,2-benzisothiazole 1,1-dioxides.

Tetraethoxypropane (TEP) reacted with 3-hydrazino-1,2-benzisothiazole 1,1-dioxide[1] (I) in dilute H_2SO_4 to give a crystalline product, $C_{10}H_9N_3O_3S$ (Scheme I). Upon treatment with acetic anhydride, this compound gave 3-(pyrazol-1-yl)-1,2-benzisothiazole 1,1-dioxide (**11**) identical with that obtained from the fusion of pyrazole and I. The cyclic pyrazolinyl structure for the $C_{10}H_9N_3O_3S$ product was established as 3-(5-hydroxypyrazolin-1-yl)-1,2-benzisothiazole 1,1-dioxide.

SCHEME I

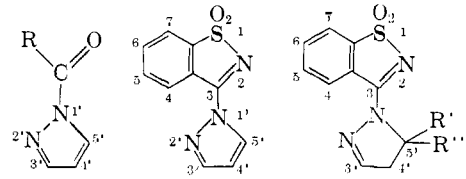


The reaction of I with mesityl oxide gave 3-(3,5,5-trimethylpyrazolin-1-yl)-1,2-benzisothiazole 1,1-dioxide (**3**). Condensation of 3-ketobutyraldehyde 1-dimethyl acetal yielded 3-(3-methylpyrazol-1-yl)-1,2-benzisothiazole 1,1-dioxide (**12**). Ethoxymethyleneacetylacetone reacted with I to furnish 3-(4-acetyl-3-methylpyrazol-1-yl)-1,2-benzisothiazole 1,1-dioxide (**17**).

(1) E. Schrader, *J. Prakt. Chem.*, [2] **95**, 312 (1917).
(2) J. R. Meadow and E. E. Reid, *J. Am. Chem. Soc.*, **65**, 457 (1943).

TABLE I

ASSIGNMENT OF POSITIONS OF THE SUBSTITUENTS ON THE PYRAZOLE AND PYRAZOLINE RINGS AND THE CHEMICAL SHIFTS OF THEIR NMR SIGNALS[a]



A, B, R = CH_3 11–23 1–7
C, D, R = C_6H_5

	Substitution			Chemical shift, δ, ppm				
Compd	3′	4′	5′	4	5,6,7	3′	4′	5′
A	H	H	H			7.71	6.44	8.25
B	CH_3	H	CH_3			2.22	5.96	2.52
C	H	H	H	8.03	7.54	7.81	6.49	8.46
D	CH_3	H	CH_3	8.19	7.54	2.24	6.07	2.64
11	H	H	H	9.02	7.90	8.05	6.66	8.53
12	CH_3	H	H	9.17	7.88	2.47	6.50	8.47
15	CH_3	H	CH_3	9.13	7.83	2.37	6.20	2.73
20	C_2H_5	H	C_2H_5	9.13	7.83	1.33[b]	6.27	1.33[b]
						2.75[c]		3.20[c]
23	CH_3	H	C_6H_5	9.23	7.88	2.82	6.73	
18	CH_3	CH_3	CH_3	9.12	7.76	2.32	2.00	2.65
17	CH_3	CH_3CO	H	9.07	7.92	2.57[d]	2.65[d]	9.08
1	H	H	H, OH	8.63	7.93	7.78	3.12[e]	6.12
							3.07	6.47
2	CH_3	H, H	CH_3, OH	8.58	7.80	2.23	3.12	2.03
3	CH_3	H, H	CH_3, CH_3	8.62	7.72	2.20	2.92	1.77
5	C_2H_5	H, H	C_2H_5, OH	8.57	7.75		3.03	
6	CH_3	H, H	C_6H_5, OH	8.72	7.77	2.22	3.25	
7	CH_3	H, H	C_6H_5, CH_3CO_2		7.78[f]	2.22[g]	4.28	2.32[g]

[a] In $CDCl_3$ solution except for 1, for which the first line entry is from DMSO and the second from pyridine. [b] CH_3 of C_2H_5. [c] CH_2. [d] These assignments could well be reversed. [e] This average shift for AB of the methylene. [f] For all four protons. The pyrazole ring is not coplanar; see text. [g] These assignments may well be reversed.

