New Benzothiazines. 4.[1] 1*H*-2,3-Benzothiazin-4(3*H*)-one 2,2-Dioxide and 2*H*-1,2-Benzothiazin-3(4*H*)-one 1,1-Dioxide Nitrogen Derivatives with Central Nervous System Activity

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The title compounds, bearing an alkyl, aminoalkyl, or aryl substituent on the nitrogen atom, were synthesized and tested for CNS activity; some *N*-alkyl derivatives showed appreciable hypnotic and anticonvulsant properties in mice.

This laboratory has been concerned with the preparation and pharmacological study of a number of 1,2-, 2,3-, and 2,1-benzothiazine *S,S*-dioxide derivatives. The sulfamyl group as a part of heterocyclic, particularly six-membered, rings has long been recognized of great value, as, for example, in the 1,2,4-benzothiadiazine 1,1-dioxide series where, besides the well-known diuretic derivatives, others with antihypertensive[2] and/or hyperglycemic[3] activities are found; *N*-aryl-substituted 1,4-butanesultams also exhibit anticonvulsant properties.[4]

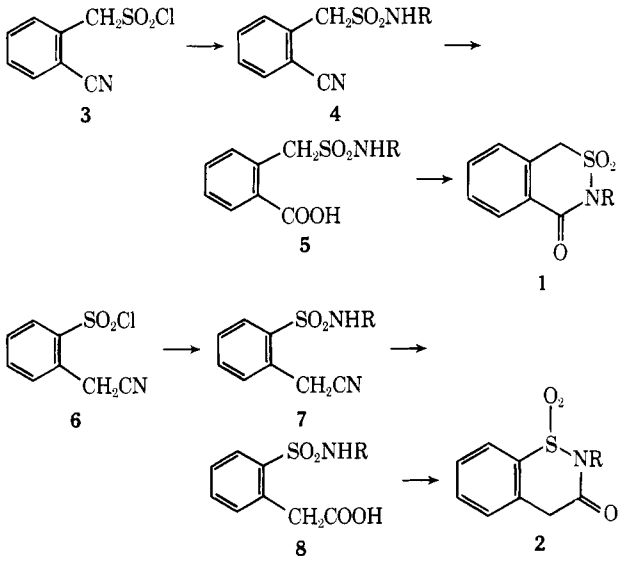
Physicochemical analogies exist to some extent between sultam and lactam functions, and compounds containing these structures show also pharmacological analogies that were discovered in a few cases between such analogous heterocycles;[5] bioisosteric relations between the carbonyl and sulfonyl groups are known.[6] The amide group is undoubtedly of great importance in cyclic structures acting on the CNS and, also, simple lactams have recently been found to have significant central activity.[7] We therefore considered it of interest to explore the significance of the analogous sultam group in benzothiazine-type rings, such as those mentioned above, for this kind of activity.

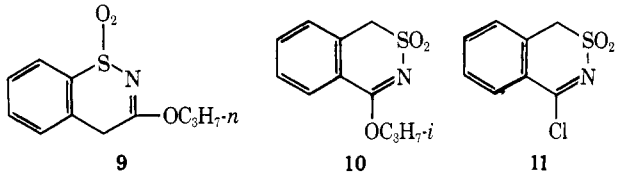
This paper describes the preparation and pharmacological evaluation of a first series of N-substituted 1*H*-2,3-benzothiazin-4(3*H*)-one 2,2-dioxides (**1**) and 2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxides (**2**); it is to be noted that in these molecules a carbonyl group associated with the sultam group simulates cyclic mixed imide function, which could appear, at least formally, interesting in our structural comparisons.

Chemistry. The benzothiazinones **1b–r** (Table I)† and **2b–o** (Table II)‡ were obtained either by cyclization of the appropriate carboxysulfonamides **5** or **8** (Scheme I) or by alkylation of 1*H*-2,3-benzothiazin-4(3*H*)-one 2,2-dioxide (**1a**) and 2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxide (**2a**), as outlined in a preceding paper.[10] In the latter case the anions of **1a** and **2a** are susceptible to an electrophilic attack either on the nitrogen or on the oxygen atom, depending on the reaction conditions and the nature of the reagents used; generally the N-substitution product was largely preponderant and in most cases could be isolated and purified readily. For **2d** (R = *n*-Pr), when **2a** was alkylated with *n*-PrBr in DMF and in the presence of $NaHCO_3$, the O derivative **9** was also isolated and characterized. In another case, by the reaction of the potassium salt of **1a** with *i*-PrBr in DMF, **10** was obtained as the major reaction product and **1e** (R = *i*-Pr) is more conveniently prepared by cyclizing **5b** (R = *i*-Pr). The structure of **10** was also further established through synthesis from the chloro derivative **11** (obtained from **1a** with PCl_5) and *i*-PrOH.

