P. Catsoulacos and Ch. Camoutsis

Laboratory of Pharmaceutical Chemistry, University of Patras, Patras, Greece

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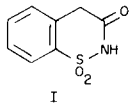
I. Introduction.

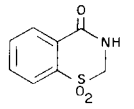
In order to discover new useful therapeutic agents, many new compounds are continually being synthesized and tested. Benzothiazinone dioxides have been reported to show considerable biological activity. In recent years the literature has shown a great increase both in university and in commercial research involving the preparations, reactions and the physiological activities of these compounds.

The thiazinone dioxide nucleus is a six member ring which has two heteroatoms, a nitrogen atom and a sulfur atom. Several structural isomers are possible for the benzothiazinone dioxide ring system. The structures and names of the isomeric benzothiazinone dioxides are shown.



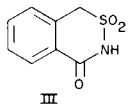
I

2*H*-1,2-Benzothiazin-3(4*H*)one 1,1-Dioxide



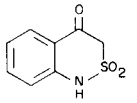
II

2*H*-1,3-Benzothiazin-4(3*H*)one 1,1-Dioxide



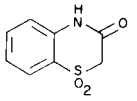
III

1*H*-2,3-Benzothiazin-4(3*H*)one 2,2-Dioxide



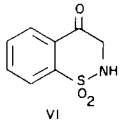
IV

1*H*-2,1-Benzothiazin-4(3*H*)one 2,2-Dioxide



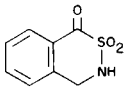
V

2*H*-1,4-Benzothiazin-3(4*H*)one 1,1-Dioxide



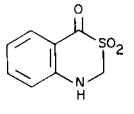
VI

2*H*-1,2-Benzothiazin-4(3*H*)one 1,1-Dioxide



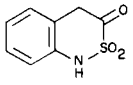
VII

3*H*-2,3-Benzothiazin-1(4*H*)one 2,2-Dioxide



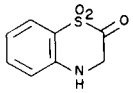
VIII

3*H*-2,4-Benzothiazin-1(4*H*)one 2,2-Dioxide



IX

1*H*-2,1-Benzothiazin-3(4*H*)one 2,2-Dioxide



X

4*H*-1,4-Benzothiazin-2(3*H*)one 4,4-Dioxide

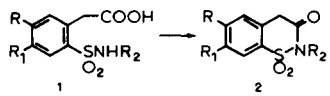
Of the above ten possible isomers, the first six (I-VI) have been synthesized and their properties have been reported. The latter four (VII-X) have not been reported in the literature. Each of the six reported isomeric benzothiazinone dioxides will be considered separately in this review.

A. 2*H*-1,2-Benzothiazin-3(4*H*)one 1,1-Dioxide.

Synthesis.

Procedures for the synthesis of 1,2-benzothiazin-3(4*H*)-one dioxide derivatives are typical of those for the formation of cyclic compounds. The heterocyclic ring is formed by a condensation reaction in which water or a halogen acid are eliminated from a suitable open chain compound.

The direct synthesis of *N*-substituted 1,2-benzothiazin-3(4*H*)one 1,1-dioxides from 2-carboxymethylbenzenesulfonamides, using polyphosphoric acid (1-3) *p*-toluenesulfonic acid (5-6), acetic anhydride (1,4) or phosphorus pentachloride (1,7-9) as catalysts, has been reported. The reaction of cyclization occurs according to the following equation.

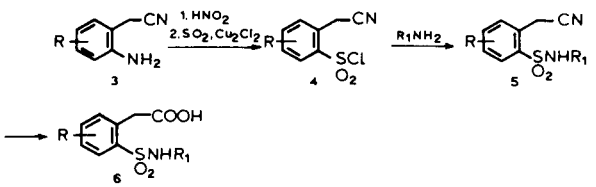


1 2

Three synthetic routes are known for the preparation of the starting 2-carboxymethylbenzenesulfonamide (**1**).

a.

o-Aminophenylacetonitrile (**3**) has been converted to *o*-cyanomethylbenzenesulfonyl chloride (**4**), which reacts with ammonia or primary amines to give the sulfonamide (**5**). Compound **5** is easily transformed to the corresponding 2-carboxymethylbenzenesulfonamide (**6**) (1).

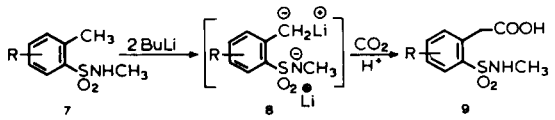


3 4 5 6

0022-152X/79/081503-22$02.25

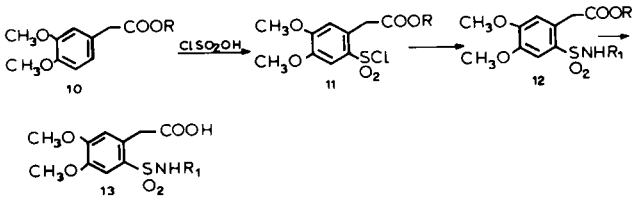
b.

The second synthetic method for the preparation of 2-carboxymethylbenzenesulfonamide was achieved by the lithiation of *N*-methyl-*o*-toluenesulfonamide (7) (5). The resultant dilithio salt, upon reaction with carbon dioxide followed by acidification, produced the desired compounds as follows.



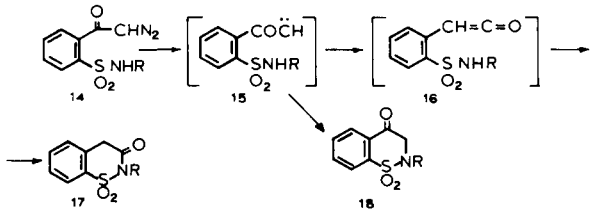
c.

Since the position *para* to one of the methoxy groups in ethyl 3,4-dimethoxyphenylacetate (**10**) is activated, direct chlorosulfonation at low temperature was applied to produce 4,5-dimethoxy-2-carboethoxymethylbenzenesulfonyl chloride (**11**), which reacts readily with ammonia and primary amines to produce the sulfonamido derivatives (**12**). Basic hydrolysis of the ester produced the corresponding acid **13** (7-9).



The various *N*-substituted 2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxides are listed in Table I.

There is also a description of another method for the preparation of such compounds, *viz.*, heating *o*-diazoacetyl-*N*-phenylbenzenesulfonamide in boiling chlorobenzene provided the thiazinone dioxide **17** and it's isomer **18**.

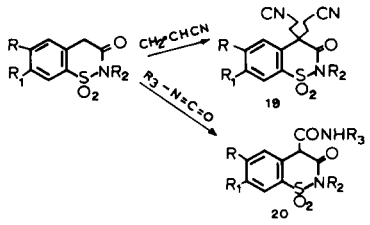


The compounds produced in this manner are thought to originate from an acylcarbene which may either cyclise directly to the thiazinone dioxide (**18**) or undergo the Wolff rearrangement to the ketene, the cyclization of which provides the thiazinone dioxide. Photolytic rearrangement of *o*-diazoacetyl-*N*-methylbenzenesulfonamide produced mainly the product of the Wolff rearrangement (10).

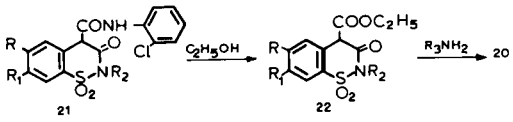
Reactions of 2*H*-1,2-Benzothiazin-3(4*H*)one 1,1-Dioxide

a. Acidity of the C-H Bond.

The procedure that involves the formation and subsequent reaction of the anion derived from the active methylene group of the thiazinone ring, produces an important class of compounds of pharmacological interest. Using the active methylene group, several workers have prepared *N*-substituted 4,4-dicyanoethyl-1,2-benzothiazin-3(4*H*)one 1,1-dioxides (12) and *N*-substituted 1,2-benzothiazin-3(4*H*)one-4-carboxamide 1,1-dioxides (5,12) by treatment of the *N*-substituted 1,2-benzothiazin-3(4*H*)one 1,1-dioxides with acrylonitrile and phenylisocyanate in the presence of a base, as illustrated in the equations below (the formation of **19** and **20**.)



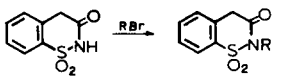
In the synthesis of a large number of carboxamides for biological purposes, the above mentioned procedures are not applicable, due to the difficulty in obtaining the required isocyanates. Therefore, the ester **22** reacted with various aromatic amines forming 3,4-dihydro-2-alkyl-3-oxo-2*H*-1,2-benzothiazin-4-carboxamide 1,1-dioxides (**20**) (5).



The various compounds thus synthesized are listed in Table II.

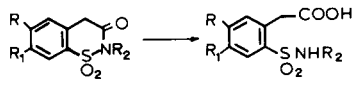
b. Alkylation of NH.

The N-H of 1,2-benzothiazin-3(4*H*)one 1,1-dioxide can be alkylated with alkyl bromides in *N*,*N*-dimethylformamide in the presence of sodium bicarbonate (4).



c. Base Induced Ring Cleavage.

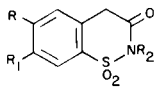
N-Substituted 1,2-benzothiazin-3(4*H*)one 1,1-dioxide is readily cleaved by dilute sodium hydroxide forming the 2-carboxymethylbenzenesulfonamide (12).



Similarly, when secondary aliphatic amines react with 1,2-benzothiazin-3(4*H*)one 1,1-dioxides, the corresponding 2-carboxyamidomethylbenzenesulfonamides (**23**) are formed (8,13).