The nmr spectra of compounds **1–23** (Table I) are arranged to support the assignment of the positions of the substituents on the pyrazole and pyrazoline rings and also to demonstrate coplanarity of these rings with the benzisothiazole moiety. Positions of the substituents in the 5-hydroxypyrazolinyl derivatives (**1**, **2**, **5**, **6**) are assigned on the basis of the more easily demonstrated positions in their corresponding dehydration products, the pyrazole compounds. The latter are compared with pyrazole models A–D, Table I. Data tabulated by Tensmeyer and Ainsworth[3] show that the chemical shifts for methyl protons are nearly equal for the 3-methyl-, 5-methyl-, and 3,5-dimethylpyrazoles whether a hydrogen, methyl, or phenyl is attached to the nitrogen in position one. The 3-proton signal at 7.31 ppm in 1,5-dimethylpyrazole is little different from the 5-proton signal at 7.26 ppm in pyrazole. Large and consistent differences in field appear, however, between the 3 and 5 positions for both protons as well as between 3-methyl and 5-methyl protons when a coplanar acyl group is on the nitrogen at position one. Dreiding models show that the carbonyl, for steric reasons, is probably oriented toward the 5′-pyrazole position as represented in Table I. The similar aspect of fields for positions 3′, 4′, and 5′ for both proton and methyl signals in pyrazoles A–D and the pyrazolyl-1,2-benzisothiazole 1,1-dioxides **11**, **12**, **15**, 18, and **20** leaves no doubt that the signals are assigned correctly, that the methyl group in **12** is in fact at position 3′, and that the two series of compounds resemble each other sterically and inductively as well as magnetically. The methyl position for **23** is established by its origin from **6** in which the signal at 2.22 ppm places the methyl at 3′, and the ultraviolet spectrum of the neutral molecule does not allow the phenyl to be conjugated to the extended chromophore (as it would be if at position 3′). In the case of **17**, it is more reasonable to propose that an acetyl known to be at 4′ shifts the signals for a 3′-methyl downfield 0.10 (or 0.18) ppm, and for a 5′-proton downfield 0.61 ppm (compare **17** with **12**, Table I), rather than that of a 5′-methyl upfield 0.1 ppm and of a 3′-hydrogen downfield 1.0 ppm (compare **17** with **11**, Table I). This is especially true since there is less steric hindrance for the carbonyl to be oriented toward the adjacent methyl than for the acetyl methyl to be so oriented.

The signal for the proton at position 4 on the benzisothiazole ring is split into an approximate quartet (X of ABCX) with $J_{4,5} \simeq 6.0$ cps and $J_{4,6} \simeq 3.5$ cps in all the compounds of Table I with the exception of **7**. This multiplet is fairly constant in chemical shift at 8.62 ±0.04 ppm for the pyrazolinyl compounds, and a similar multiplet at 9.13 ± 0.05 ppm is noted for the pyrazolyl derivatives. The remaining three protons, 5, 6, and 7, show a rather narrow unresolved signal at 7.79 ± 0.05 ppm and 7.06 ± 0.04 ppm, respectively, in the two series. Signals for the four protons (4, 5, 6, and 7) of the benzisothiazole portion of **7** appear in a narrow envelope centered at 7.78 ppm and this is nearly identical in position and shape for the signals of the four corresponding protons in 3-methoxy-1,2-

(3) L. Tensmeyer and C. Ainsworth, *J. Org. Chem.*, **31**, 1878 (1966).

