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The Synthesis of 1,2-Benzothiazine-3-carboxamidylhydantoin Derivatives and their Antiinflammatory and Analgesic Activities

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Abstract □ A number of 4-hydroxy-2H (or alkyl)-N-(3-aralkyl-2-thio-1-hydantoinyl)-1,2-benzothiazine-3-carboxamide 1,1-dioxides were synthesized through the reaction of 4-hydroxy-2H (or alkyl)-1,2-benzothiazine-3-carboxylic methyl ester 1,1-dioxide and 1-amino-2-thio-3-aralkyl-4-imidazolones in xylene. The compounds synthesized were screened for antiinflammatory effect on carrageeenin-induced edema in rat and for analgesic effect on acetic acid-induced Writhing syndrome in mice. Most compounds were inhibitors of carrageenin-induced rat foot edema and some showed significant antiinflammatory activity comparable to that of indomethacin and significant analgesic activity comparable to that of indomethacin and aspirin.

Keywords □ Oxicams, 1,2-benzothiazine 3-carboxamidylhydantoin derivatives, antiinflammatory, analgesic.

In order to discover new useful theapeutic agents, many new compounds are continually being synthesized and tested. 1,2-Benzothiazine derivatives have been reported to show considerable biological activities. In recent years the literature has shown a great increase in commercial research involving the preparations, reactions and the physiological activities of these compounds.

Piroxicam is the first member of a recently discoverd novel family of NSAIDS[1]. The new class of 4-hydroxy-1,2-benzothiazine-3-carboxamide derivatives is characterized by long-acting and often very potent anti-inflammatory activity[2]. The introduction of a heterocyclic ring in the amide side chain of a 4-hydroxy-1,2-benzothiazine-3-carboxamide increases significantly anti-inflammatory activity. Another N-heterocyclic oxicams are isoxicam[3] and sudoxicam[4]. Tenoxicam[5] resembles piroxicam in all respects except that a thieno ring has been replaced with a benzo ring in the molecule.

Thus, to develop novel NSAIDS, we describe here a series of related compounds of structure 3 in which the amide nitrogen is substituted with a hydantoinyl group. In this paper we report the modification of the structure of piroxicam.

EXPERIMENTAL

Melting points were determined on a Büchi 535 melting point apparatus and uncorrected. NMR spectra were recorded on a JEOL UNM-PMX 60 SI NMR spectrometer using TMS as internal standard. IR spectra were recorded on a Bomen Michelson FT-IR spectrometer using KBr discs. The elemental analysis(C, H, N) were carried out with a Perkin Elmer Model CHN 2400 elemental analyzer.

3-Oxo-1,2-benzisothiazoline-2-acetic acid methyl ester 1,1-dioxide, 1

A mixture of benzoisothiazoline-3-one 1,1-dioxide (50g, 0.24 mole), methyl chloroacetate (26g, 0.24 mole), DMF (50 m*l*) was heated for 3 hours in reflux. The reaction mixture was cooled to room temperatures, was poured into 150 m*l* of water with stirring. After cooling, the resulting precipitate was filtered off, washed with water and dried. The crude product was recrystallized from methanol to give

the desired compound. Yield: 90.2%; mp: 120-121℃; IR (KBr) cm^{-1}: 2980 (C-H), 1750 (C=O), 1310 (SO_2), 1170 (SO_2); NMR ($CDCl_3$+DMSO-d_6) δ: 3.77 (s, 3H, OCH_3), 4.43 (s, 2H, N-CH_2-), 7.85 (m, 4H, C_6H_4).

4-Hydroxy-2H-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide, 2

A solution of sodium methoxide was prepared from sodium (32.2g, 1.4 mole) in the absolute methanol. To the cooled solution in an ice-bath 3-oxo-1,2-benzothiazoline-2-acetic acid methyl ester 1,1-dioxide (0.2 mole) was added all at once as powder. Color changes from yellow to orange. After a few minutes, the mixture was refluxed for 30 minutes. The orange slurry was poured into 100 m*l* of ice-cold concentrated hydrochloric acid. The mixture was cooled thoroughly in an ice bath. The precipitate was filtered off, washed with water and the residue was recrystallized from *d*-MeOH to give the desired compound **2**. Yield: 89.8%; mp: 179-181℃; IR(KBr) cm^{-1}: 2970 (C-H), 1700 (c=O), 1330 (SO_2), 1160 (SO_2); NMR ($CDCl_3$) δ: 3.93 (s, 3H, OCH_3), 7.76 (m, 4H, C_6H_4).