Table I

N-Substituted 2*H*-1,2-Benzothiazin-3(4*H*)one 1,1-Dioxides



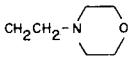
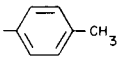
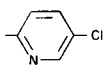
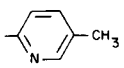
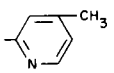
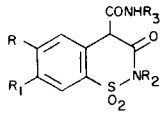
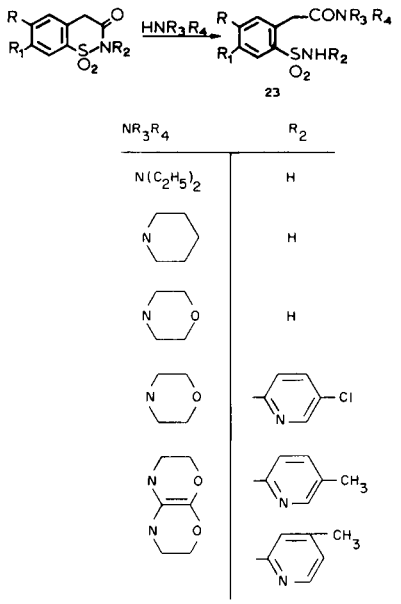
R	R_1	R_2	Yield %	Reference
H	H	H	66	1
H	H	C_2H_5	66,89	1
H	H	C_6H_5	100	1
H	NO_2	H	94	1
H	NH_2	H	60	1
H	H	$CH_2CH{=}CH_2$	64	2,3,4
H	H	$CH_2CON(R_3R_4)$	—	2,3
H	H	CH_3	61,77	3,4,5
H	NO_2	C_2H_5	31	4
H	H	$CH_3CH_2CH_2$	38	3,4
H	H	$CH(CH_3)_2$	73	3,4
H	H	$CH_3(CH_2)_3$	43	3,4
H	H	$CH_2{\equiv}CH$	45	4
H	H	$CH_2C_6H_5$	70	4
H	H	*o*-C_6H_4Cl	77	4
H	H	*m*-C_6H_4Cl	89	4
H	H	*p*-C_6H_4Cl	82	4
H	H	*p*-$C_6H_4SO_2NH_2$	48	4
H	H		24	4
H	$NHCOOC_2H_5$	H	62	4
H	$NHCOOC_2H_5$	C_2H_5	30	4
H	NH_2	C_2H_5	69	4
H	H	$CH_2C_6H_5$	51	5
H	CH_3	CH_3	51	5
H	Cl	CH_3	81	5
CH_3O	CH_3O	H	48	7
CH_3O	CH_3O	$CH(CH_3)_2$	74	7
CH_3O	CH_3O		89	7
CH_3O	CH_3O		83	7
CH_3O	CH_3O		—	9
CH_3O	CH_3O		78	8
CH_3O	CH_3O		76	8
CH_3O	CH_3O	CH_3	90	11

Table II

3,4-Dihydro-2-alkyl-3-oxo-2*H*-1,2-benzothiazin-4-carboxamide 1,1-Dioxides



R	R_1	R_2	R_3	Yield %	Reference
H	H	CH_3	C_6H_5	52	5
H	H	CH_3	2-ClC_6H_4	74	5,6
H	H	CH_3	4-FC_6H_4	51	5,6
H	H	CH_3	4-ClC_6H_4	61	5,6
H	H	CH_3	3-$CF_3C_6H_4$	38	5,6
H	H	CH_3	4-$CH_3C_6H_4$	57	5,6
H	H	CH_3	4-$CH_3OC_6H_4$	75	5,6
H	H	CH_3	2,4-$Cl_2C_6H_3$	58	5
H	H	CH_3	4-BrC_6H_4	42	5,6
H	H	CH_3	4-$NO_2C_6H_4$	22	5,6
H	H	CH_3	1-Naphthyl	54	5
H	H	CH_3	3-$CH_3C_6H_4$	71	5,6
H	H	CH_3	4-$EtOC_6H_4$	72	5,6
H	H	CH_3	3-ClC_6H_4	46	5,6
H	H	CH_3	2-$CH_3C_6H_4$	71	5,6
H	H	CH_3	2,5-$Cl_2C_6H_3$	37	5,6
H	H	CH_3	2-$CH_3OC_6H_4$	67	5,6
H	H	CH_3	3,4-$Cl_2C_6H_3$	24	5,6
H	H	CH_3	2-CH_3-4-$NO_2C_6H_3$	35	5
H	H	CH_3	$CH_2CH{=}CH_2$	40	5
H	H	CH_3	COC_6H_5	67	5
H	H	CH_3	4-$CF_3C_6H_4$	6	5
H	H	CH_3	4-$CH_3SO_2C_6H_4$	22	5
H	H	CH_3	4-$CH_3COC_6H_4$	22	5
H	H	CH_3	6-CH_3-2-pyridyl	12	5
H	H	CH_3	2-pyridyl	24	5
H	H	CH_3	2,4-$(CH_3O)_2C_6H_3$	25	5
H	H	CH_3	4-$CH_3SC_6H_4$	48	5
H	H	CH_3	3-Cl-4-$CH_3C_6H_3$	21	5
H	H	CH_3	4-IC_6H_4	21	5
H	H	CH_3	4-(*n*-C_4H_9)C_6H_4	30	5
H	H	CH_3	$CH_2C_6H_5$	25	5
H	H	CH_3	*n*-C_5H_{11}	24	5
H	H	CH_3	$CH_2CH_2C_6H_5$	35	5
H	H	CH_3	C_6H_{11}	32	5
H	H	$CH_2C_6H_5$	C_6H_5	50	5
H	H	$CH_2C_6H_5$	4-ClC_6H_4	60	5
H	H	H	C_6H_5	48	5
H	CH_3	CH_3	C_6H_5	69	5
H	CH_3	CH_3	4-BrC_6H_4	33	5
H	CH_3	CH_3	4-$NO_2C_6H_4$	61	5
H	CH_3	CH_3	4-$CH_3OC_6H_4$	57	5
H	CH_3	CH_3	2,4-$Cl_2C_6H_3$	39	5
H	Cl	CH_3	C_6H_5	68	5
H	Cl	CH_3	4-BrC_6H_4	37	5
H	Cl	CH_3	2,4-$Cl_2C_6H_3$	38	5
CH_3O	CH_3O	$CH(CH_3)_2$	C_6H_5	50	12



Nuclear Magnetic Resonance Spectra.

For 2-isopropyl-6,7-dimethoxy-1,2-benzothiazin-3(4*H*)one 1,1-dioxide (7), the proton chemical shift values are: τ 2.8 and 3.3 (2, aromatic protons), 5.2 (-CH <), 6.2 (singlet, CH_2, $2CH_3O$), 8.48 and 8.60 [$C(CH_3)_2$] (7). Similarly, 2-methyl-1,2-benzothiazin-3(4*H*)one 1,1-dioxide showed chemical shifts of: τ 2.1 (m, 4, aromatic protons), 5.78 (s, 2, exchange in deuterium oxide, CH_2), 6.83 (s, 3, NCH_3) (5). 2-Benzyl-1,2-benzothiazin-3(4*H*)one 1,1-dioxide showed τ 1.8-2.5 (m, 4, aromatic protons), 2.69 (s, 5, C_6H_5), 5.02 (s, 2, $CH_2C_6H_5$), 5.70 (s, 2, CH_2, exchange in deuterium oxide) (5).

Infrared Spectra.

The ir spectra of 1,2-benzothiazine-3(4*H*)one 1,1-dioxide derivatives showed the following characteristic absorptions (7). The strong band at 1700-1710 cm^{-1} was assigned to the carbonyl group. The frequency of the S-O stretching vibration appeared at 1130-1150 and 1320-1340 cm^{-1}.

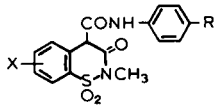
Pharmacology of *N*-Substituted 1,2-Benzothiazin-3(4*H*)one 1,1-Dioxides and their Derivatives.

With the intent of discovering new useful physiologically active compounds, various benzothiazinones have been tested in order to obtain a correlation of the pharmacological properties.

When tested in animals, *N*-alkyl derivatives which are unsubstituted on the aromatic ring showed excitement and then CNS depression after administering one fourth of the LD_{50} (4). Substitution on the aromatic ring of the benzothiazinone nucleus, such as by a nitro or an amino group, resulted in elimination of CNS activity in animals. Also, no symptoms of CNS activity were observed for *N*-propargyl and benzyl derivatives, as well as for the unsubstituted compounds (4).

A few *N*-alkyl derivatives showed significant anticonvulsant and hypnotic activities, which disappeared when the *N*-substituent was propargyl or benzyl (4). The introduction of substituents into the aromatic ring resulted in inactive products or in products less active than the corresponding unsubstituted compounds (4).

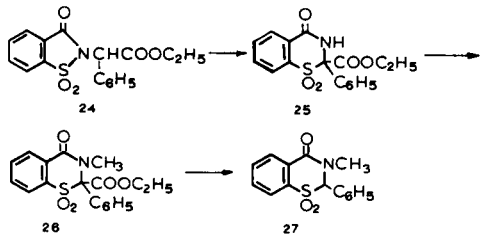
Antiinflammatory activity was assessed by inhibition of edema formation in the hind paw of the rat (5). The most satisfactory antiinflammatory activity occurs in the compounds in which the heterocyclic ring contains carboxanilide (particularly where R is a halogen atom or a nitro group), as is shown (5).



B. 2*H*-1,3-Benzothiazin-4(3*H*)one 1,1-Dioxide.

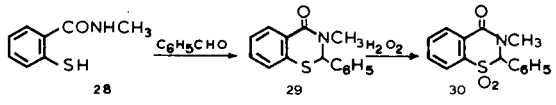
Synthesis.

It is known that *N*-(carbethoxymethyl)saccharin gives 2*H*-1,2-benzothiazin-4(3*H*)one 1,1-dioxide on reaction with sodium ethoxide (14). Zinnes and co-workers (15) reported that *N*-(α-phenylcarbethoxymethyl)saccharin (**24**) on reaction with sodium ethoxide resulted in the formation of ethyl 3,4-dihydro-4-oxo-2-phenyl-2*H*-1,3-benzothiazin-2-carboxylate 1,1-dioxide (**25**). This compound with sodium hydride and methyl iodide gave the *N*-methyl derivative (**26**), which saponifies and decarboxylates in aqueous ethanolic sodium hydroxide, to produce 3-methyl-2-phenyl-2*H*-1,3-benzothiazin-4(3*H*)one 1,1-dioxide (**27**).



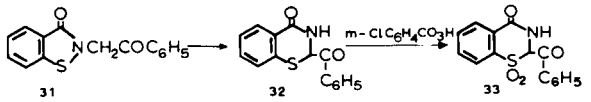
This reaction is believed to proceed *via* stabilization of the carbanion formed by abstraction of a α-hydrogen, followed directly by attack of the electrophilic SO_2 group to give the 1,3-benzothiazinone.

This type of compound has also been synthesized by the reaction of *N*-methylthiosalicylamide with benzaldehyde, followed by oxidation with hydrogen peroxide (15).

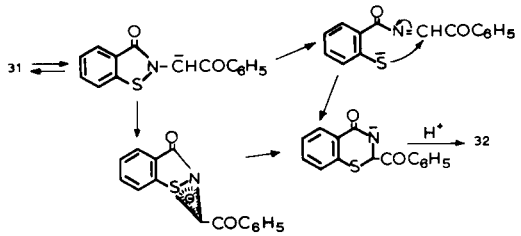


A great deal of attention has been given to the mechanistic aspects of the preparation of 2-benzoyl-2*H*-1,3-benzothiazin-4(3*H*)one 1,1-dioxide (**33**) (16). The syn-

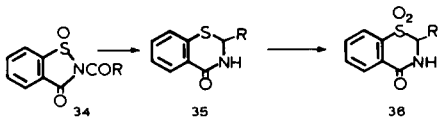
thesis of 1,3-benzothiazinone (**32**) was accomplished under mildly basic reaction conditions using 2-phenacyl-1,2-benzothiazolin-3-one (**31**) as the starting material.



Evidence supports a general base-catalyzed mechanism for this reaction, which proceeds by abstraction of a proton from the α-carbon atom, followed by a nucleophilic attack on the sulphur atom and heterolytic cleavage of the S-N bond as shown. Oxidation of **32** with *m*-chloroperbenzoic acid gave the benzothiazinone dioxide (**33**).