TABLE II

BLOOD PRESSURE RESPONSE IN RENAL HYPERTENSIVE RATS[a]

No.	Mean %[b]	Max % (hr[c])
1	−8.0	−10.4 (7)
2	+2.7	+4.2 (5)
3	−10.6	−13.5 (7)
5	−0.6	−5.6 (6)
6	+0.3	+6.7 (2, 3)
7	−12.5	−21.5 (7)
8	−2.1	−4.2 (5, 7)
9	−1.9	−2.8 (3)
10	−10.2	−19.0 (5)
11	−10.0	−17.2 (5)
12	−6.5	−15.6 (6, 7)
14	−7.0	−10.3 (2)
15[d]	−9.3	−15.6 (7)
17	−1.0	−6.0 (5)
18	−4.8	−6.2 (3, 5)
20	−5.3	−9.7 (3)
22[e]	+7.7	+10.2 (6)
23	−5.2	−10.0 (3)
24	+2.1	+3.0 (2)

[a] All doses are 20 mg/kg unless otherwise indicated. [b] Mean value for per cent decrease of blood pressure from control over a 7-hr period for three hypertensive rats. [c] Maximum per cent depression of blood pressure during a 7-hr period and hour(s) at which maximum(s) occurred. [d] 40 mg/kg *po*. [e] 100 mg/kg *po*.

benzisothiazole 1,1-dioxide. That the three protons (5, 6, and 7 of **1**–**23**, Table I) show little difference in chemical shift from each other or from all four protons in **7** and in 3-methoxy-1,2-benzisothiazole 1,1-dioxide indicates the pyrazoline and pyrazole rings are coplanar with the benzisothiazole moiety in all but **7**. The magnetic anisotropy of the pyrazoline and pyrazole rings, coplanar with the benzisothiazole, is responsible for the low-field signal for the proton at position 4. It is apparent that inductive and resonance effects through the bonds are small by comparison to the transannular effect. The phenyl and acetoxy substituents both on position 5′ of the pyrazoline ring of **7** prevent this ring from being coplanar with the benzisothiazole rings. The Dreiding model of **15** shows serious steric hindrance of a methyl group at 5′ with the proton at 4 if a rotation of 180° is attempted. This observation together with the constancy in chemical shift for the multiplet for proton 4 supports the orientation as shown in Table I for both series.

Attempts to prepare 3-(3-methylpyrazolinyl-5-one)-1,2-benzisothiazole 1,1-dioxide led to alcoholysis products. For example, when I was heated with ethyl acetoacetate a small amount of 3-ethoxy-1,2-benzisothiazole 1,1-dioxide[2] was isolated. When equivalent amounts of the reactants were heated in Cellosolve, the product was identified as 3-(2-ethoxyethoxy)-1,2-benzisothiazole 1,1-dioxide. The pyrazolinone may be formed with displacement of the benzisothiazole moiety by solvolysis.

The condensations of 1,3-diketones and benzoylacetonitrile with I in Cellosolve occasionally produced a rather insoluble, high-melting side product. This was shown to be 1,2-bis(1,2-benzisothiazol-3-yl 1,1-dioxide)hydrazine. It was also obtained by warming I in 1 *N* HCl and collecting the insoluble product. The bis product could arise in the Cellosolve reaction from the displacement of the pyrazole portion by I or by exchange amination between two molecules of I.

The 3,5-disubstituted pyrazolyl derivatives (**14**, **15**, **18**, **20**, **21**, **23**, **24**) did not titrate throughout the pH range of 3–12, but 3-(pyrazol-1-yl)-1,2-benzisothiazole 1,1-dioxide (**11**) gradually consumed titrant between pH of 6.5 and 13. The 5-hydroxypyrazoline derivatives (**1**, **2**) have definite titratable end points (pk_a = **9.7**, 10.9), but the titrations are not reversible. Hydrolysis undoubtedly occurs with those examples where titrant is consumed.

