New Synthetic Approaches to 3-Carboxamides of 4-Hydroxy-2*H*-1,2-benzothiazine 1,1-Dioxide

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Two new synthetic approaches to the title compounds are reported. In the first of these, starting with *N*-carbobenzyloxysarcosine, four synthetic steps are employed to finally assemble the C^3-C^4 bond of the 1,2-benzothiazine ring. In the second approach, an enol ether is employed as a protecting group to allow formation of the 3-carboxamide function, which is followed by cleavage of the ether function to yield the desired 4-hydroxy-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

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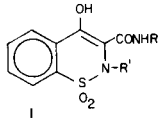
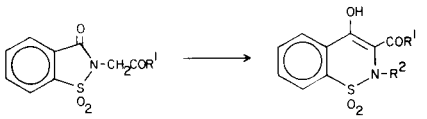
A number of 3-carboxamides of 2-alkyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxides (I) have been reported (1,2) to be potent antiinflammatory agents in various animal models. As part of our continuing interest in this hetero-



I

cyclic ring system, two new synthetic approaches have been developed for the preparation of compounds of type I. Previous syntheses (3-8) of the 4-hydroxy-1,2-benzothiazine system utilized essentially one synthetic route. This route, which is based on the original work of Abe, *et al.*, (3), involves the sodium alkoxide isomerization of saccharin derivatives (II) to 4-hydroxy-1,2-benzothiazines (IIIa).

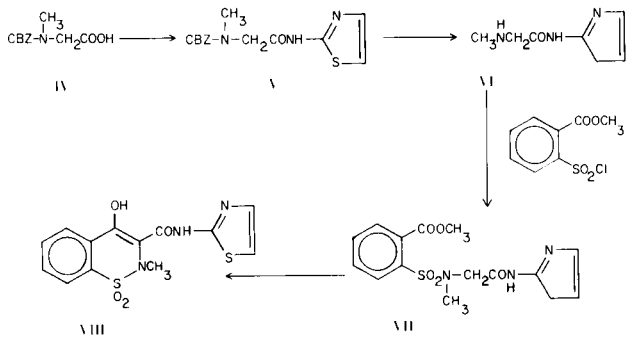


II IIIa R_2 = H; b R_2 = CH_3

The carboxamides I are then made either from aminolysis of the ester IIIb, R^1 = OCH_3 (1) or by treatment of 2-methyl-2*H*-1,2-benzothiazine-4(3*H*)one 1,1-dioxide with isocyanates (1,9). The present report describes two alternative synthetic routes to carboxamides of type I.

Procedure I

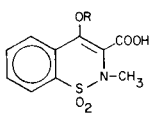
The amide VI was prepared in two steps from commercially available *N*-carbobenzyloxysarcosine (IV). Combination of VI with 2-chlorosulfonylbenzoic ester gave the sulfonamide-ester VII. The last step in this procedure, involving formation of the C^3-C^4 bond, is a base-catalyzed cyclization to the desired 4-hydroxy-2*H*-1,2-benzothiazine VIII.



IV V VI VIII VII

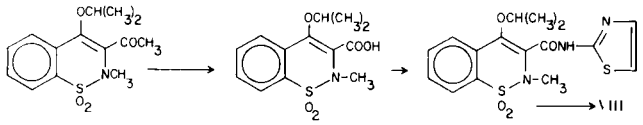
Procedure II

Although the carboxylic acid IXa has not been described, probably due to the ease of decarboxylation of this β-keto acid (10), 3-acetyl-4-isopropoxy-2-methyl-2*H*-1,2-benzothiazine 1,1-dioxide (X) can be oxidized to 4-iso-



IXa R = H; b R = $CH(CH_3)_2$

propoxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (IXb), which is stable.



X IXb XI

The carboxylic acid IXb is then readily converted to an amide, for example the 2-thiazolyl amide XI. Cleavage of the ether moiety in XI with hydrobromic acid yields the desired 4-hydroxy-2-methyl-*N*-(2-thiazolyl)-2*H*-1,2-benzothiazine 1,1-dioxide (VIII).

The two new routes to the title compounds described here offer greater flexibility in the type of amines that can be incorporated into amides of type I in addition to allowing the preparation of examples of I with a greater variety of substituents in the benzo ring portion of the molecule.