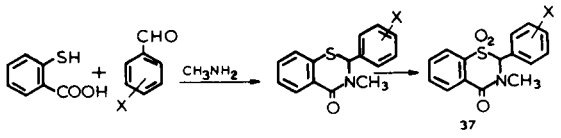


The synthesis of 1,3-benzothiazin-4(3*H*)one 1,1-dioxide has also been achieved by the conversion of 2-acyl-1,2-benzothiazolin-3-one oxide (**34**) into 1,3-benzothiazin (**35**) with zinc and acid, followed by oxidation with hydrogen peroxide (17).



Use of condensation products formed by the reaction of aldehydes and ketones with thiosalicylamide has resulted in the development of a new method for the synthesis of 1,3-benzothiazin-4(3*H*)one derivatives. These derivatives produce the corresponding 1,3-benzothiazin-4(3*H*)one 1,1-dioxide derivatives on reaction with peracetic acid (18).

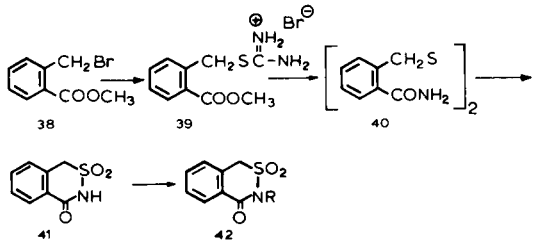
Finally, new data have been obtained by Loev (19), concerning the synthesis of 1,3-benzothiazin-4(3*H*)one 1,1-dioxide (**37**) in a study of the condensation of thiosalicylic acid with an aromatic aldehyde and a primary amine.



C. 1*H*-2,3-Benzothiazin-4(3*H*)one 2,2-Dioxide.

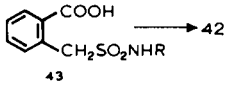
Synthesis.

2,3-Benzothiazin-4(3*H*)one 2,2-dioxide has been prepared from methyl bromobenzylcarboxylate (**38**) and thiourea. The reaction occurs *via* formation of thiouronium salt (**39**), from which bis(*o*-carbamidobenzyl) disulfide (**40**) is prepared with ammonia and hydrogen peroxide. Compound **40** after treatment with chlorine and dimethyl formamide (20-21) produced the desired compound **41**.



N-Alkylation of the thiazinone nucleus can be effected with dimethyl and diethyl sulfate or with alkyl halides and potassium carbonate in dimethylformamide.

The most frequent approach for the synthesis of 2,3-benzothiazin-4(3*H*)one 2,2-dioxide involves cyclization of 2-carboxybenzylsulfonamides (**43**) (1-2,4).



Pharmacology.

A systematic study of the pharmacology of 2,3-benzothiazin-4(3*H*)one 2,2-dioxide derivatives has been made by Sianesi and co-workers (4). A series of *N*-substituted 2,3-benzothiazin-4(3*H*)one 2,2-dioxides were tested for hypnotic and anticonvulsant activity.

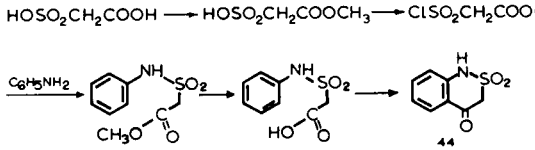
N-Aryl and *N*-aminoalkyl compounds did not show central nervous system activity. Also, no CNS activity was observed in the propargyl, and in the benzyl derivatives, as well as in the unsubstituted compound. Only a few *N*-alkyl compounds showed significant anticonvulsant and hypnotic activity. The introduction of substituents into the aromatic ring resulted in inactive compounds. The new compounds which were prepared and tested are reported in Table III.

Finally, 2,3-benzothiazin-4(3*H*)one 2,2-dioxide showed hypoglycemic and antiphlogistic activity (22).

D. 1*H*-2,1-Benzothiazin-4(3*H*)one 2,2-Dioxide.

Synthesis.

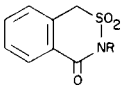
Two separate groups simultaneously reported (23-25) the synthesis of 2,1-benzothiazin-4(3*H*)one 2,2-dioxide by virtually identical routes.

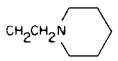
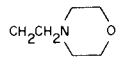


Starting from the sulfoacetic acid, after esterification and preparation of the sulfonyl chloride, treatment with

Table III

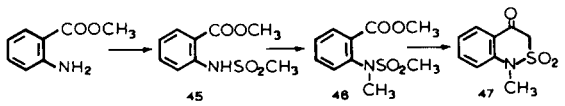
N-Substituted 2,3-Benzothiazin-4(3*H*)one 2,2-Dioxides



R	Yield %	Reference
CH_3	85	4,20,21
n-C_3H_7	70	4
i-C_3H_7	86	4,20
n-C_4H_9	69,47	4,20,21
$CH_2CH{=}CH_2$	54	2,4
$CH_2C{\equiv}CH$	78	4
$CH_2C_6H_5$	63	4
o-C_6H_4Cl	89	4
m-C_6H_4Cl	85	4
p-C_6H_4Cl	89	4
p-$C_6H_4SO_2NH_2$	71	4
$CH_2CH_2N(C_2H_5)_2$	30	4,21
$CH_2CH_2N(i\text{-}C_3H_7)_2$	51	4
	28	4
	32	4
C_2H_5, 6-NO_2	55	4
$CH_2CH{=}CH_2$, 6-NO_2	65	4
C_2H_5, 6-NH_2	79	4
$CH_2CH{=}CH_2$, 6-NH_2	58	4
H, 6-Cl	39	4
$CH_2CH{=}CH_2$, 6-Cl	56	4
C_2H_5, 6-Cl	75	4
$CH_2CON(R_1R_2)$	—	2
C_2H_5	64	20,21
$CH_2CH_2N(CH_3)_2$	—	20,21
$CH_2CH_2CH_2N(CH_3)_2$	—	20

aniline produced methyl *N*-phenylsulfamoylacetate, which after hydrolysis gave the *N*-phenylsulfamoylacetic acid. Cyclization of the latter with polyphosphoric acid gave the desired product **44**.

An additional preparation has been reported by Lombardino (26-27). This three step reaction sequence occurs according to the following equation.

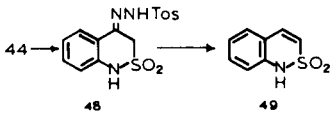


Methyl anthranilate was used as the starting material and was treated with methanesulfonyl chloride to give the sulfonamide (**45**), which was reacted to give the methylated derivative **46**. Cyclization, employing sodium hydride, produced compound **47** in 95% yield.

Reactions of 1*H*-2,1-benzothiazin-4(3*H*)one 2,2-Dioxide.

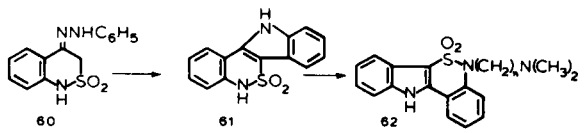
a. Sulfostyril (2,1-Benzothiazine 2,2-Dioxide).

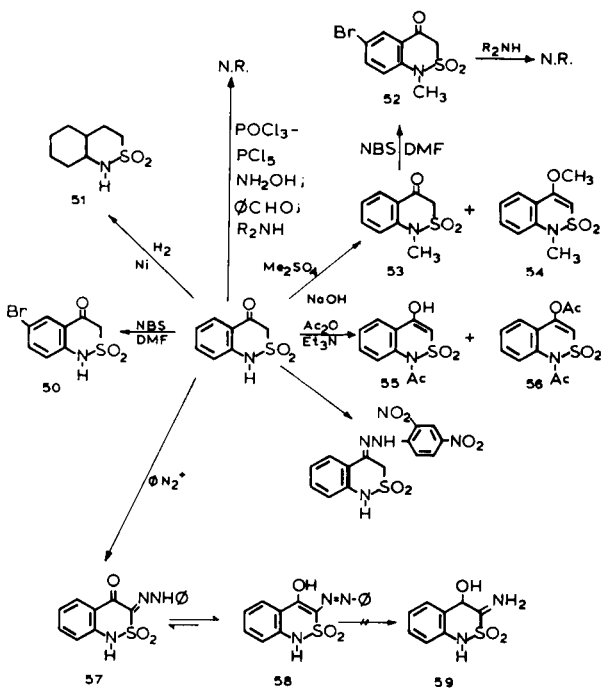
When compound **44** was transformed to the tosylhydrazone (**48**) and applied to the Bamford-Stevens reaction, the desired sulfostyril compound (**49**) was obtained (23).



The most important reactions of 2,1-benzothiazin-4(3*H*)-one 2,2-dioxides (44) are summarized in the scheme below (28). The main product **44** failed to form oximes and semicarbazones, and it did not form enamines with secondary amines. Also, it did not undergo condensation with aldehydes or reduction by ordinary catalytic means.

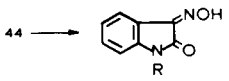
The Fischer indole synthesis can be effected when the phenylhydrazone (**60**) was treated with polyphosphoric acid. The indole derivative (**61**) could be alkylated on the sultam nitrogen with dimethylaminoethyl or propyl halides (28).





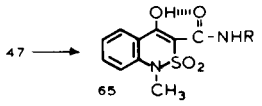
When **44** was treated with nitrous acid, isatin β-oxime (**63**) was obtained. These results can be explained by sulfur

dioxide extrusion giving isatin α-oxime, followed by *trans* oximination to give the isatin β-oxime (28) **63** or **64**.



b. Reaction of Compound **47** with Isocyanates (26).

Treatment of compound **47** with isocyanates in dimethyl sulfoxide gave carboxanilides (**65**). The nmr and ir data support the enol form for the carboxanilides.



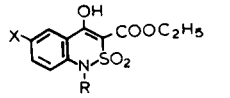
R	Yield %
C_6H_5	28
4-$CH_3OC_6H_4$	100
4-Br C_6H_4	69
3-ClC_6H_4	54
4-$NO_2C_6H_4$	69
4-$CH_3C_6H_4$	70
2-$CH_3OC_6H_4$	76
$CH_2CH{=}CH_2$	56

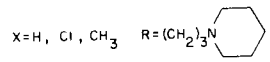
Infrared and Nmr Data of 2,1-Benzothiazin-4(3*H*)one 2,2-Dioxide (23,26).

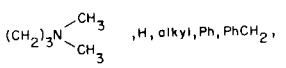
The ketone group of the heterocyclic ring absorbs at 5.95 μ and the SO_2 absorbs at 7.50 and 8.70 μ in the ir. In the nmr the methylene group appears at 4.65 ppm.

Pharmacology

Compounds of the following structure are useful as diuretics, antiinflammatory agents and antispasmodics (29-30).





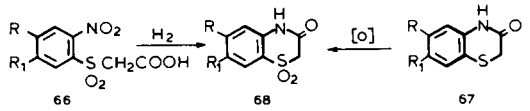


haloalkyl

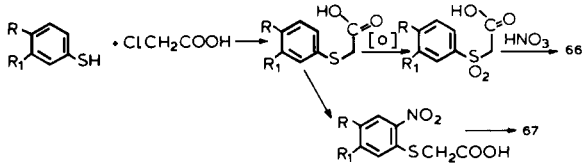
E 2*H*-1,4-Benzothiazin-3(4*H*)one 1,1-Dioxide.