The N-substituted benzothiazinones **1s,t, 1x,y, 2p,** and **2s,** with a substituent in the aromatic ring, were prepared by terminal alkylation of the corresponding NH compounds. These NH compounds were obtained either as described[10] previously [the 6-nitro-1*H*-2,3-benzothiazin-4(3*H*)-one 2,2-dioxide and 7-nitro-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxide] or by conventional methods: **1w** (R = H, 6-Cl) by the Sandmeyer reaction on 6-amino-1*H*-2,3-benzothiazin-4(3*H*)-one 2,2-dioxide[10] and **2r** (R = H, 7-NHCOOEt) from 7-amino-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxide[10] with ethyl chloroformate. Reduction of the nitro groups in **1s,t** and **2p** gave the corresponding *ar*-aminobenzothiazinones **1u, 1v,** and **2q.**

Scheme I





Pharmacology. All compounds were tested for toxicity and for hypnotic and anticonvulsant activities on NMRI albino mice (18–20 g) and were administered as suspension in 10% gum-arabic solution. LD_{50} values were determined in mice intraperitoneally and the mortality over 48 hr was recorded; the animals (30 animals/drug) were also observed for behavior symptoms according to the Irwin scheme,[11] particular attention being payed to hypnotic effects. For the anticonvulsant activity test,[12] compounds were given orally and intraperitoneally to groups of ten mice, 60 and 30 min, respectively, before the animals were subjected to electroshock. Methaqualone and pentobarbital sodium were reference standard compounds. In Tables III and IV only the data of the more interesting compounds are reported.§

† **1b** (R = Me), **1f** (R = *n*-Bu), and **1o** (R = $CH_2CH_2NEt_2$) were recently described.[8]

‡ **2b** (R = Me) and **2i** (R = CH_2Ph) were recently described.[9]

§ See paragraph at end of paper regarding supplementary material.

Table I. 1*H*-2,3-Benzothiazin-4(3R)-one 2,2-Dioxides **1**

No.[a]	R	Method	Mp or bp (mm), °C	Yield, %	Recrystn solvent	Formula	Analyses
1b[b]	CH_3	A, F[c]	143–145[r]	85, 64	EtOH (95°)	$C_9H_9NO_3S$	C, H, N, S
1d	*n*-C_3H_7	D[d]	130–132	70	Hexane–C_6H_6	$C_{11}H_{13}NO_3S$	C, H, N, S
1e	*i*-C_3H_7	B[e]	91–92	86	Hexane–C_6H_6	$C_{11}H_{13}NO_3S$	C, H, N, S
1f[b]	*n*-C_4H_9	D[f]	138–140 (0.3), 80–82[s]	69	Hexane–C_6H_6	$C_{12}H_{15}NO_3S$	C, H, N, S
1g	$CH_2CH{=}CH_2$	D[g]	99–101	54	2-PrOH	$C_{11}H_{11}NO_3S$	C, H, N, S
1h	$CH_2C{\equiv}CH$	D	180–182	78	EtOH (95°)	$C_{11}H_9NO_3S$	C, H, S
1i	$CH_2C_6H_5$	A,[h] B	141–143	58, 63	EtOH (95°)	$C_{15}H_{13}NO_3S$	C, H, S
1k	*o*-C_6H_4Cl	B[i]	192–194	89	EtOH (95°)	$C_{14}H_{10}ClNO_3S$	C, H, N
1l	*m*-C_6H_4Cl	B[j]	141–143	85	EtOH (95°)	$C_{14}H_{10}ClNO_3S$	C, H, N, S
1m	*p*-C_6H_4Cl	B[k]	178–179	89	EtOH (95°)	$C_{14}H_{10}ClNO_3S$	C, H, N
1n	*p*-$C_6H_4SO_2NH_2$	C	231–233	71	H_2O–EtOH	$C_{14}H_{12}N_2O_5S_2$	C, H, N
1o[b]	$CH_2CH_2N(C_2H_5)_2$	F[l]	219–223[t]	30	EtOH	$C_{14}H_{20}N_2O_3S\cdot HCl$	C, H, Cl, N
1p	$CH_2CH_2N(i\text{-}C_3H_7)_2$	F	180–184	51	EtOAc–EtOH	$C_{16}H_{24}N_2O_3S\cdot HCl\cdot C_2H_5OH$	Cl, N, EtO
1q	CH_2CH_2(piperidino)	F	131–133	28	EtOAc–EtOH	$C_{15}H_{20}N_2O_3S\cdot HCl\cdot C_2H_5OH$	Cl, N, EtO
1r	CH_2CH_2(morpholino)	F[m]	200–204	32	EtOH	$C_{14}H_{18}N_2O_4S\cdot HCl$	C, H, Cl, N
1s	C_2H_5, 6-NO_2	D[n]	167–169	55	C_6H_6	$C_{10}H_{10}N_2O_5S$	C, H, S
1t	$CH_2CH{=}CH_2$, 6-NO_2	D[o]	79–81	65	EtOH (95°)	$C_{11}H_{10}N_2O_5S$	C, H, N
1u	C_2H_5, 6-NH_2	H	194–196	79	EtOH	$C_{10}H_{12}N_2O_3S$	C, H, N
1v	$CH_2CH{=}CH_2$, 6-NH_2		131–133	58	2-PrOH	$C_{11}H_{12}N_2O_3S$	C, H, N
1w	H, 6-Cl		205–207	39	H_2O	$C_8H_6ClNO_3S$	C, H, Cl, S
1x	C_2H_5, 6-Cl	E[p]	147–149	75	EtOH (95°)	$C_{10}H_{10}ClNO_3S$	C, H, N, S
1y	$CH_2CH{=}CH_2$, 6-Cl	E[q]	74–76	56	H_2O–EtOH	$C_{11}H_{10}ClNO_3S$	C, H, N, S