4-Hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide, 2a

A yellow solution was resulted from a combination of 4-hydroxy-2H-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide (12.75g, 0.05 mole), methyl iodide (12 m*l*), water (55 m*l*), ethanol (200 m*l*), and 1 N NaOH (60 m*l*). After standing at room temperature for 18 hrs the resulting heavy yellow precipitate was filtered, washed with water, and the residue was recrystallized from *d*-EtOH, dried to give 15.5g of compound **2a**. Yield: 90%;mp: 169-170℃; IR (KBr) cm^{-1}: 2950 (C-H), 1660 (C=O), 1600 (C=O), 1320 (SO_2), 1170 (SO_2); NMR ($CDCl_3$) δ: 2.93 (s, 3H, NCH_3), 3.95 (s, 3H, OCH_3), 7.77 (m, 4H, C_6H_4).

1-Amino-2-thioxo-3-phenyl-4-imidazolone, 5[11]

Ethyl hydrazinoacetate hydrochloride[12] (3.11g, 0.02 mole) was added to a stirred solution of the isothiocyanate (14 m*l*, 0.02 mole) and triethylamine (8.3g, 0.06 mole) in 80 m*l* dichloromethane. When the solution becomes homogeneous, it was left for 4 days. The solvent was then evaporated and the residue was washed with cold water, filtered. After dissolving the residue in a minimum of boiling methanol, the hot solution was filtered and cooled to −20℃. The crystals were filtered off, washed with a small amount of cold methanol and finally dried in vacua to give pure 5. Yield: 66.5%; mp: 170-172℃ (dec); IR (KBr) cm^{-1}: 3250 (NH_2), 3180 (NH), 2890 (CH), 1730 (C=O); NMR (DMSO-d_6) δ: 4.43 (s, 2H, CH_2), 5.35 (s, 2H, NH_2), 7.44 (m, 5H, C_6H_5).

4-Hydroxy-2-methyl-N-(3-phenyl-2-thio-1-hydantoinyl)-1,2-benzothiazine-3-carboxamide 1,1-dioxide, 3k

A mixture of 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide **2a** (10.76g, 0.04 mole), 1-amino-2-thioxo-3-phenyl-4-imidazolone **5d** (11.6g, 0.056 mole), and xylene (600 m*l*) was heated to reflux for 24 hrs in a soxhlet apparatus, the thimble of which contained 30g of 4 Å molecular sieves. The mixture was cooled to room temperature, and the resulting crystslline precipitate was collected and washed with ether to give crude product. Recrystallization from 1,4-dioxane gave 6.75 g of **3a**. Yield: 75.8%; mp: 275-276℃ (dec); IR (KBr) cm^{-1}: 3280 (NH), 2900 (CH), 1755 (C=O), 1350 (SO_2), 1115 (SO_2); NMR ($CDCl_3$+DMSO-d_6) δ: 2.99 (s, 3H, NCH_3), 4.60 (s, 2H, CH_2), 7.48 (s, 5H, C_6H_5), 7.92 (s, 4H, C_6H_4), 11.3 (s, 1H, OH); Mass m/e: 444 (M^+)

4-Hydroxy-2H-N-(3-phenyl-2-thio-1-hydantoinyl)-1,2-benzothiazine-3-carboxamide 1,1-dioxide, 3d

Yield: 79.7%; mp: 271-272℃; IR (KBr) cm^{-1}: 3316 (NH), 2970 (CH), 1740 (C=O), 1610 (C=O), 1330 (SO_2), 1170 (SO_2); NMR (DMSO-d_6) δ: 4.65 (s, 2H, CH_2), 7.49 (m, 5H, NC_6H_5), 7.92 (m, 4H, C_6H_4).

4-Hydroxy-2-allyl-N-(3-phenyl-2-thio-1-hydantoinyl)-1,2-benzothiazine-3-carboxamide 1,2-dioxide, 3r

Yield: 80.7%; mp: 225-227℃; IR (KBr) cm^{-1}: 3309 (NH), 2948 (CH), 1757 (C=O), 1634 (C=O), 1340 (SO_2), 1119 (SO_2); NMR (DMSO-d_6+$CDCl_3$) δ: 3.87 (s, 2H, $=CH_2$), 4.35 (s, 2H, CH_2), 5.09 (m, 1H, CH), 5.18 (m, 2H, NCH_2), 7.35 (m, 5H, NC_6H_5), 7.84 (m, 4H, C_6H_4), 10.82 (s, 1H, OH).