Synthesis.

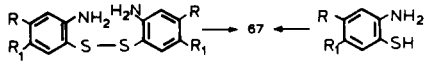
The formation of the 1,4-benzothiazin-3(4*H*)one 1,1-dioxide ring system requires derivatives of 2-nitrophenylsulfonylacetic acid (**66**) or 2*H*-1,4-benzothiazin-3(4*H*)one (**67**) as starting materials. In the first case, reductive cyclization occurs (31-36), and in the second case, oxidation with hydrogen peroxide (36-37) leads to the formation of the desired heterocyclic nucleus, according to the following equation.



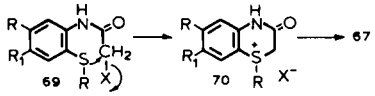
Many synthetic routes are known for the preparation of the starting materials.



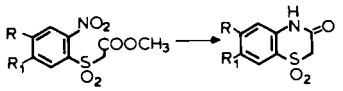
Compound **67** was obtained either by the reductive cyclization of 2-nitrophenylthioacetic acid or by the reaction of chloroacetic acid with bis(2-aminophenyl) disulfide or *o*-mercaptoaniline.



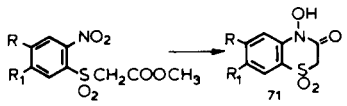
1,4-Benzothiazin-3(4*H*)one (**67**) was also prepared from (2-α-haloacetamido)phenyl alkyl and arylalkyl sulfides (**69**) by elimination of the alkyl halide through a six membered cyclic sulfonium halide (**70**) (38).



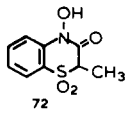
The reductive cyclization of methyl *o*-nitrophenylsulfonyl acetate with iron powder in 50% aqueous methanol containing concentrated hydrochloric acid also gave benzothiazinone (39).



Reduction with sodium borohydride and palladium on charcoal produced 2*H*-4-hydroxy-1,4-benzothiazin-3(4*H*)-one 1,1-dioxide (**71**) (40-41).



In contrast, methyl (*o*-nitrophenylsulfonyl)propionate gave 2*H*-4-hydroxy-2-methyl-1,4-benzothiazin-3(4*H*)one 1,1-dioxide (**72**) (42).



The various 2*H*-1,4-benzothiazin-3(4*H*)one 1,1-dioxides which have been prepared are listed in Table IV.

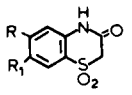
Reactions of 2*H*-1,4-Benzothiazin-3(4*H*)one 1,1-Dioxide.

a. Replacement of Oxygen by Sulfur.

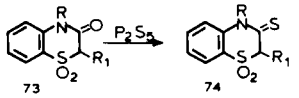
The oxygen atom of the keto-group on the thiazinone nucleus could be replaced by sulfur after treatment with phosphorus pentasulfide (43).

Table IV

2*H*-1,4-Benzothiazin-3(4*H*)one 1,1-Dioxides



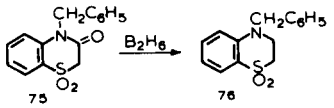
R	R_1	Yield %	Reference
H	H	62, 81, 68	31,38,37
NH_2	H	—	31
H	NO_2	—	32
H	SO_3H	—	32
H	SO_2CH_2COOH	—	33
CH_3O	CH_3O	90	34
NH_2	CH_3	—	35
SO_2Cl	Cl	—	36
SO_2Cl	H	—	36
H	SO_2Cl	—	36
CF_3	H	60	38



a. R=R_1=H
b. R=H, R_1=$CH_2C_6H_5$
c. R=$CH_2C_6H_5$, R_1=H

b. Reduction of the Carbonyl Group to a Methylene Group.

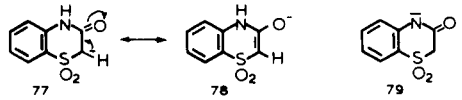
In contrast to 1,4-benzothiazin-3(4*H*)one 1,1-dioxide which is not reduced to diborane or lithium aluminum hydride, thiazinone **75** can be reduced by diborane in tetrahydrofuran to give 4-benzyl-3,4-dihydroxy-2*H*-1,4-benzothiazine 1,1-dioxide (**76**) (38).



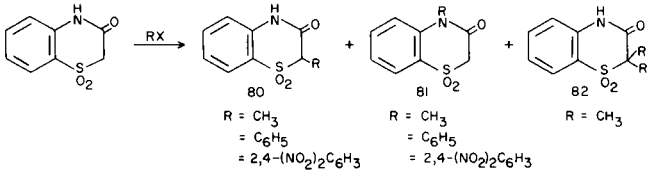
c. Acidity of the C-H Bond.

Because of the sulfonyl function, the methylene group of 1,4-benzothiazin-3(4*H*)one 1,1-dioxide is active. 2-Substituted 1,4-benzothiazin-3(4*H*)one 1,1-dioxides were prepared owing to this active methylene group.

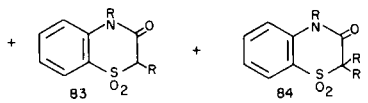
In alkaline media, benzothiazinone is presented in the form of two anions, **77** ⟷ **78** and **79**, as shown below.



Alkylation or benzylation occurs at the more nucleophilic negative carbon atom and at the nitrogen atom to produce a mixture of 2- and 4-alkyl or 2- and 4-benzyl, 2,2- and 2,4-dialkyl or 2,4-dibenzyl and 2,2,4-trialkyl derivatives, which have been separated by chromatography (44). 2,2-Dibenzyl and 2,2,4-tribenzyl derivatives were not formed owing to steric hindrance.



80: R = CH_3, C_6H_5, 2,4-$(NO_2)_2C_6H_3$
81: R = CH_3, C_6H_5, 2,4-$(NO_2)_2C_6H_3$
82: R = CH_3

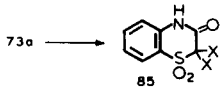


83: R = CH_3, C_6H_5, 2,4-$(NO_2)_2C_6H_3$
84: R = CH_3

Many 2-substituted thiazinone were also prepared due to the active methylene group.

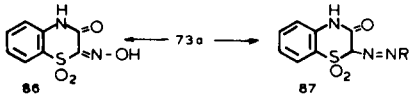
d. Halogenation.

The benzothiazinone nucleus is easily halogenated with halogens producing the 2,2-haloderivatives (32).



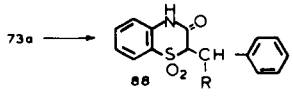
e. Reaction of Benzothiazinone with Sodium Nitrite and Diazonium Salts.

Sulfazones react with sodium nitrite and diazonium salts to form 2-oximino (**86**) and 2-azo compounds (**87**), respectively (31-32,34).



f. Amidoalkylation.

Reaction of the benzothiazinone with $PhCH(NHCOCH_3)_2$ and $PhCH(NHCONH_2)_2$ or $PhCH{=}NCONH_2$ in acetic acid resulted in the formation of the 2-(α-acetamidobenzyl)- (**88**) and 2-(α-ureidobenzyl)benzothiazinones (**88a**), respectively (45).

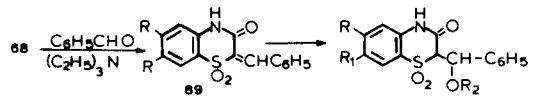


88 R = $NHCOCH_3$
88a R = $NHCONH_2$

g. Reaction of Benzothiazinone with Benzaldehyde.

The benzalsulfothiazinone derivative (**89**) could be ob-

tained by heating benzothiazinone (**68**) with benzaldehyde in the presence of triethylamine (45). The latter compound with ethanol or methanol and 10% sodium hydroxide gave 2-(α-ethoxybenzyl)benzothiazinone (**90**) and 2-(α-methoxybenzyl)benzothiazinone (**91**).

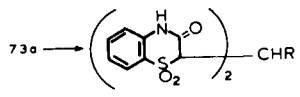


90 $R_2 = C_2H_5$

91 $R_2 = CH_3$

h. The Mannich Reaction with Benzothiazinone.

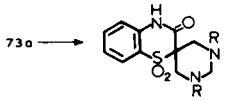
The reaction of benzothiazinone with equimolar amounts of morpholine or piperidine and formaldehyde or benzaldehyde in acetic acid produced dibenzothiazinylmethane (**92**) and phenyldibenzothiazinylmethane (**93**), respectively (46).



92 R = H

93 $R = C_6H_5$

When benzothiazinone was treated with 40% aqueous formaldehyde and benzylamine in the presence of acetic acid, the spiro-(1,3-dibenzylhydropyrimidine-5,2′-benzothiazinone) (**94**) was isolated.

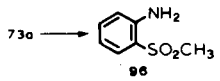


94 $R = CH_2C_6H_5$

95 $R = CH_3$

i. Reaction of Benzothiazinone with Ammonia.

Treatment of 2*H*-3,4-dihydro-1,4-benzothiazin-3(4*H*)one 1,1-dioxide with ammonia gave the (2-aminophenyl)-methylsulfone (**96**) (48).



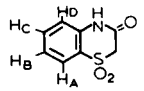
Infrared Spectra.

The 2*H*-1,4-benzothiazin-3(4*H*)one 1,1-dioxide nucleus shows strong infrared absorption bands at 1670-1700 cm^{-1} and at 3200-3300 cm^{-1}, indicating the presence of carbonyl and amine groups, respectively (38-39). The frequency of the S-O stretching vibration (39) appear at 1295 and at 1120-1155 cm^{-1}.

Ultraviolet Spectra.

2*H*-1,4-benzothiazin-3(4*H*)one 1,1-dioxide **73a** has uv maxima (39) in water at *p*H 1, at 251 and 295 mμ (log ε 3.91 and 3.67, respectively) and at *p*H > 10, at 257 and 305 mμ (log ε 3.92 and 3.49, respectively).

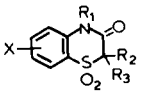
Nuclear Magnetic Resonance Spectra.



The nmr of 2*H*-1,4-benzothiazin-3(4*H*)one 1,1-dioxide in trifluoroacetic acid shows double doublets, which correspond to H_A (8.1 ppm) and H_D (7.35 ppm), with, superimposed multiplets corresponding to H_B and H_C (J_{AB} = 7.5 cps and J_{AC} = 2 cps) in between. The signal of the imine proton appears at 10 ppm and that of the methylene proton is shifted to 4.63 ppm, because of the combined effects of the carbonyl and sulfone groups (49).

Pharmacology.

Compounds of the following structure were therapeutically effective as muscle relaxants (37).



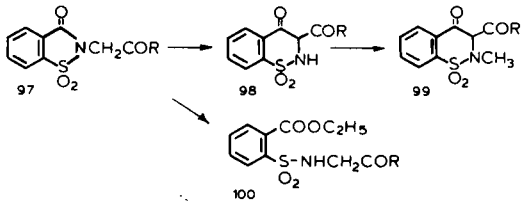
R_1, R_2, R_3 = H, alkyl

X = H, halogen, alkyl, alkoxyl, alkonoyl

F. 2*H*-1,2-Benzothiazin-4(3*H*)one 1,1-Dioxide.

Synthesis.