[a] For **1a** (R = H), **1c** (R = C_2H_5), and **1j** (R = C_6H_5), see ref 10. [b] See ref 8. [c] MeI as alkylating agent. [d] At 90–100° for 24 hr with 1-bromopropane and KI. [e] At 60–70° for 1 hr. [f] At 120° for 24 hr with 1-bromobutane and KI; purified by distillation. [g] At room temperature for 24 hr with allyl bromide; the product was purified first by 45 min of boiling in concentrated HCl–dioxane (1:2.5 v/v) and then, after evaporation and separation from the acid materials, by crystallization. [h] At 90° for 3 hr with 1.5 mol equiv of $SOCl_2$. [i] At 85° for 1.5 hr. [j] At 80–90° for 3 hr. [k] At 100° for 1 hr. [l] The base was first distilled at 185–195° (air bath temperature), 1 mm. [m] Twice crystallized. [n] At 50–60° for 6 hr with EtI. [o] At 65–70° for 3 hr with allyl bromide. [p] With K_2CO_3 and EtI; twice crystallized. [q] With K_2CO_3 and allyl bromide; twice crystallized. [r] Reported[8] 145°. [s] Reported[8] 85–86°. [t] Reported[8] 218°.

Results

After injection of *N*-aryl derivatives **1j-n** and **2j-n** of *N*-aminoalkyl (**1o-r** and **2o**) and of the *N*-alkyl derivatives **1s-v,x,y** and **2p,q,s**, the animals did not show symptoms of CNS activities. After treatment with the *N*-alkyl derivatives **1b-g**, the animals showed symptoms of CNS depression, which began to appear at approximately one-fourth the LD_{50}, and went on until the doses became toxic; several animals died in their sleep not later than 24 hr after the administration of products. After administration of the *N*-alkyl derivatives **2b-g**, the animals showed first symptoms of excitement and then symptoms of CNS depression after approximately one-fourth the LD_{50}. The animals fell asleep and dropped from the inclined screen; while sleeping the animals died within 10 hr after the administration of the test compounds. No symptoms of CNS activity were observed for propargyl (**1h, 2h**) and benzyl (**1i, 2i**) derivatives and for unsubstituted (**1a, 2a**) compounds.

Only a few *N*-alkyl derivatives of structures **1** and **2** showed significant anticonvulsant and hypnotic activities which disappeared almost completely when the N substituent was propargyl or benzyl. The introduction into the aromatic ring of substituents (**1s-y**, and **2p-s**) resulted in inactive products or less active than the corresponding unsubstituted compounds.

It is interesting to note that there was little biological difference between analogous derivatives of the structures **1** and **2**, in which the only structural difference is the exchange of the CO and SO_2 groups; thus, the two structures appear to act as bioisosteres.

Experimental Section[=]

2′-Chloro-2-cyano-α-toluenesulfonanilide (4d). A solution of 19.4 g (0.09 mol) of 2-cyano-α-toluenesulfonyl chloride[13] and 23 g (0.18 mol) of 2-chloroaniline in 250 ml of $CHCl_3$ was refluxed for 10 hr. The mixture was filtered, washed (dilute HCl and H_2O), and evaporated, and the residue was crystallized to yield 16.1 g of **4d**.

The other sulfonamides in Tables V and VI were similarly prepared (solvent, temperature, and reaction time given): **4a**, $CHCl_3$, room temperature, 5 hr ($MeNH_2$ used as 35% aqueous solution); **4b**, the same, 10 hr; **4c**, C_6H_6, 60°, 0.5 hr; **4e**, boiling $CHCl_3$, 1.5 hr; **4f**, the same, 3 hr; **4g**, boiling Me_2CO, 2.5 hr (pyridine was substituted for the second equivalent of amine); **7a**, $CHCl_3$, 0°, 3 hr ($MeNH_2$ as 35% aqueous solution); **7b**, $CHCl_3$, room temperature, 10 hr; **7c**, C_6H_6, 45°, 0.5 hr; **7d**, without solvent, 100°, 2 hr; **7e**, boiling C_6H_6, 9 hr; **7f**, the same, 7 hr; **7g**, boiling Me_2CO, 3 hr. **4a,b** and **7a,b** were preliminarily purified by dissolution in cold diluted NaOH, clarification, and reprecipitation with HCl.