Pharmacology.—The hydroxypyrazolines (**2**, **5**, **6**) and the phenyl-substituted pyrazole derivatives (**22**, **24**) did not have desirable blood pressure lowering activity (Table II). Unsubstituted hydroxypyrazoline (**1**) and phenyl pyrazole (**23**) showed some activity. The acetyl derivative **7** of inactive compound **6** showed good activity. 3-(3,5,5-Trimethylpyrazolin-1-yl)-1,2-benzisothiazole 1,1-dioxide (**3**) had good blood pressure lowering activity without ganglionic blocking activity. None of the active compounds exhibited significant monoamine oxidase inhibition or ganglionic blocking effects. The pharmacological methods are described in a following paper.[4]

Experimental Section[5]

3-(3,5-Disubstituted 5-Hydroxy-2-pyrazolin-1-yl)-1,2-benzisothiazole 1,1-Dioxides. Table III, 2, 4–6.—One-tenth mole of I and 0.1 mole of the appropriate β-diketone were heated under reflux in dioxane for 2 hr. The dioxane was removed under reduced pressure and the residue was dissolved in hot ethyl acetate then filtered. The filtrate was concentrated and cooled to yield the crystalline product. The 5-hydroxypyrazolines were purified by crystallization from ethyl acetate.

3-(3,5-Disubstituted Pyrazol-1-yl)-1,2-benzisothiazole 1,1-Dioxides. Table IV, 14, 24.—A solution containing 0.05 mole of the appropriately substituted 3-hydrazino-1,2-benzisothiazole 1,1-dioxide[6] and 0.06 mole of the appropriate 1,3-diketone in Cellosolve was heated under reflux for 5 hr. The solvent was removed under reduced pressure and the solid product crystallized from ethyl acetate.

3-(3,5,5-Trimethyl-2-pyrazolin-1-yl)-1,2-benzisothiazole 1,1-Dioxide. Table III, 3.—A mixture of 10 g (0.05 mole) of I and 100 ml of redistilled mesityl oxide was heated on the steam bath for 2 hr. The excess mesityl oxide was removed under reduced pressure. The residue was crystallized from ethyl acetate.

3-(5-Amino-3-phenylpyrazol-1-yl)-1,2-benzisothiazole 1,1-Dioxide. Table IV, 22.—A solution of I (6 g, 0.03 mole) and benzoylacetonitrile (5 g, 0.03 mole) in 150 ml of Cellosolve was heated under reflux for 4 hr. The solvent was evaporated under reduced pressure. The product was recrystallized from alcohol.

3-(4-Bromo-3,5-dialkylpyrazol-1-yl)-1,2-benzisothiazole 1,1-Dioxides. Table IV, 13, 19.—A solution of 0.1 mole of the 3-(3,5-dialkylpyrazol-1-yl)-1,2-benzisothiazole 1,1-dioxide in 300 ml of chloroform was treated dropwise with 16 g (0.1 mole) of bromine. The solution was allowed to stand at ambient room temperature for 12 hr. The solvent was evaporated on the steam bath. The solid product was crystallized from ethyl acetate.

3-(5-Hydroxy-2-pyrazolin-1-yl)-1,2-benzisothiazole 1,1-Dioxide. Table III, 1.—I (20 g, 0.1 mole) was suspended in 250 ml of water with 30 g (0.13 mole) of tetraethoxypropane. Concentrated H_2SO_4 (8 g) was added dropwise to the stirred suspension. After 1.5 hr at room temperature the reactants dissolved and the product crystallized from solution. The solid was collected and washed with water to yield 24 g (95%) of 3-(5-hydroxy-2-pyrazolin-1-yl)-1,2-benzisothiazole 1,1-dioxide. This melted at 230° after repeated crystallization from ethyl acetate.

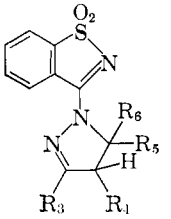
(4) P. W. Willard, C. W. Whitehead, and J. J. Traverso, *J. Med. Chem.* **10**, 849 (1967).

(5) 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 specific melting ranges in accordance with the U. S. Pharmacopeia.

(6) C. W. Whitehead, J. J. Traverso, J. F. Bell, and P. W. Willard, *J. Med. Chem.*, **10**, 844 (1967).