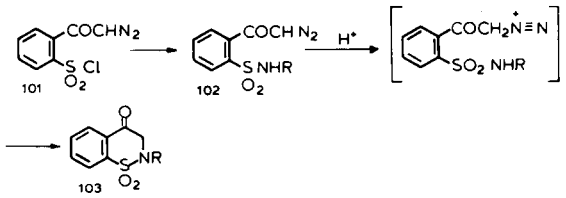
The first methods for the synthesis of this type of compound were reported by von Braun (50), and Abe and coworkers (14). These reactions have been extensively studied by Zinnes and co-workers (51).



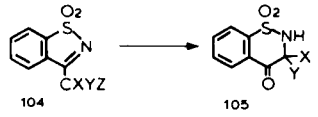
N-Acetonylsaccharin (**97**) with 2 equivalents of sodium ethoxide gave the 3-acetyl compound **98** in 80% yield. With one equivalent of sodium ethoxide, compound **100** was obtained, which readily converted to **98** on reacting with 2 equivalents of sodium ethoxide.

The *N*-methyl compound **99** was obtained by reacting methyl iodide with the sodium salt of **98** in either aqueous or non-aqueous solution. Evidence is presented which supports a mechanism involving ethanolysis of the carboxamide linkage of **97** followed by a Dieckmann ring closure forming 3-acetyl-2*H*-1,2-benzothiazin-4(3*H*)one 1,1-dioxide (**98**) (51).

o-Diazoacetylbenzenesulfonyl chloride (**101**), reacted with aniline and with methylamine to give the corresponding sulfonamide (**102**). The latter cyclised with formic acid to produce 2-methyl- or 2-phenyl-2*H*- 1,2-benzothiazin-4(3*H*)one 1,1-dioxide (**103**) (10).

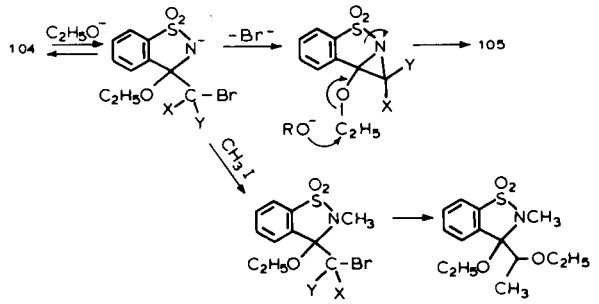


Abramovitch and co-workers (52) produced 1,2-benzothiazin-4(3*H*)one 1,1-dioxide (**105**) by base-mediated ring-expansion of 3-(α-bromoalkyl)-1,2-benzothiazole 1,1-dioxides (**104**).



a, X = Y = Z = H
b, X = Y = Z = Br
c, X = Y = H, Z = Br
d, X = H, Y = CH_3, Z = Br
e, X = CH_3, Y = C_2H_5, Z = Br

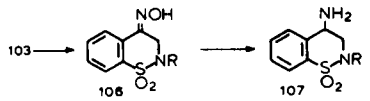
A possible mechanism for this ring enlargement could be hydrolysis of **104b** to give an *o*-(α-bromoacyl)benzenesulfonamide anion, followed by recyclization with loss of bromide ion. This is possible since both **104a** and 3-phenyl-1,2-benzothiazole 1,1-dioxide were stable to boiling alkali. These authors have also proposed two additional possible mechanisms which are shown below.



Reactions on the Carbonyl Group and on the Acidic Hydrogen of the Methylene Carbon Atom.

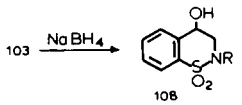
a. Reduction of *N*-Substituted-1,2-benzothiazin-4(3*H*)one 1,1-Dioxide Oxime.

Reduction of the oxime (**106**) in the presence of Raney nickel afforded the corresponding amino compound (**107**) (53).



R = CH_3

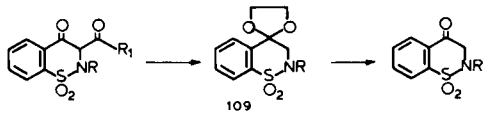
b. Reduction of *N*-Substituted-1,2-benzothiazin-4(3*H*)one 1,1-Dioxide.



a, R = H
b, R = $CH_2CH_2N(C_2H_5)_2$

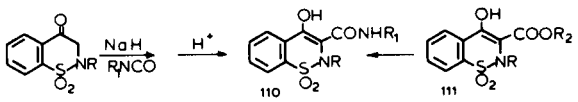
Conversiton of the keto group in the thiazinone ring to an hydroxy group can be effected with sodium borohydride in ispropyl alcohol (53).

c. Acid Catalyzed Deacetylation of the β-Diketone.



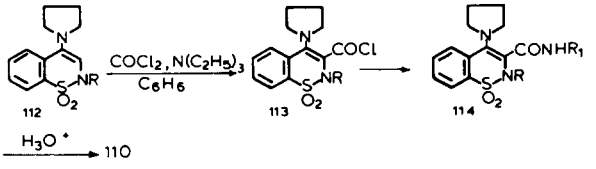
By refluxing 3-acetyl-2*H*-1,2-benzothiazin-4(3*H*)one 1,1-dioxide with ethylene glycol in the presence of *p*-toluenesulfonic acid in benzene, the ketal (**109**) was obtained. Compound **109** was then hydrolyzed to the corresponding ketone (53).

d. 3-Carboxamides of 2-Alkyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxide.

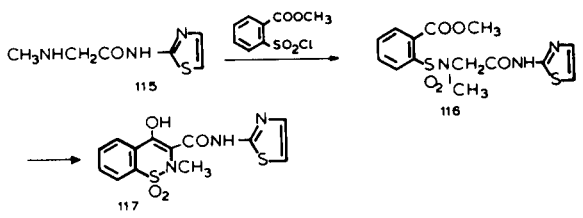


Lombardino, *et al* (54), have described the synthesis of a number of 3-carbamoyl benzothiazine derivatives (**110**) by the base catalyzed reaction of the thiazinone nucleus with a variety of aromatic isocyanates. All of these amides are completely enolized. Similar reactions have been used by Zinnes, *et al* (55). These carbamoyl derivatives can also be obtained by reacting *N*-substituted 4-hydroxy-2*H*-1,2-benzothiazin-3-carboxylic acid methyl ester (**111**) with an appropriate amine in refluxing xylene (55).

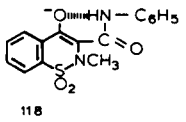
Further, formation of the enamine (**112**) followed by reaction with phosgene gave the corresponding acid chloride (**113**). On reaction with amines, compound **113** gave the desired carbomoyl compound (**110**) (55).



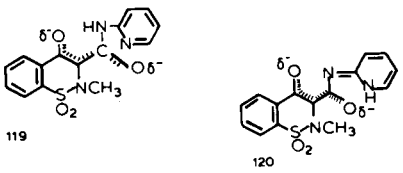
For the synthesis of compounds with structure such as **110**, Lombardino and Watson (56) have used the reaction of *N'*-methyl-*N*-(2-thiazolyl)glycinamide dihydrobromide (**115**) with 2-chlorosulfonyl benzoic ester, giving the sulfonamide ester (**116**). Base catalyzed cyclization produces the 4-hydroxy-2*H*-1,2-benzothiazine (**117**).



Those carboxanilides of the general structure **110** are acidic. The acidity is due to the stabilization of the enolate anion through hydrogen bonding to the carboxanilide proton as shown in the structure of compound **118** (54).

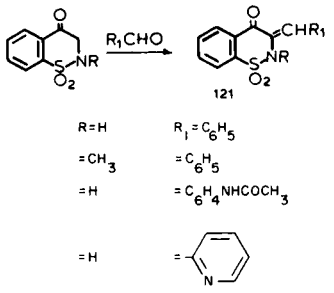


Lombardino and Wiseman (57) suggested in their recent work on *N*-(2-pyridyl)carboxamide, that in addition to **119**, contribution from the tautomeric structure **120** may impart further stability to the enolate anion.

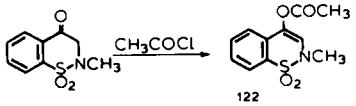


e. Reaction of Benzothiazinone with Aromatic Aldehydes and Acetyl Chloride.

The condensation of the benzothiazinone with benzaldehyde, *p*-acetamidobenzaldehyde and pyridine-2-carboxaldehyde in the presence of sodium hydride in dimethylformamide gave compounds of the general structure **121** (53).

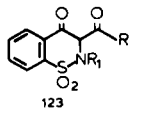


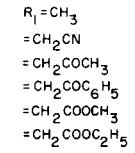
When *N*-methylbenzothiazinone was treated with acetyl chloride, the corresponding acetate compound **122** was obtained (53).



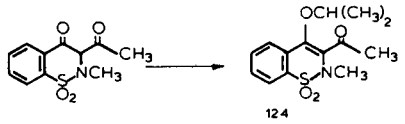
f. Alkylation of Benzothiazinone with Alkyl Halides.

N-Methyl derivatives of 3-acyl-2*H*-1,2-benzothiazin-4(3*H*)one 1,1-dioxide can be prepared by reaction of its sodium salt with methyl iodide at room temperature in either aqueous or nonaqueous solution. Thus, several derivatives of the general structure **123** were obtained (51).

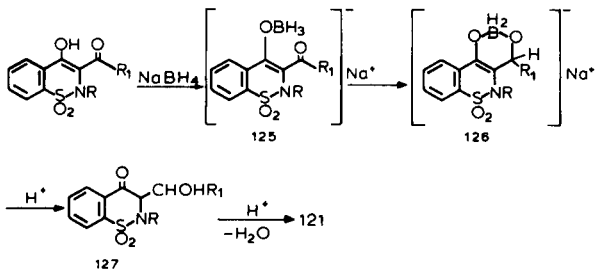




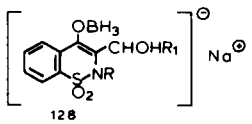
O-Alkylation was achieved by refluxing *N*-substituted thiazinones with isopropyl iodide and potassium carbonate in acetone (51).



g. Sodium Borohydride Reduction of 3-Acyl-2*H*-1,2-benzothiazin-4(3*H*)one 1,1-Dioxide.



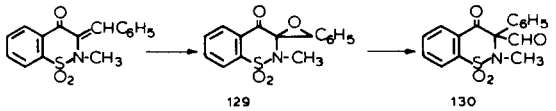
3-Ethylidene and 3-benzylidene derivatives were obtained by reduction of 3-acyl-2*H*-1,2-benzothiazin-4(3*H*)one 1,1-dioxide with sodium borohydride in a mixture of isopropyl alcohol and 1,2-dimethoxyethane at -5°. The preparation of ethylidene and benzylidene derivatives resulted from the reaction of sodium borohydride on the more acidic enolic form of the β-diketone. The mechanism involves an enolate complex (**126** or **128**) (51).



h. Borontrifluoride Catalyzed Rearrangement of the Epoxide Derived from 3-Benzylidene Compounds.