2-Carboxy-*N*-methyl-α-toluenesulfonamide (5a). A solution of 2.1 g (0.01 mol) of 2-cyano-*N*-methyl-α-toluenesulfonamide (**4a**) in 10 ml of 2.5 *N* NaOH was boiled for 120 hr, then cooled, filtered, acidified, and refrigerated overnight to complete precipitation; after being collected and purified by dissolution in 5% aqueous $NaHCO_3$, filtration, and reprecipitation (HCl), the solid (1.57 g, mp 150°) was recrystallized; yield 1.28 g.

Carboxy derivatives in Tables VII and VIII were analogously obtained by boiling the corresponding nitriles in excess alkali until the NH_3 evolution had practically ceased: **5b** (1 *N* NaOH, for 30 hr), **5c** and **8c** (0.5 *N*, 16 hr), **5d** (1 *N*, 10 hr), **5e** (6 *N*, 4 hr), **5f** and **8g** (1 *N*, 12 hr), **5g** (1 *N*, 20 hr), **8a** (1 *N*, 9 hr), **8b** (1 *N*, 13 hr), **8d** (1 *N*, 8 hr), **8e** (0.5 *N*, 24 hr), and **8f** (1 *N*, 6 hr).

3-Methyl-1*H*-2,3-benzothiazin-4(3*H*)-one 2,2-Dioxide (1b)[8] (Method A). A suspension of 2.29 g (0.01 mol) of 2-carboxy-*N*-methyl-α-toluenesulfonamide (**5a**) in 25 ml of $SOCl_2$ was boiled for 3 hr. Excess $SOCl_2$ was evaporated, the residue treated with ice and aqueous Na_2CO_3, and the solid extracted with $CHCl_3$; the extract was washed (H_2O), dried, and evaporated to give 2.0 g of crude **1b**, 1.8 g after recrystallization.

3-Benzyl-1*H*-2,3-benzothiazin-4(3*H*)-one (1i) (Method B). A mixture of 0.61 g (2 mmol) of *N*-benzyl-2-carboxy-α-toluenesulfonamide (**5c**) with 0.42 g (2 mmol) of PCl_5 was heated at 70–80° for 2 hr, then cooled, triturated with ice–water, and treated with an excess of Na_2CO_3; the solid was collected, washed, dried, and crystallized; yield 0.37 g.

2-(4-Sulfamoylphenyl)-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-

[=] Melting points were taken in capillaries and are uncorrected; boiling points are uncorrected. Analytical results are represented by the symbols of the elements and the values obtained were within ±0.4% of the calculated values.

Table II. 2R-1,2-Benzothiazin-3(4*H*)-one 1,1-Dioxides **2**

No.[a]	R	Method	Mp or bp (mm), °C	Yield, %	Recrystn solvent	Formula	Analyses
2b[b]	CH_3	B,[c] D[d]	91–93[l]	77, 38	Ligroine	$C_9H_9NO_3S$	C, H, S
2d	*n*-C_3H_7	E	137–138 (0.3)	38		$C_{11}H_{13}NO_3S$	C, H, N, S
2e	*i*-C_3H_7	B[e]	90–91	73	Hexane	$C_{11}H_{13}NO_3S$	C, H, N, S
2f	*n*-C_4H_9	E[f]	158–159 (0.9), 43–44	43	Hexane–PhH	$C_{12}H_{15}NO_3S$	C, H, S
2g	$CH_2CH{=}CH_2$	D[g]	148–150 (0.2)	64		$C_{11}H_{11}NO_3S$	C, H, S
2h	$CH_2C{\equiv}CH$	D[h]	165–167	45	EtOH (95°)	$C_{11}H_9NO_3S$	C, H, N
2i[b]	$CH_2C_6H_5$	B[i]	150–153[m]	70	2-PrOH	$C_{15}H_{13}NO_3S$	C, H, S
2k	*o*-C_6H_4Cl	B	125–127	77	2-PrOH	$C_{14}H_{10}ClNO_3S$	C, H, N
2l	*m*-C_6H_4Cl	B	208–211	89	EtOH (95°)	$C_{14}H_{10}ClNO_3S$	C, H, N
2m	*p*-C_6H_4Cl	B	151–153	82	EtOH (95°)	$C_{14}H_{10}ClNO_3S$	C, H, N
2n	*p*-$C_6H_4SO_2NH_2$	C	202–205	48	EtOH	$C_{14}H_{12}N_2O_5S_2$	C, H, N
2o	CH_2CH_2(morpholino)	G	235–238	24	EtOH	$C_{14}H_{18}N_2O_4S\cdot HCl$	C, H, Cl, N
2p	C_2H_5, 7-NO_2	D[j]	144–147	31	Ligroine	$C_{10}H_{10}N_2O_5S$	C, H, N
2q	C_2H_5, 7-NH_2	H	152–155	69	EtOH (95°)	$C_{10}H_{12}N_2O_3S$	C, H, N
2r	H, 7-$NHCO_2Et$		185–186	62	2-PrOH	$C_{11}H_{12}N_2O_5S$	C, H, S
2s	C_2H_5, 7-$NHCO_2Et$	E[k]	160–162	30	2-PrOH	$C_{13}H_{16}N_2O_5S$	C, H, N