RESULT

Twenty one 1,2-benzothiazine 3-carboxamidyl hydantoin derivatives were prepared for developing the new potential antiinflammatory and analgesic drugs.

Table I. Biological activity of 4-hydroxy-2H (or alkyl)-N-(3-aralkyl-2-thio-1-hydantoinyl-1,2-benzothiazine-3-carboxamide 1,1-dioxides (3a-u).

No.	R_1	R_2	Formular	M.P. (℃)	Yield (%)	Recrystn Solvent	Antiinflammatory[a] 3.3 mg/kg p.o	Analgesic[b] 16.5 mg/kg p.o
3a	H	Methyl	$C_{13}H_{12}N_4O_5S_2$	264-268	97.3	Dioxane	IN	IN
3b	H	Allyl	$C_{15}H_{14}N_4O_5S_2$	249-250	12.8	Dioxane	IN	SL
3c	H	Cyclohexyl	$C_{18}H_{20}N_4O_5S_2$	233-236	80.2	Dioxane	IN	SL
3d	H	Phenyl	$C_{18}H_{14}N_4O_5S_2$	271-272	79.7	Dioxane	IN	MO
3e	H	4-Chlorophenyl	$C_{18}H_{14}ClN_4O_5S_2$	280-282	54.3	Dioxane	IN	SL
3f	H	Benzyl	$C_{19}H_{16}N_4O_5S_2$	232-234	18.4	Dioxane	IN	SL
3g	H	Benzoyl	$C_{19}H_{14}N_4O_5S_2$	288-290	15.5	Dioxane	IN	MO
3h	CH_3	Methyl	$C_{14}H_{14}N_4O_5S_2$	261-262	57.1	Dioxane	MK	MK
3i	CH_3	Allyl	$C_{16}H_{16}N_4O_5S_2$	226-228	70.7	Dioxane	MK	MK
3j	CH_3	Cyclohexyl	$C_{19}H_{22}N_4O_5S_2$	262-265	31.1	Dioxane	MK	MK
3k	CH_3	Phenyl	$C_{19}H_{16}N_4O_5S_2$	275-276	75.8	Dioxane	MK	MK
3l	CH_3	4-Chlorophenyl	$C_{19}H_{15}ClN_4O_5S_2$	282-284	70.8	Dioxane	MK	MO
3m	CH_3	Benzyl	$C_{20}H_{18}N_4O_5S_2$	256-258	86.9	Dioxane	MO	MK
3n	CH_3	Benzoyl	$C_{20}H_{16}N_4O_6S_2$	284-287	22.3	Dioxane	MO	IN
3o	$-CH_2CH=CH_2$	Methyl	$C_{15}H_{18}N_4O_5S_2$	164-166	38.5	Dioxane	MO	SL
3p	$-CH_2CH=CH_2$	Allyl	$C_{17}H_{20}N_4O_5S_2$	220-221	64.7	Dioxane	IN	In
3q	$-CH_2CH=CH_2$	Cyclohexyl	$C_{20}H_{26}N_4O_5S_2$	217-220	42.6	Dioxane	IN	SL
3r	$-CH_2CH=CH_2$	Phenyl	$C_{20}H_{20}N_4O_5S_2$	225-227	80.7	Dioxane	IN	MO
3s	$-CH_2CH=CH_2$	4-Chlorophenyl	$C_{20}H_{19}ClN_4O_5$	246-248	70.7	Dioxane	MO	MO
3t	$-CH_2CH=CH_2$	Benzyl	$C_{21}H_{22}N_4O_5S_2$	213-214	12.6	Dioxane	IN	SL
3u	$-CH_2CH=CH_2$	Benzoyl	$C_{21}H_{20}N_4O_6S_2$	250-254	13.8	Dioxane	IN	IN
	Indometacin (8 mg/kg)						MK	MO
	Aspirin (165 mg/kg)						—	MO