The reaction of 3-benzylidene-2-methyl-2*H*-1,2-benzothiazin-4(3*H*)one 1,1-dioxide with hydrogen peroxide in the presence of sodium hydroxide in tetrahydrofuran produced the epoxide **129**. Treatment of the latter compound with borontrifluoride etherate in dichloromethane gave

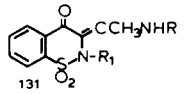
3-formyl-2-methyl-3-phenyl-2*H*-1,2-benzothiazin-4(3*H*)one 1,1-dioxide (**130**) (58).



129 130

i. Reaction of Ammonia and Amines with 3-Acetyl-2*H*-1,2-benzothiazin-4(3*H*)one 1,1-Dioxide.

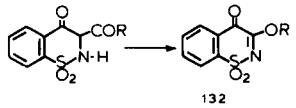
When 3-acetyl-2*H*-1,2-benzothiazin-4(3*H*)one 1,1-dioxide was treated with ammonia, methylamine, benzylamine and aniline, compounds of the general structure **131** were prepared (59).



131

k. 3-Alkoxy-1,2-benzothiazin-4(3*H*)one 1,1-Dioxide.

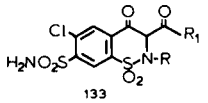
When 3-acetyl-2*H*-1,2-benzothiazin-4(3*H*)one 1,1-dioxide was treated with silver carbonate or *t*-butyl hypochlorite, the 3-alkoxy-1,2-benzothiazin-4(3*H*)one 1,1-dioxides (**132**) were obtained (60-61).



132

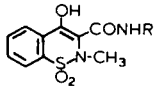
Pharmacology of *N*-Substituted-1,2-benzothiazin-4(3*H*)one 1,1-Dioxide Derivatives.

Compounds of the general structure **133** show diuretic, saluretic and hypotensive activity (62-64).



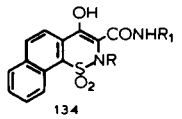
133

In an extensive structure-activity study regarding the effect of the substituted benzothiazinone nucleus, the *N*-methyl group of carboxamides of the following general structure was shown to be critical in conferring antiinflammatory properties. In contrast, the desmethyl derivatives appear less active (54). Further extension of the *N*-substituent side chain to isopropyl or aromatic groups produced compounds with essentially no activity (54).



4-Hydroxy-2-methyl-2*H*-1,2-benzothiazin-3-carboxanilide 1,1-dioxide in rat, dog, monkey and man had a plasma half-life of 6, 30, 4.5 and 21 hours, respectively. The major metabolite formed by hydroxylation of the carboxanilide moiety was excreted in the urine as an acid-labile conjugate (65).

Pharmacologically Active 4-Hydroxy-2*H*-naphtho[2,1-*e*]-1,2-thiazine-3-carboxamide 1,1-Dioxide Derivatives.

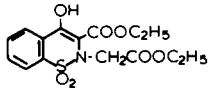


134

The title compounds **134** (R = CH_3, C_2H_5, H; R_1 = Ph, 3-ClC_6H_4, 2-FC_6H_4, 3-$CH_3OC_6H_4$, 4-methyl-2-pyridyl, 3-hydroxy-2-pyridyl, 6-chloro-3-pyridazinyl, 6-chloro-2-pyrazinyl or -4-pyrimidinyl, 4-ethyl-2-thiazolyl, 4,5,6,7-tetrahydro-2-benzothiazolyl, 3-methyl-5-isothiazolyl, 1,3,4-thiadiazol-2-yl) are useful in inhibiting blood platelet aggregation. At 10^{-6} mole/ℓ, the above compounds produced a 35-91% decrease in platelet aggregation; at 10^{-5} mole/ℓ, a 78-79% decrease (68).

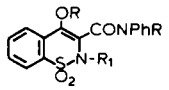
3-Alkoxy-1,2-benzothiazin-4(3*H*)one 1,1-dioxide (**132**) are useful as an urease enzyme inhibitor in mammals (60-61), while 4-substituted-2-alkyl-3-phenyl-2*H*-1,2-benzothiazine 1,1-dioxides are effective antiinflammatory agents in rats and guinea pigs (69). A study of the acidic antiinflammatory 1,2-benzothiazin-4(3*H*)one 1,1-dioxide derivatives has been done by Lombardino and co-workers (70). They found a high degree of correlation between the clinically useful dose in arthritis and the potency in the carrageenan-induced rat foot edema test.

Cardiac arrhythmias were produced in anesthetized rats by ethyl 3-ethoxycarbonyl-4-hydroxy-2*H*-1,2-benzothiazin-2-acetate 1,1-dioxide (**135**), and the effect exerted thereon by propranolol and sodium 3,4,5-trimethoxybenzoyl-ε-aminocaproate (71).



135

Electrocardiographic changes were produced by procaine amide and dihydroquinidine in rats by pretreatment with ethyl-3-ethoxycarbonyl-4-hydroxy-2*H*-1,2-benzothiazin-2-acetate 1,1-dioxide (**135**) (72). It has been reported that ethyl 3-ethoxycarbonyl-4-hydroxy-2*H*-1,2-benzothiazin-2-acetate 1,1-dioxide (**135**) produces ventricular arrhythmias in anesthetized dogs (73). Further, esters of benzothiazine 1,1-dioxides of the general structure **136** (R = $COOC_2H_5$, R_1 = CH_3) reduced rat paw edema by 47.3% at a dose of 50 mg./kg. (74).

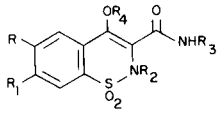


136

R = C_2H_5OOC R_1 = CH_3, C_2H_5
= $PhCH_2OOC$

Table V

Pharmacologically Active 2*H*-1,2-Benzothiazin-3-carboxanilide 1,1-Dioxide Derivatives



R	R_1	R_2	R_3	R_4	Reference
H	H	CH_3	C_6H_5	H	54,55,66
H	H	CH_3	2,4-$Cl_2C_6H_3$	H	54
H	H	CH_3	2,4-$(CH_3O)_2C_6H_3$	H	54
H	H	CH_3	4-$CF_3C_6H_4$	H	54
H	H	CH_3	3-BrC_6H_4	H	54
H	H	CH_3	5-Cl-2-$CH_3OC_6H_3$	H	54
H	H	CH_3	3-FC_6H_4	H	54
H	H	CH_3	4-HOC_6H_4	H	54
H	H	CH_3	2,5-$F_2C_6H_4$	H	54
H	H	CH_3	2,4-$F_2C_6H_3$	H	54
H	H	CH_3	2-FC_6H_4	H	54
H	H	CH_3	5-F-2-$CH_3C_6H_3$	H	54
H	H	CH_3	3-$NO_2C_6H_4$	H	54
H	H	$CH_2C_6H_5$	C_6H_5	H	54
H	H	$CH_2C_6H_5$	3-ClC_6H_4	H	54
H	H	$CH_2C_6H_5$	3-Cl-4-$CH_3C_6H_3$	H	54
H	H	H	C_6H_5	H	54,55
H	H	H	3-ClC_6H_4	H	54
H	H	H	3-Cl-4-$CH_3C_6H_3$	H	54
H	H	$CH_2CH{=}CH_2$	C_6H_5	H	54
H	H	$CH_2CH{=}CH_2$	3-ClC_6H_4	H	54
H	H	CH_2CH_3	C_6H_5	H	54
H	H	CH_2CH_3	3-ClC_6H_4	H	54
H	H	$CH_2CH_2CH_3$	C_6H_5	H	54
H	H	$CH_2CH_2CH_3$	3-ClC_6H_4	H	54
H	H	CH_3	C_6H_5, CH_3	H	54
H	H	CH_3	Cyclooctyl	H	54
H	H	CH_3	$C_6H_5CH_2$	H	54
H	H	CH_3	$C_6H_5CH_2CH_2$	H	54
H	H	CH_3	4-ClC_6H_4	H	54
H	H	CH_3	2-$CH_3OC_6H_4$	H	54
H	H	CH_3	2,5-$Cl_2C_6H_3$	H	54
H	H	CH_3	3-$CF_3C_6H_4$	H	54
H	H	CH_3	4-$CH_3C_6H_4$	H	54
H	H	CH_3	3-ClC_6H_4	H	54
H	H	CH_3	3,4-$Cl_2C_6H_3$	H	54
H	H	CH_3	2-Cl-C_6H_4	H	54
H	H	CH_3	4-$NO_2C_6H_4$	H	54
H	H	CH_3	4-FC_6H_4	H	54
H	H	CH_3	1-Naphthyl	H	54
H	H	CH_3	4-BrC_6H_4	H	54
H	H	CH_3	3-$CH_3C_6H_4$	H	54
H	H	CH_3	4-$C_2H_5OC_6H_4$	H	54
H	H	CH_3	C_6H_{11}	H	54
H	H	CH_3	$CH_2{=}CH{\cdot}CH_2$	H	54
H	H	CH_3	CH_3	H	54
H	H	CH_3	*n*-C_4H_9	H	54
H	H	CH_2COOCH_3	C_6H_5	H	55
H	H	CH_2CN	C_6H_5	H	55
H	H	CH_3	C_6H_5	$CH_2CH_2CH_3$	55

Table V continued

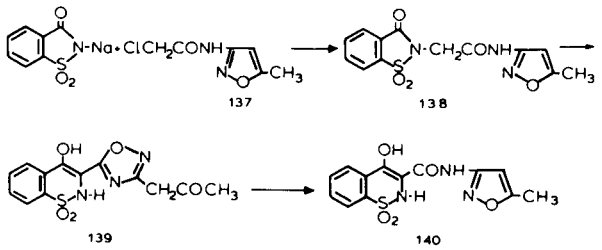
R	R_1	R_2	R_3	R_4	Reference
H	H	CH_3	C_6H_5	$CH(CH_3)_2$	55
H	H	CH_3	C_6H_5	CH_3CO	55,67
H	H	CH_3	*o*-$NO_2C_6H_4$	H	55
H	H	CH_3	*o*-$CO_2CH_3C_6H_4$	H	55
H	H	CH_3	*o*-$C_6H_5C_6H_4$	H	55
H	H	CH_3	*p*-$C_6H_5C_6H_4$	H	55
H	H	CH_3	3,4-$CH_2O_2C_6H_3$	H	55
H	H	CH_3	2,3-$CH_2O_2C_6H_3$	H	55
H	H	CH_3	adamantan	H	55

Some benzothiazin-4-one 1,1-dioxide derivatives **131** are used as ultraviolet light absorbers in plastics. They also exhibit antiinflammatory activity in kaolin-induced rat paw edema or cotton pellet granuloma assays when orally administered to rats (59). These compounds also exhibit central nervous system depressant activity in mice (59).