[a] For **2a** (R = H), **2c** (R = C_2H_5), and **2j** (R = C_6H_5), see ref 10. [b] See ref 9. [c] At room temperature for 20 hr. [d] MeI as alkylating agent; three times crystallized. [e] At room temperature for 3 hr. [f] Purified by distillation. [g] With allyl bromide at 65–70° for 6 hr and at 100° for 0.5 hr. [h] KI was also added; twice crystallized. [i] At 80–90° for 3 hr. [j] From the sodium salt of 7-NO_2 **2a** and EtI at 0° for 8 days; two crystallizations. [k] At 50° with EtI; three crystallizations. [l] Reported[9] 92–95°. [m] Reported[9] 152–155°.

Dioxide (2n) (Method C). A mixture of 7.4 g (0.02 mol) of 2-carboxymethyl-4′-sulfamoylbenzenesulfonanilide (**8g**), 9 g of anhydrous NaOAc, 80 ml of glacial AcOH, and 8 ml of Ac_2O was refluxed for 6 hr. The solution was concentrated to about half-volume and then poured into ice; the solid was separated, triturated with aqueous Na_2CO_3, filtered off, washed, and crystallized: yield 3.4 g.

3-Propargyl-1*H*-2,3-benzothiazin-4(3*H*)-one 2,2-Dioxide (1h) (Method D). To 4.7 g (0.02 mol) of dry 1*H*-2,3-benzothiazin-4(3*H*)-one 2,2-dioxide (**1a**)[10] potassium salt (obtained by concentrating a MeOH solution of equimolar amounts of **1a** and KOH) in 20 ml of DMF, 2.2 g (0.03 mol) of propargyl chloride was added and the mixture was kept at 65–70° for 6 hr. After concentration the residue was triturated with 5% aqueous Na_2CO_3; the solid was collected, washed, and crystallized: yield 3.7 g.

2-(*n*-Propyl)-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-Dioxide (2d) (Method E). To 9.86 g (0.05 mol) of 2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxide (**2a**)[10] in 120 ml of DMF was added 4.2 g (0.05 mol) of $NaHCO_3$ and 6.85 g (0.05 mol) of 1-bromopropane and the mixture was kept at 70° for 8 hr and then evaporated; the residue was partitioned between 5% aqueous $NaHCO_3$ and $CHCl_3$ and the organic phase was washed, dried, and evaporated; the oily residue was three times distilled: yield 4.1 g.

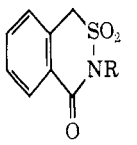
3-(2-Diisopropylaminoethyl)-1*H*-2,3-benzothiazin-4(3*H*)-one 2,2-Dioxide Hydrochloride (1p) (Method F). To a stirred solution of NaOEt (0.02 mol; from 0.46 g of Na) in 50 ml of absolute EtOH was added 1.97 g (0.01 mol) of **1a** and, after 15 min, a solution of 2.0 g (0.01 mol) of 2-diisopropylaminoethyl chloride hydrochloride in 30 ml of absolute EtOH. After 5 hr of refluxing, the solution was filtered and evaporated, the residue was treated with 40 ml of 5% NaOH, and the oily product was taken up in ether; from the organic solution, washed with brine and dried, the product was precipitated with dry HCl and recrystallized: yield 2.1 g.

2-(2-Morpholinoethyl)-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-Dioxide Hydrochloride (2o) (Method G). To a suspension of 11.83 g (0.06 mol) of **2a** in 350 ml of dry toluene, 11.8 g (0.085 mol) of dry K_2CO_3 pulver, 11.2 g (0.06 mol) of 2-morpholinoethyl chloride, and a catalytic amount of Cu pulver were added, and the mixture was boiled and stirred for 12 hr; after cooling and filtering the solution was extracted with 2 *N* HCl (2 × 100 ml), the aqueous phase was saturated with Na_2CO_3 and extracted with ether, and the organic solution was washed (brine), dried, and evaporated. The oily residue, taken up in EtOH (50 ml) and treated with dry HCl at 0°, gave 9 g of the crude salt, pure (5.0 g) after two crystallizations.