TABLE III

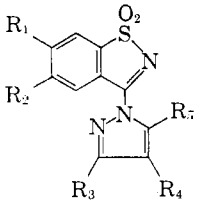
3-(PYRAZOLIN-1-YL)-1,2-BENZISOTHIAZOLE 1,1-DIOXIDES



No.	R_3	R_4	R_5	R_6	Mp, °C	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
1	H	H	H	OH	243	95.0	$C_{10}H_9N_3O_3S$	47.79	47.80	3.61	3.86	16.72	16.73
2	CH_3	H	CH_3	OH	205	45.0	$C_{12}H_{13}N_3O_3S$	51.44	51.60	4.69	4.86	15.05	15.12
3	CH_3	H	CH_3	CH_3	209	40.0	$C_{13}H_{15}N_3O_2S$	56.06	56.29	5.45	5.52	15.15	14.88
4	CH_3	CH_3	CH_3	OH	180	27.3	$C_{13}H_{15}N_3O_3S$	53.97	53.24	5.16	5.13	14.33	13.77
5	C_2H_5	H	C_2H_5	OH	200	69.0	$C_{14}H_{17}N_3O_3S$	54.79	54.70	5.57	5.61	13.67	14.01
6	CH_3	H	C_6H_5	OH	194	58.0	$C_{17}H_{15}N_3O_3S$	59.94	59.81	4.42	4.63	12.31	12.28
7	CH_3	H	C_6H_5	CH_3CO_2	206	30.0	$C_{19}H_{17}N_3O_4S$	59.64	59.51	4.46	4.58	10.96	10.74

TABLE IV

3-(PYRAZOL-1-YL)-1,2-BENZISOTHIAZOLE 1,1-DIOXIDES



No.	R_1	R_2	R_3	R_4	R_5	Mp, °C	Yield, %	Formula	C, % Calcd	C, % Found	H, % Calcd	H, % Found	N, % Calcd	N, % Found
8	H	Cl	H	H	H	216	35.0	$C_{10}H_6ClN_3O_2S$	44.86	44.77	2.25	2.44	15.70	15.75
9	Cl	H	H	H	H	238	30.0	$C_{10}H_6ClN_3O_2S$	44.86	44.94	2.25	2.37	15.70	15.64
10	H	H	H	Cl	H	145	31.0	$C_{10}H_6ClN_3O_2S$	44.86	45.17	2.25	2.48	15.70	15.63
11	H	H	H	H	H	233	54.5	$C_{10}H_7N_3O_2S$	51.49	51.39	3.03	3.09	18.02	17.91
12	H	H	CH_3	H	H	251	80.0	$C_{11}H_9N_3O_2S$	53.43	53.63	3.66	3.83	16.99	17.23
13	H	H	CH_3	Br	CH_3	265	76.5	$C_{12}H_{10}BrN_3O_2S$	42.36	42.53	2.96	3.25	12.35	12.37
14	Cl	H	CH_3	H	CH_3	208	60.0	$C_{12}H_{10}ClN_3O_2S$	48.73	48.81	3.40	3.21	14.21	13.88
15	H	H	CH_3	H	CH_3	202	92.0	$C_{12}H_{11}N_3O_2S$	55.15	55.40	4.24	4.48	16.08	15.74
16	CH_3O	CH_3O	H	H	H	257	15.0	$C_{12}H_{11}N_3O_4S$	49.14	49.06	3.78	3.96	14.33	14.06
17	H	H	CH_3	CH_3CO	H	263	50.0	$C_{13}H_{11}N_3O_3S$	53.80	54.02	4.12	4.23	14.50	14.59
18	H	H	CH_3	CH_3	CH_3	276	60.0	$C_{13}H_{13}N_3O_2S$	56.71	56.88	4.75	4.73	15.26	14.89
19	H	H	C_2H_5	Br	C_2H_5	150	75.0	$C_{14}H_{14}BrN_3O_2S$	...	...	...	...	11.41	11.30
20	H	H	C_2H_5	H	C_2H_5	146	42.0	$C_{14}H_{15}N_3O_2S$	58.11	57.98	5.22	5.25	14.52	14.26
21	CH_3O	CH_3O	CH_3	H	CH_3	140	50.0	$C_{14}H_{15}N_3O_4S$	52.32	51.81	4.71	4.97	13.08	13.10
22	H	H	C_6H_5	H	NH_2	>360 dec	59.0	$C_{16}H_{12}N_4O_2S$	59.24	59.50	3.72	3.69	17.27	17.16
23	H	H	CH_3	H	C_6H_5	240	50.0	$C_{17}H_{13}N_3O_2S$	63.14	63.25	4.05	4.09	12.99	13.08
24	H	H	C_6H_5	H	C_6H_5	179	70.0	$C_{22}H_{15}N_3O_2S$	68.55	68.77	3.92	4.31	10.90	10.57