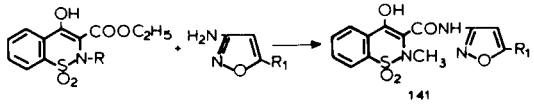
Heterocyclic 3-Carboxamide Derivatives of 4-Hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxide.

A wide variety of 3-carboxamides of 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide, in which the carboxamide group contains a heterocyclic ring such as isoxazole and thiazole, have found application in the biomedical field.

A series of 3-carboxamides of 4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide were obtained by rearrangement of substituted saccharins (75). 3-(Chloroacetamido)-5-methylisoxazole (**137**) was treated with saccharin sodium salt to give compound **138**, which rearranged on treatment with sodium methoxide producing compound **139**. Compound **139** was methylated and rearranged to afford 4-hydroxy-3-(5-methyl-3-isoxazolylcarbamoyl)-2-methyl-2*H*-1,2-benzothiazine 1,1-dioxide (**140**).



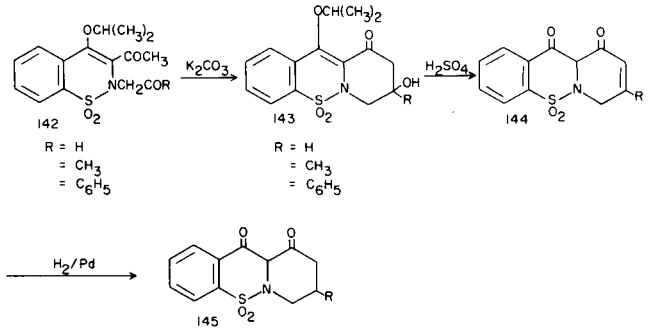
Another method of preparation for these derivatives is an adaptation of an older synthesis of carboxamides, *i.e.*, the reaction of aminoisoxazoles with 3-(ethoxycarbonyl)-benzothiazine 1,1-dioxide (76) in refluxing xylene to give compounds **141**.



Lombardino and Watson (56) have studied extensively the base catalyzed cyclization of *N'*-methyl-*N*-(2-thiazolyl)-*N'*-(2'methoxycarbonylbenzenesulfonyl)glycinamide to give the desired 4-hydroxy-2*H*-1,2-benzothiazine (**117**). Zinnes and co-workers (55) have synthesized 3-carbamoyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides (**110**) using the acid chloride (**113**) and heterocyclic amines as starting materials.

1,2-Benzothiazine Derivatives. Polycyclic Compounds.

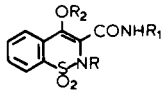
The basic idea of Zinnes and co-workers (99-100) was to synthesize 1,2-benzothiazine analogs of partial tetracycline structure with the hope that these compounds could be formed through their β-diketone moiety. The attachment of a third ring containing a β-diketone is effected by cyclising 3-acetyl-4-isopropyloxy-2*H*-1,2-benzothiazin-2-acetaldehyde, 2-acetonyl or 2-phenacyl 1,1-dioxide (**142**) according to the following scheme.



The same authors (99) have attempted the rearrangement of *N*-(5-chloro-2-oxopentyl)saccharin (**146**) in order to synthesize 3-(4-chloro-1-butyryl)-2*H*-1,2-benzothiazin-4(3*H*)one 1,1-dioxide. Their efforts were unsuccessful,

Table VI

Heterocyclic 3-Carboxamido Derivatives of 4-Hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxide



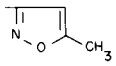
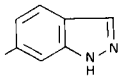
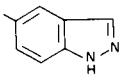
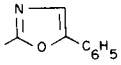
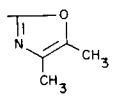
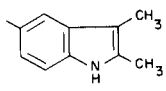
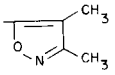
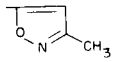
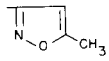
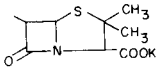
R	R_1	R_2	Pharmacological Activity	Reference
CH_3	 (a)	H	antiinflammatory antipyretic antithrombotic	57,91,93,95 91 90,92
H		H	antiinflammatory antipyretic analgesic	76 76 76
CH_3		H	antiinflammatory antipyretic analgesic	75-76,78-83,88-89 76,78 76,75,78
CH_3		H	antiinflammatory	55
CH_3		H	antiinflammatory	55
CH_3		H	antiinflammatory	55
CH_3		H	antiinflammatory	55
CH_3		H	antiinflammatory	55
CH_3		H	antiinflammatory	55
CH_3		H	antiinflammatory	55
CH_3		$COOC_2H_5$	analgesic	77
CH_3		$COOCH_3$	analgesic	77
CH_3		$COOCH_2C_6H_5$	analgesic	77

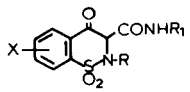
Table VI continued

R	R_1	R_2	Pharmacological Activity	Reference
CH_3		H	reduces the swelling in rat paws, induces with carrageenin	84
CH_3		H	reduces the swelling in rat paws, induces with carrageenin	84
CH_3		CH_3CO	analgesic in mice hyperthermia in rats	85
CH_3		H	antimicrobial activity	86,87
CH_3		H	neuroleptic antiinflammatory	94,95
CH_3	4-methyl-2-thiazolyl	H	antiinflammatory	95
CH_3	4-phenyl-2-thiazolyl	H	antiinflammatory	95
CH_3	4,5-dimethyl-2-thiazolyl	H	antiinflammatory	95
CH_3	1,2,4-triazol-3-yl	H	antiinflammatory	95
CH_3	5-phenyl-1,2,4-triazol-3-yl	H	antiinflammatory	95
CH_3	2-benzothiazolyl	H	antiinflammatory	95
CH_3	6-methyl-2-benzothiazolyl	H	antiinflammatory	95
CH_3	6-bromo-2-benzothiazolyl	H	antiinflammatory	95
CH_3	5-methyl-1,3,4-thiadiazolyl	H	antiinflammatory	95
CH_3	2-pyrimidinyl	H	antiinflammatory	95
CH_3	2-pyrazinyl	H	antiinflammatory	95
CH_3	6-methoxy-3-pyridazinyl	H	antiinflammatory	95
CH_3	1,2,4-triazin-3-yl	H	antiinflammatory	95
CH_3	3-hydroxy-2-pyridyl	H	antiinflammatory	95
CH_3	5-bromo-2-pyridyl	H	antiinflammatory	95
CH_3	5-chloro-2-pyridyl	H	antiinflammatory	95
CH_3	3-methyl-2-pyridyl	H	antiinflammatory	95
CH_3	4-methyl-2-pyridyl	H	antiinflammatory	95
CH_3	5-methyl-2-pyridyl·HCl	H	antiinflammatory	95
CH_3	6-methyl-2-pyridyl	H	antiinflammatory	95
CH_3	4,6-dimethyl-2-pyridyl	H	antiinflammatory	95
CH_3	3-pyridyl·HCl	H	antiinflammatory	95
CH_3	4-pyridyl·HCl	H	antiinflammatory	95
CH_3	2-quinolyl	H	antiinflammatory	95

(a) This compound was prepared in radio-labeled form and administered to rats, dogs and monkeys. In addition to some unchanged product, the urine contained two major metabolites. These were identified as the thiohydantoic acid and thiourea [D. C. Hobbs and T. M. Twomey, *Drug. Metab. Dispos.*, **5**, 75 (1977); *Chem. Abstr.*, **86**, 150274g (1977)].

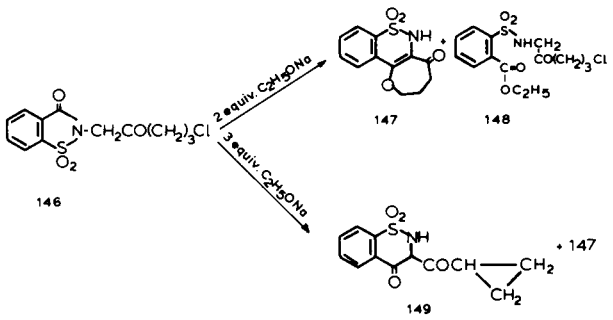
Table VII

Heterocyclic 3-Carboxamido Derivatives of 2*H*-1,2-Benzothiazin-4(3*H*)one 1,1-Dioxide

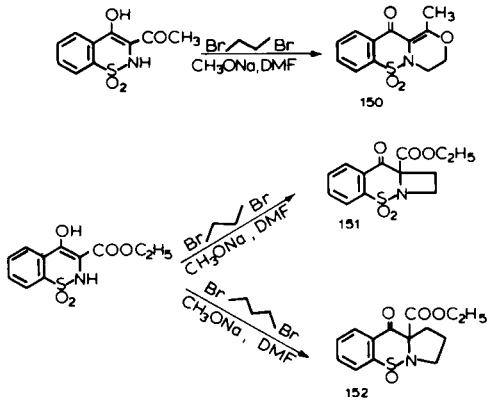


R	R_1	Pharmacological Activity	Reference
CH_3		antiinflammatory	96-98
CH_3		antiinflammatory	96-98

however, and only the tricyclic compound 2,3-dihydro-6*H*-oxepino[3,2-*c*][1,2]benzothiazin-5-(4*H*)one 7,7-dioxide (**147**) was obtained in low yield.

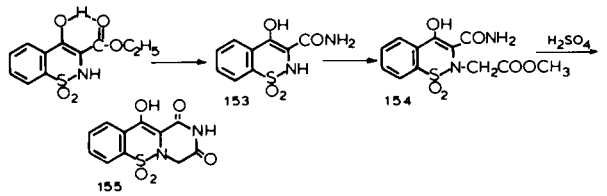


Recently (101) the synthesis of tricyclic derivatives was accomplished by cycloalkylation of 3-acetylbenzothiazine and 3-carboethoxybenzothiazine with 1,2-dibromoethane. By these reactions, the oxazine (**150**) and azetidine (**151**), respectively, were obtained.

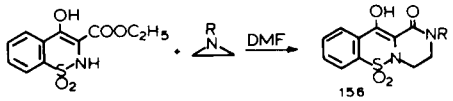


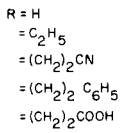
Under the same reaction conditions with 1,3-dibromopropane, pyrrolidines (**152**) analogous to compound **151** were obtained.

Reaction of ethyl 4-hydroxy-2*H*-1,2-benzothiazin-3-carboxylate 1,1-dioxide with aqueous ammonia gave a 3-carboxamide derivative (**153**), which after alkylation with methyl bromoacetate produced the 2-acetate derivative (**154**). When the latter compound was treated with warm sulfuric acid, cyclization occurred to give the corresponding imide (**155**) (101-102).

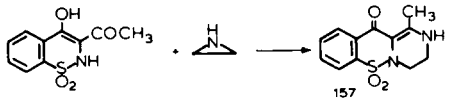


The new derivatives of piperazine (**156**) were obtained by analogous conversion of benzothiazine carboxylate with ethylenimines in dimethylformamide (103-104).