6-Amino-3-ethyl-1*H*-2,3-benzothiazin-4(3*H*)-one 2,2-Dioxide (1u) (Method H). The nitro compound **1s** (5.4 g, 20 mmol) in MeOH (450 ml) was shaken under H_2 over 10% Pd/C (0.5 g) until absorption ceased; after filtration and evaporation, the residue was crystallized: yield 3.8 g.

3-Allyl-6-amino-1*H*-2,3-benzothiazin-4(3*H*)-one 2,2-Dioxide (1v). To a solution of 9.6 g (0.034 mol) of the nitro derivative **1t** in 45 ml of AcOH was added 18 g of granular Sn and dropwise, while cooling and stirring, 70 ml of concentrated HCl; the mixture was further stirred at room temperature for 18 hr, the unreacted Sn was separated, and the solution was made strongly alkaline with 20% NaOH and allowed to stand at 0° for 2 hr; the precipitated solid was washed, dried, and crystallized: yield 5.0 g.

Table III. Hypnotic and Anticonvulsant Effects in Mice of 1*H*-2,3-Benzothiazin-4(3R)-one 2,2-Dioxides **1**



No.	R	LD_{50}, mg/kg ip	HD_{50},[a] mg/kg ip	Anticonvulsant[b] activity, mg/kg ip	Anticonvulsant[b] activity, mg/kg Orally
1a	H	750	[c]	>150	>150
1b	CH_3	1150	575	230	>230
1c	C_2H_5	2800	500	300	>300
1d	*n*-C_3H_7	>3000	[c]	>520	>520
1e	*i*-C_3H_7	2400	400	75	150
1f	*n*-C_4H_9	870	750	>174	>174
1g	$CH_2CH{=}CH_2$	500	250	100	>100
1h	$CH_2C{\equiv}CH$	2400	[c]	300	300
1i	$CH_2C_6H_5$	>3000	[c]	>300	>300

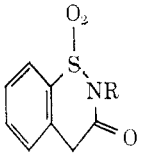
[a] Dose suppressing the righting reflex when the mice are placed on their backs. [b] Dose protecting 70% of the animals. [c] Inactive up to toxic doses.

6-Chloro-1*H*-2,3-benzothiazin-4(3*H*)-one 2,2-Dioxide (1w). A suspension of powdered 6-amino-1*H*-2,3-benzothiazin-4(3*H*)-one 2,2-dioxide[10] (11.7 g, 55 mmol) in 110 ml of H_2O and 66 ml of concentrated HCl was stirred for 0.5 hr, then was treated dropwise at 0° with a solution of $NaNO_2$ (3.9 g, 55 mmol) in H_2O (11 ml), and additionally stirred at this temperature for 0.5 hr; then it was portionwise poured into a stirred solution of CuCl (5.6 g, 56.5 mmol) in concentrated HCl (56 ml) and after 1 hr of additional stirring was kept in the cold overnight. The separated solid was washed and twice crystallized: yield 5.0 g.

7-Carbethoxyamino-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-Dioxide (2r). Into a solution of 6.58 g (31 mmol) of 7-amino-2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxide[10] in 390 ml of H_2O and 22 ml of concentrated HCl, 16.9 g (155 mmol) of ethyl chloroformate was added dropwise at 5°; after further stirring at room temperature for 3.5 hr, the suspension was filtered, and the solid was washed, dried (6.6 g), and crystallized: yield 5.5 g.

3-*n*-Propyloxy-4*H*-1,2-benzothiazine 1,1-Dioxide (9). The thick brown residue left in the still after the first distillation of **2d** (see method E) gradually solidified; it was ground in a mortar

Table IV. Hypnotic and Anticonvulsant Effects in Mice of 2R-1,2-Benzothiazin-3(4*H*)-one 1,1-Dioxides **2**



No.	R	LD_{50}, mg/kg ip	HD_{50},[a] mg/kg ip	Anticonvulsant[b] activity, mg/kg ip	Anticonvulsant[b] activity, mg/kg Orally
2a	H	750	*e*	>150	>150
2b	CH_3	1000	240	100	200
2c	C_2H_5	650	180	130	>130
2d	*n*-C_3H_7	3000	1800	200	200
2e	*i*-C_3H_7	2850	400	>300	>300
2f	*n*-C_4H_9	>3000	*e*	300	300
2g	$CH_2CH{=}CH_2$	800	150	160	>160
2h	$CH_2C{\equiv}CH$	3000	*e*	>300	>300
2i	$CH_2C_6H_5$	3000	*e*	>300	>300
Pentobarbital sodium[c]		117	40	>23	>23
Methaqualone[d]		455	44	34.5	138

[a,b] See Table III. [c] In 0.9% NaCl aqueous solution. [d] As suspension in 10% gum-arabic solution. [e] Inactive up to toxic doses.