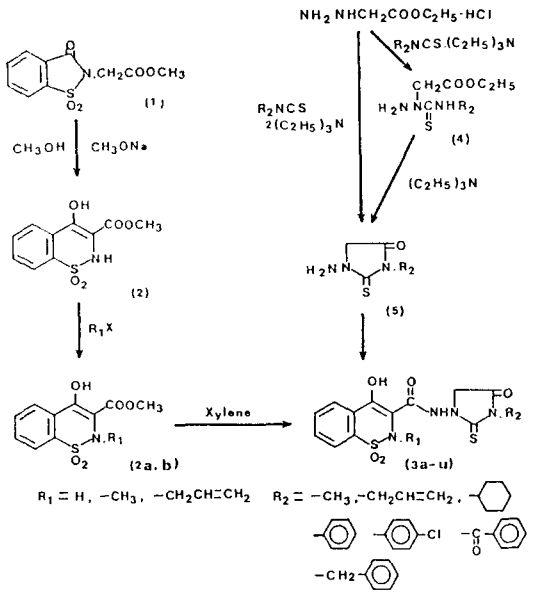
[a](% inhibition of edema) MK=marked activity(>45); MO=moderate activity (35~44); SL=slight activity (20~34); IN=insignificant activity (<20) b (% inhibition of Writhing) MK(>60); MO (50~59); SL (40~49); IN (<39), significant $p<0.01$.

Biological results

All the synthesized 1,2-benzothiazine-3-carboxamides were screened for biological activity by means of the carrageenin-induced rat paw edema (CIRPE) test and acetic acid writhing test. The results are presented in Table I. The most active compounds of the series were derivatives of methyl substitution on the sulfonamide nitrogen of the benzothiazine nucleus. The present investigation indicated that the presence of free sulfonamide hydrogen or allyl substitution showed moderate or slight activities.

Biological test procedures. Carrageenin-induced Rat Paw Edema (CIRPE) test

Antiinflammatory activity was assessed as inhibition of the rat (Sprague-Dawley, male, 145-195g) in response to a subplantar injection of carrageenin. The experimental procedure followed that of Winter, *et al*[9]. The drugs were administered orally as 0.5% CMC saline suspension containing 3.3 mg/kg. And then 0.1 m*l* of 1.0% carrageenin saline solution as an edema inducer was injected subcutaneously 60 minutes after drug administration. Differences in volume displacement produced by the administered and nonadministered paws were recorded, and a statistical analysis of measurements with controls and treated groups was obtained. Superior antiinflammatory activity was observed in the 2-methyl substituents of carboxamides of 4-hydroxy-2H-1,2-benzothiazine 1,1-dioxide compounds in comparison with any other 2-substituents, ie., allyl. The 2-H analogs were also somewhat less active than the corresponding 2-methyl compounds.



Scheme 1. Synthetic routes of 1,2-benzothiazine 3-carboxamidylhydantion derivatives.

Acetic acid writhing test[10]

Male mice of weighing 18-22g, were used. The test compound or vehicle (0.5% CMC) was administered (16.5 mg/kg) orally, and 30 min later 0.7% acetic acid solution was injected intraperitoneally. The number of writhes induced in each mouse was observed for a 10 min period from beginning 10 min after injection of acetic acid. The analgesic activity was expressed in terms of % inhibition(I), I (%)=(1−the mean number of writhes in mices administered a test compound/the mean number of writhes in mice administered the vehicle)×100. Superior analgesic activity was also observed in the 2-methyl substituents of carboxamides of benzothiazines.

DISCUSSION

The thiazine nucleus is a six member ring which has two heteroatoms, a nitrogen atom and a sulfur atom. The first method for the synthesis of this type of compound was reported by von Braun. Abe[6] and co-workers applied the base induced rearrangement of phthalimides (Gabriel-colman reaction) to N-phenacylsaccharin. Later, Zinnes, *et al.*[7], applied this reaction to N-acetonylsaccharin, Lombardino to saccharin-2-acetic acid methyl ester and Rasmussen[8] to the corresponding ethyl ester.

Now, in general, the benzothiazine derivatives are prepared via the ester route which is applied for the synthesis of piroxicam. The 3-oxo-1,2-benzisothiazoline-2-acetic acid methyl ester 1,1-dioxide(**1**) is prepared from sodium saccharin. We applied here a method of Eckenroth and Koerppen, then the reaction time was three hours shorter. The benzisothiazoline ester is isomerized to a 4-hydroxy-2H-1,2-benzothiazine-3-carboxylic acid methyl ester (**2**) by sodium methoxide in methanol. This rearrangement appears to be very sensitive to reaction condition. By treatment of compound 1 with seven equivalents of sodium alkoxide and higher temperature in drastic conditions, 1,2-benzothiazine **2** was rapidly obtained. The 2-position of the benzothiazine can be easily substituted with alkyl group (**2a-b**).