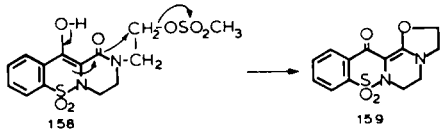




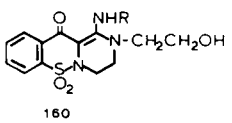
A new ring closure has been described for the formation of 3,4-dihydro-1-methylpyrazino[1,2-*b*][1,2]benzothiazin-11(2*H*)one 6,6-dioxide (**157**). It involves cyclocondensation of 3-acetyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide with aziridine in dimethylformamide (103,105).



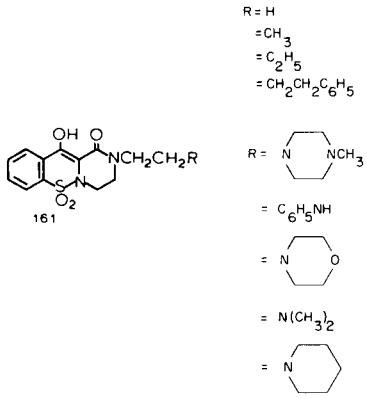
The availability of (1,2,3,4-tetrahydro-11-hydroxy-1-oxopyrazino[1,2-*b*][1,2]benzothiazin-2-yl)ethyl methanosulfonate 6,6-dioxide (**158**) (106) has directed the research of Rasmussen and Shaw (103,107) in the synthesis of 2,3,5,6-tetrahydro-13*H*-oxazolo[2′,3′:3,4]pyrazino [1,2-*b*]-[1,2]benzothiazin-13-one 8,8-dioxide (**159**). This reaction can be effected with either dimethylamine or sodium methyl mercaptide



For pharmacological purposes, Rasmussen has synthesized derivatives of 3,4-dihydro-2-(2-hydroxyethyl)-1-substituted amino)pyrazino[1,2-*b*][1,2]benzothiazin-11(2*H*)-one 6,6-dioxides (**160**) (108) and 1,2,3,4-tetrahydro-11-hydroxy-2-[2-(1-amino)]ethylpyrazino[1,2-*b*][1,2]benzothiazin-2(*H*)one 6,6-dioxide (**161**) (109).

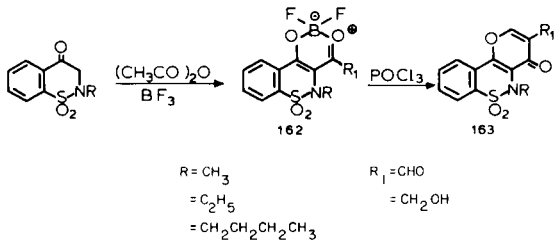


160



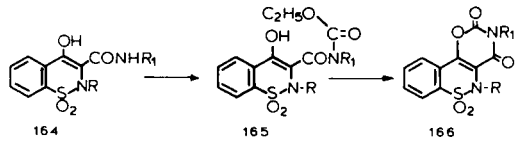
161

The attachment of the pyrano ring to the benzothiazine skeleton is effected by refluxing 2-alkyl-2*H*-1,2-benzothiazin-4(3*H*)one 1,1-dioxide in acetic anhydride with boron trifluoride and then by treating **162** with phosphorus oxychloride in dimethylformamide (110-111).



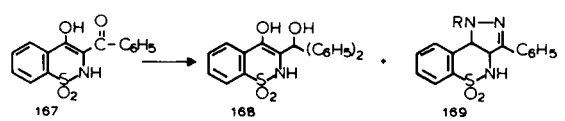
162 163

For the synthesis of oxazinobenzothiazine 6,6-dioxide (**166**), Rasmussen (112) has used an amide (**164**) as the starting material which with ethyl chloroformate in the presence of a base was transformed to the 3-*N*-ethoxycarbonylamide (**165**). The latter compound was cyclized with acetic acid to give the desired compound.



164 165 166

It was recently shown (113) that on treating benzothiazine (**167**) with phenylmagnesium bromide in a mixture of ether and benzene, and with hydrazine and phenylhydrazine in acetic acid afforded compound **168** and the pyrazolo[4,5-*c*][1,2]benzothiazine dioxide (**169**).



167 168 169

Pharmacology of the 1,2-Benzothiazine Polycyclic Derivatives.

The work of Zinnes, Comes and Shavel (99-100) have described the synthesis of 7,8-dihydropyrido[1,2-*b*][1,2]-benzothiazine-10,11-(9*H*,10*H*)dione 5,5-dioxides as 1,2-benzothiazine analogs of partial tetracycline structure.

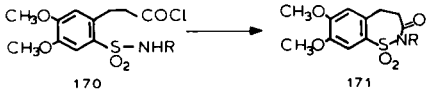
Compounds of the structure **144** and **145** demonstrated some antifungal activity (99-100). Also, tricyclic compounds such as **155** are useful as uv light absorbers in plastics (102). Oxazinobenzothiazine 6,6-dioxides (**166**) have been proven useful as inflammation inhibitors and as components of antiarthritic agents (112). As reported oxazolopyrazinobenzothiazinone dioxide (**159**) showed diuretic activity at a dose of 100 mg./kg.; at the same dose it inhibited kaolin-induced rat paw edema by 24% (107). Pyrazinobenzothiazines (**156**) with substituents on the nitrogen atom, such as H, C_2H_5, $C_6H_5(CH_2)_2$, $(CH_2)_2CN$ or $(CH_2)_2COOH$, are useful as central nervous system depressants (104).

Rasmussen (108) has synthesized and tested 3,4-dihydro-2-(2-hydroxyethyl)-1-(substituted amino)pyrazino[1,2-*b*]-[1,2]benzothiazin-11(2*H*)one 6,6-dioxides for pharmacological action. At a dose of 100 mg./kg., compound **160** (R = H) inhibited kaolin-induced rat paw edema by 14-37%. At 0.001 *M* (R = $C_6H_5CH_2CH_2$) it inhibited tyrosine hydroxylase. Further, at a dose of 5-10 mg./kg. (R = H) it reduced blood pressure in anesthetized dogs by 40-100 mm.

Miscellaneous Compounds.

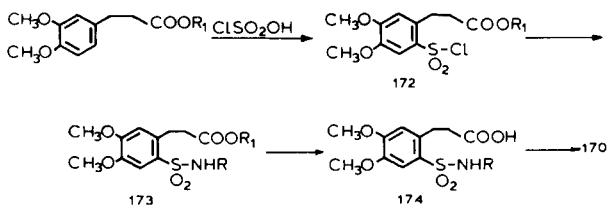
N-Substituted 4,5-Dihydro-7,8-dimethoxybenzothiazepin-3-one 1,1-Dioxides.

4,5-Dihydro-7,8-dimethoxybenzothiazepin-3-one 1,1-dioxide (**171**) is obtained (11,114) by a condensation reaction, in which hydrochloric acid is removed from the 4,5-dimethoxy-2-chlorocarboxyethylbenzenesulfonamide (**170**).



170 171

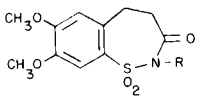
A convenient method for the preparation of this type of compound is the chlorosulfonation of the 3,4-dimethoxyphenylpropionic ester, since the position *para* to one of the methoxy groups is activated. However, direct chlorosulfonation of the latter compound at low temperature produced the 4,5-dimethoxy-2-carboethoxyethylbenzenesulfonyl chloride (**172**). For the preparation of 2-carboethoxyethyl-4,5-dimethoxybenzenesulfonamides (**173**), ammonia, primary aliphatic and aromatic amines were used. Hydrolysis of **173** with a base formed the corresponding sulfonamido acids (**174**). The latter were transformed to 2-chlorocarboxyethyl-4,5-dimethoxybenzenesulfonamides (**170**) by the action of phosphorus pentachloride in anhydrous benzene.



In Table VIII the known 4,5-dihydro-7,8-dimethoxybenzothiazepin-3-one 1,1-dioxides are presented. Tables IX and X summarize the ir and nmr of the above compounds.

Table VIII

N-Substituted 4,5-Dihydro-7,8-dimethoxybenzothiazepin-3-one 1,1-Dioxides



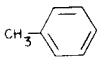
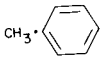
R	Yield %	Reference
CH_3CH_2	80	11
$CH_3(CH_2)_2$	86	11
$(CH_3)_2CH$	78	11
H	68	114
	77	114
	70	114
	65	114
	55	114
	62	114

Table IX

Infrared Absorption of Compounds **171** (11,114)

R	CO Stretching Vibrations (cm^{-1})	S-O Stretching Vibrations (cm^{-1})
C_2H_5	1690	1325, 1135
$CH_3(CH_2)_2$	1695	1330, 1140
$(CH_3)_2CH$	1680	1340, 1140
H	1700	1330, 1145
	1710	1350, 1130
	1710	1350, 1120
	1700	1350, 1130
	1700	1350, 1130
	1720	1345, 1130

Conclusions.

The main purpose of this review is to present a survey of the literature of the known benzothiazinone dioxides and their derivatives. The chemistry and some of the therapeutic applications of benzothiazine dioxide derivatives are also discussed.

The simple carboxanilide [*N*-(2-thiazolyl)-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide] in human plasma was more potent than aspirin. When the above carboxanilide was prepared in radio-labeled form and administered to rats, dogs and monkeys, their urine contained 60, 25 and 49% of the label given, respectively. In addition, two major matabolites were isolated and characterized as the thiohydantoic acid and thiourea.

N-(2-Pyridyl)-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide is a potent acidic antiinflammatory agent, which is structurally distinct from agents currently used, such as indomethacin phenylbutazone or noproxen. Pharmacokinetic studies indicated a longer plasma half-life for the above carboxanilide than for the previously mentioned drugs.

These observations served as an impetus for the extension of the investigations in the field of the synthesis of benzothiazine dioxide derivatives, with the hope of discovering new compounds with interesting pharmacological properties. The peak of research activity has not yet been reached in this vast and interesting area of study.

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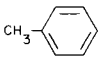
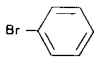
Table X

Nmr of Compounds **171** (11,114)

R	C_9-H(τ)	C_6-H(τ)	CH_3O	CH_2CH_2(τ)
C_2H_5	2.47 s	3.15 s	5.97 s	6.53 m, 6.1 (CH_2CH_3), 8.82 (t, CH_2CH_3)
$CH_3(CH_2)_2$	2.47 s	3.17 s	5.97 s	6.53 m, 6.15 [m, $(CH_2)_2CH_3$], 8.40 [m, $(CH_2)_2CH_3$] and 9.16 (t, $CH_2CH_2CH_3$)
$(CH_3)CH$	2.48 s	3.20 s	5.98 s	6.60 m, 5.12 [m, $CH(CH_3)_2$], 8.55 and 8.67 ($2CH_3$)
H	2.70 s	2.93 s	6.13 s	6.83 s
	2.77 s	2.88 s	6.14, 6.23 s	6.53 s
	2.85 s	3.0 s	6.12, 6.22 s	6.55 s
	2.77 s	2.85 s	6.10, 6.20 s	6.53 s
	2.77 s	2.85 s	6.12, 6.22 s	6.53 s
	2.73 s	2.88 s	6.13, 6.20 s	6.53 s

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