Table V. 2-Cyano-α-toluenesulfonamides **4**

No.	R	Mp, °C	Yield, %	Recrystn solvent	Formula	Analyses
4a	CH_3	120–123	52	EtOAc	$C_9H_{10}N_2O_2S$	C, H, N, S
4b	*i*-C_3H_7	93–95	45	Hexane–C_6H_6	$C_{11}H_{14}N_2O_2S$	C, H, N
4c	$CH_2C_6H_4$	116–118	67	C_6H_6	$C_{15}H_{14}N_2O_2S$	C, H, S
4d	*o*-C_6H_4Cl	125–127	58	C_6H_6–ligroine	$C_{14}H_{11}ClN_2O_2S$	C, H, N
4e	*m*-C_6H_4Cl	147–149	70	H_2O–Me_2CO	$C_{14}H_{11}ClN_2O_2S$	C, H, N
4f	*p*-C_6H_6Cl	173–175	60	C_6H_6	$C_{14}H_{11}ClN_2O_2S$	C, H, N
4g	*p*-$C_6H_4SO_2NH_2$	210–212	52	H_2O–EtOH	$C_{14}H_{13}N_3O_4S_2$	C, H, N

Table VI. 2-Cyanomethylbenzenesulfonamides **7**

No.	R	Mp or bp (mm), °C	Yield, %	Recrystn solvent	Formula	Analyses
7a	CH_3	83	84	2-PrOH	$C_9H_{10}N_2O_2S$	C, H, N, S
7b	*i*-C_3H_7	155–158 (0.1)	43		$C_{11}H_{14}N_2O_2S$	C, H, N, S
7c	$CH_2C_6H_5$	84–86	82	C_6H_6–ligroine	$C_{15}H_{14}N_2O_2S$	C, H, S
7d	*o*-C_6H_4Cl	96–98	69	C_6H_6–ligroine	$C_{14}H_{11}ClN_2O_2S$	C, H, N
7e	*m*-C_6H_4Cl	136–138	73	C_6H_6–ligroine	$C_{14}H_{11}ClN_2O_2S$	C, H, N
7f	*p*-C_6H_4Cl	125–127	81	C_6H_6–ligroine	$C_{14}H_{11}ClN_2O_2S$	C, H, N
7g	*p*-$C_6H_4SO_2NH_2$	166–168	68	H_2O	$C_{14}H_{13}N_3O_4S_2$	C, H, N, S

Table VII. 2-Carboxy-α-toluenesulfonamides **5**

No.	R	Mp, °C	Yield, %	Recrystn solvent	Formula	Analyses
5a	CH_3	151	56	H_2O	$C_9H_{11}NO_4S$	C, H, N, S
5b	*i*-C_3H_7	168–170	51	H_2O	$C_{11}H_{15}NO_4S$	C, H, N, S
5c	$CH_2C_6H_5$	181–184	83	H_2O	$C_{15}H_{15}NO_4S$	C, H, S
5d	*o*-C_6H_4Cl	161–162	86	EtOH–H_2O	$C_{14}H_{12}ClNO_4S$	C, H, N
5e	*m*-C_6H_4Cl	177–179	82	EtOH–H_2O	$C_{14}H_{12}ClNO_4S$	C, H, Cl, N
5f	*p*-C_6H_4Cl	178–180	73	EtOH–H_2O	$C_{14}H_{12}ClNO_4S$	C, H, N
5g	*p*-$C_6H_4SO_2NH_2$	219–221	93	EtOH–H_2O	$C_{14}H_{14}N_2O_6S_2$	C, H, N

under *i*-Pr_2O and crystallized from C_6H_6–hexane (charcoal) to afford 2.0 g (9.4%) of yellow crystals: mp 95–97°; ir (Nujol) C=O band absent (1700 cm^{-1} in the isomer **2d**), enlarged band at 1640 cm^{-1} (C=N). *Anal.* ($C_{11}H_{13}NO_3S$) C, H, N, S. Acid hydrolysis (dioxane–concentrated HCl 10:4 v/v, 6 days at room temperature) and alkaline hydrolysis (5% Na_2CO_3 at 70° for 1 hr) gave respectively as principal products *o*-sulfamoylphenylacetic acid[10] and the benzothiazinone **2a**[10] (isolated and identified by tlc, mixture melting point, analysis and ir).**

**For 2*H*-1,2-benzothiazin-3(4*H*)-one 1,1-dioxide ir (KBr) data were previously[10] wrongly reported and are actually 3100, 3010 (NH), 1696 (CO), 1335 cm^{-1} (SO).