3-(4-Acetyl-3-methylpyrazol-1-yl)-1,2-benzisothiazole 1,1-Dioxide. Table IV, 17.—A mixture of I (10 g, 0.05 mole) and excess ethoxymethyleneacetylacetone[7] was heated in 50 ml of ethylene glycol dimethyl ether at 110° for 5 hr. After cooling, the solid product was collected and recrystallized from ethyl acetate.

3-(3-Methylpyrazol-1-yl)-1,2-benzisothiazole 1,1-Dioxide. Table IV, 12.—A solution containing 10 g (0.05 mole) of I and 8 g (0.06 mole) of 3-ketobutyraldehyde dimethyl acetal in Cellosolve was heated under reflux for 6 hr. The solvent was distilled under reduced pressure and the solid was crystallized from ethyl acetate.

3-Chloro-5,6-dimethoxy-1,2-benzisothiazole 1,1-Dioxide.—5,6-Dimethoxy-3-hydroxy-1,2-benzisothiazole 1,1-dioxide[8] (50 g) and 50 g of PCl_5 were heated together at 165° for 2 hr in a flask fitted with a condenser and drying tube. The cooled mixture was poured onto ice and the solid was extracted with ether. The ether solution was washed with water and dried over $MgSO_4$. Evaporation of the ether yielded the product which was recrystallized from ethyl acetate, yield 30 g (75%), mp 85°.

Anal. Calcd for $C_9H_8ClNO_4S$: C, 41.30; H, 3.08; N, 5.35. Found: C, 41.41; H, 3.31; N, 5.33.

3-Chloro-1,2-benzisothiazole 1,1-dioxides were prepared in this same manner from 5- and 6-chloro-3-hydroxy-1,2-benzisothiazole 1,1-dioxide.[9,10] These two products were used without complete purification.

Condensations of Pyrazole and 4-Chloropyrazole with 3-Chloro-1,2-benzisothiazole 1,1-Dioxides. Table IV, 8–10.—A mixture of the appropriate 3-chloro-1,2-benzisothiazole 1,1-dioxide (0.05 mole) and 11.2 g (0.11 mole) of 4-chloropyrazole or 7.5 g (0.11 mole) of pyrazole was fused in a flask placed in a hot oil bath. The temperature was maintained at the fusing point for 2 hr. The mixture was cooled and the solid product crystallized from benzene.

Dehydration of 3-(5-Hydroxy-2-pyrazolin-1-yl)-1,2-benzisothiazole 1,1-Dioxides to 3-(Pyrazol-1-yl)-1,2-benzisothiazole 1,1-Dioxides. Table IV, 11, 18, 20.—The 3-(5-hydroxy-2-pyrazolin-1-yl)-1,2-benzisothiazole 1,1-dioxide was heated on the steam

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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.

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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,[1] 3-hydrazino-1,2-benzisothiazole 1,1-dioxide (I)[2] was prepared by a modification of the Schrader method. Compound I had blood pressure lowering activity exempt from ganglionic blocking or monoamine oxidase inhibition.[3] 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[4] 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-benzoisothiazole 1,1-dioxide and hydrazine gave an intractable product. The reaction of hydrazine with 3-hydroxy-6-sulfamoyl-1,2-benzisothiazole 1,1-dioxide[5] 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[6] in methanol. The method of Meadow and Reid could not be successfully scaled up, but large

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