On the other hand, 1-amino-2-thioxo-3-aralkyl-4-imidazolones (**5**) were prepared from ethyl hydrazinoacetate monohydrochloride via N-amino-N-ethoxycarbonylmethyl-N′-aralkylthioureas by reaction with aralkyl isothiocyanate in the presence of two equivalent of triethylamine.

Condensation of various amines (**5a-b**) with esters (**2, 2a-b**) gave amides (**3a-u**). Related amides were prepared by heating the esters with the 1-hydantoinylamines in refluxing xylene with molecular sieves (Scheme I).

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LITERATURE CITED

1. Lombardino, J. G., Wiseman, E. H. and McLamore, W. M.: Synthesis and Antiinflammatory Activity of Some 3-Carboxamides of 2-Alkyl-4-hydroxy-2H-1,2-benzothiazine 1,1-Dioxides. *J. Med. Chem.* **14**, 1171 (1971).
2. Chiaini, J., Wiseman, E. H. and Lombardino, J. G.: Excretion and Metabolism of a Nonsteroidal Antiinflammatory Agent, 4-Hydroxy-2-methyl-2H-1,2-benzothiazine-2-carboxanilide 1,1-Dioxide. *J. Med. Chem.* **14**, 1175 (1971).

3. Zinnes, H., Sircar, J. C., Lindo, N., Schwartz, M. L., Fabian, A. C., Shavel, J., Jr., Kasulanis, C. F., Genzer, J. D., Lutomski, C. and Dipasquale, G.: Isoxicam and Related 4-Hydroxy-N-isoxazolyl-2 H-1,2-benzothiazine-3-carboxamide 1,1-Dioxides. Potent Nonsteroidal Antiinflammatory Agents. *J. Med. Chem.*, **25**, 12 (1982).
4. Lombardino, J. G., Wiseman, E. H. and Chiaini, J.: Potent Antiinflammatory N-Heterocyclic-3-Carboxamides of 4-Hydroxy-2-methyl-2H-1,2-benothiazine 1,1-Dioxide. *J. Med. Chem.*, **16**, 493 (1973).
5. Marfat, A. and Groton, C.: Antiinflammatory 2-Methyl-2H-1,2-Benzo-(or-thieno)-thiazine-3-carboxamide 1,1-Dioxide Derivatives. *U.S. Patent* 4,551,452 (1985).
6. Abe, K., Yamamoto, S. and Matsui, K.: A new method for the preparation of secondary amines III. Synthesis of phenylalkanolamines. *Yakagaju zasshi*, **76**, 1058 (1956): *Chem. Abstr.*, **51**, 3499 (1957).
7. Zinnes, H., Comes, R. A., Zuleski, F. R., Caro, A. N. and Shavel, J., Jr.: 1,2-Benzothiazines. II. The Preparation and Sodium Borohydride Reduction of 3-Acyl-2H-1,2-benzothiazine-4(3H)-one 1,1-Dioxides. *J. Org. Chem.*, **30**, 2241 (1965).
8. Rasmussen, C. R. and Ambler, P.: 3-Carbamoyl and 3-Alkoxycarbonyl benzothiazine-1,1-Dioxides., *U.S. Patent* 3,501,466. (1970).
9. Winter, C. A., Risley, E. A. and Nuss, G. W.: Carrageenin-induced Edema in Hind Paw of the Rat as an Assay for antiinflammatory Drugs. *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
10. Whittle B. A.: The use of changes in capillary permeability in mice to distinguish between narcotic and nonarcotic analgesics. *Brit. J. Pharmacol.*, **22**, 246 (1964).
11. Jacobsen, N. and Toelberg, J.: A Simple Synthesis of 3-Substituted 1-Amino-2-thioxo-4-imidazolidinones (1-Amino-Thiohydantoins). *Synthesis*, **7**, 559 (1986).
12. Shirai, H., Yashiro, T. and Hayazaki, T.: Synthesis of Hydrazinoacetic Acid Ethyl Ester Hydrochloride. *Bull. Nagoya City Univ. Pharm. School* **4**, 45 (1956).