4-Isopropyloxy-1*H*-2,3-benzothiazine 2,2-Dioxide (10). (a) **1a** potassium salt (9.4 g, 0.04 mol) in DMF (40 ml) was treated with 2-bromopropane (4.15 ml, 0.044 mol) and a catalytic amount of KI, and the mixture was heated at 90–100° for 24 hr under stirring. The solvent was then removed *in vacuo*, and the residue was partitioned between 2% NaOH and $CHCl_3$; the organic solution, washed, dried, and evaporated, left a solid that was recrystallized from C_6H_6–hexane: yield 3.0 g (31%); mp 182–183°; ir (Nujol) C=O band absent (1675 cm^{-1} in the isomer **1e**) and the three bands in the field of 1500–1700 cm^{-1} (1615, 1590, 1560) are to be attributed to the benzene ring and C=N.

When the mother crystallization liquor was evaporated and the residue was boiled in dioxane (7 ml) and 5 *N* HCl (3 ml) for 10

Table VIII. 2-Carboxymethylbenzenesulfonamides **8**

No.	R	Mp, °C	Yield, %	Recrystn solvent	Formula	Analyses
8a[a]	CH_3	174[b]	78	H_2O	$C_9H_{11}NO_4S$	C, H, N, S
8b	i-C_3H_7	115–117	45	H_2O	$C_{11}H_{15}NO_4S$	C, H, N, S
8c[a]	$CH_2C_6H_5$	124[c]	86	H_2O	$C_{15}H_{15}NO_4S$	C, H, N
8d	o-C_6H_4Cl	146–148	95	EtOH–H_2O	$C_{14}H_{12}ClNO_4S$	C, H, N
8e	m-C_6H_4Cl	159–163	86	H_2O	$C_{14}H_{12}ClNO_4S$	Cl, N, S
8f	p-C_6H_4Cl	128–130	94	EtOH–H_2O	$C_{14}H_{12}ClNO_4S$	Cl, N, S
8g	p-$C_6H_4SO_2NH_2$	202–204	84	H_2O	$C_{14}H_{14}N_2O_6S_2$	C, H, S

[a] See ref 9. [b] Lit.[9] 158–164°, uncrystallized. [c] Lit.[9] 107–109°.

hr, evaporation of this solution and treatment of the residue as above gave finally 0.27 g (2.8%) of the crystalline isomer **1e** (mixture melting point, tlc, and ir).

(b) **1a** (5.91 g, 0.03 mol) and PCl_5 (6.25 g, 0.03 mol) were mixed and heated at 160° for 30 min, then $POCl_3$ was removed *in vacuo*, and the residue was triturated with a little $CHCl_3$, collected, and crystallized (C_6H_6–CCl_4) to give 4.55 g (70%) of **4-chloro-1*H*-2,3-benzothiazine 2,2-dioxide (11)**, mp 172–174°. *Anal.* ($C_8H_6ClNO_2S$) C, H, Cl, N, S.

A suspension of **11** (3.23 g, 0.015 mol) in 2-PrOH (20 ml) was refluxed for 4 hr and the obtained solution let stand in the cold to complete separation of the product, that was collected, washed, dried, and recrystallized (2-PrOH) to afford 2.6 g (72%) of **10**, mp 182–183°, identical (analysis, tlc, mixture melting point, and ir) with the product described under (a).

Supplementary Material Available. A listing of the pharmacological data for weakly active or inactive compounds will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JMED-73-1133.

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Synthesis of the Thyrotropin-Releasing Hormone Enantiomer and Some Diastereoisomers and *in Vitro* Studies of Their Biological Activity

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The isomers of TRH with DDD, DLL, LDL, and LLD configurations were prepared unequivocally by coupling pentachlorophenyl pyroglutamate of the required configuration with the appropriate histidylprolinamide diastereoisomer. The dipeptide amide was made by condensation of *tert*-butyloxycarbonylhistidine with prolinamide mediated by dicyclohexylcarbodiimide, removal of the blocking group in trifluoroacetic acid, and treatment of the peptide amide hydrochloride with a basic ion exchanger. Protected peptide intermediates and the final isomers were purified by chromatography on silica gel. Formation of diastereoisomers of the protected dipeptide was detected by nmr and tlc techniques. The LDL isomer was approximately 2–3% as active as TRH for TSH release in rat hemipituitaries *in vitro*, the DLL and LLD isomers were about 0.1% active, and the DDD isomer was inactive. None of these analogs inhibited TSH release *in vitro*.

The recent availability of synthetic thyrotropin-releasing hormone (TRH) and analogs has made possible for the first time studies of TRH structure–activity relationships. Burgus and collaborators[1] have demonstrated the critical importance of the N-terminal pyrrolidone group and the C-terminal amide for full biological expression of TRH, and Bowers and associates[2] have shown that of several C-terminal analogs only those containing proline were inactivated by serum. Experiments with labeled TRH suggested that the C-terminal carboxamide group hydrolysis by serum is a first metabolic step[2,3] in the inactivation

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