EXPERIMENTAL

All melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were determined in potassium bromide pellets on a Perkin-Elmer model 21. Analyses were carried out by the Physical Measurements Laboratory of Pfizer, Inc. Mass spectra were determined on an Hitachi Perkin-Elmer RMU-6E Mass Spectrometer.

N'-Benzyloxycarbonyl-*N'*-methyl-*N*-(2-thiazolyl)glycinamide (V).

To a solution of 9.44 g. (42.3 mmoles) of *N*-carbobenzyloxysarcosine (IV) (Cyclo Chemical Co.) in 75 ml. of dry tetrahydrofuran was added 4.8 g. (48.0 mmoles) of 2-aminothiazole dissolved in 25 ml. of dry tetrahydrofuran. To the resulting solution, 13.0 g. (53.0 mmoles) of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) dissolved in 75 ml. of dry tetrahydrofuran was added dropwise. The reaction was allowed to stand for one hour at room temperature and then refluxed for two hours. Upon standing for two days at room temperature, white solids precipitated from the reaction, 5.4 g. (42%), m.p. 203-205°; ir: 5.89 and 6.27 (C=O), 3.45 μ (NH).

Anal. Calcd. for $C_{14}H_{15}O_3N_3S$: C, 55.06; H, 4.95; N, 13.76. Found: C, 55.02; H, 4.94; N, 13.71.

N'-Methyl-*N*-(2-thiazolyl)glycinamide dihydrobromide (VI).

To 50 ml. of 33% hydrogen bromide in acetic acid was slowly added 5.0 g. (16.4 mmoles) of *N'*-benzyloxycarbonyl-*N'*-methyl-*N*-(2-thiazolyl)glycinamide (V). After 16 hours at room temperature, the suspension was diluted with 300 ml. of ether. The resultant white solids were filtered, washed well with ether and dried, 5.4 g. (99%) m.p. 242-244° dec.; ir: 2.92 (NH); 5.82 (C=O).

Recrystallization from ethanol produced the ***mono*-hydrobromide** for analysis.

Anal. Calcd. for $C_6H_9ON_3S$·HBr: C, 28.58; H, 4.00; N, 16.66. Found: C, 28.54; H, 3.84; N, 16.23.

N'-Methyl-*N*-(2-thiazolyl)-*N'*-(2'-methoxycarbonylbenzenesulfonyl)glycinamide (VII).

A solution of 111 mg. (0.333 mmole) of *N'*-methyl-*N*-(2-thiazolyl)glycinamide dihydrobromide (VI) in 2 ml. of water and 0.67 ml. of 1*N* sodium hydroxide (0.67 mmole) was evaporated to dryness under reduced pressure. The residue was treated twice with 10 ml. portions of dry benzene and evaporated to dryness each time. The resulting white solids were slurried in 2 ml. of dry benzene, filtered and the filtrate combined with a solution of 78 mg. (0.33 mmole) of 2-chlorofulfonylbenzoic acid, methyl ester (12) dissolved in 2 ml. of dry benzene. The reaction was stirred at room temperature for four days and then refluxed for 24 hours. Upon cooling, white solids were obtained which were filtered and washed with benzene. Recrystallization from methanol afforded 15 mg. (12%) of white solid, m.p. dec., 216-218°.

Anal. Calcd. for $C_{14}H_{14}O_4N_3S_2$: C, 45.52; H, 4.09; N, 11.37. Found: C, 45.22; H, 4.12; N, 11.71.

4-Hydroxy-2-methyl-*N*-(2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (VII).

To 50 mg. (0.135 mmole) of *N'*-methyl-*N*-(2-thiazolyl)-*N'*-(2'-methoxycarbonylbenzenesulfonyl)glycinamide (VII), in 5 ml. of dry tetrahydrofuran was added 6.5 mg. of sodium hydride (0.135 mmole) (50% dispersion in mineral oil, washed with hexane). The resulting suspension was refluxed for one hour. An additional 6.5 mg. of sodium hydride was added and reflux continued for 9 days. The reaction was concentrated to dryness under reduced pressure and the resulting tan solid taken up in 10 ml. chloroform and washed with 10 ml. water. The aqueous layer was separated and acidified with 3*N* hydrochloric acid. The acidic layer was then extracted with chloroform, the extracts dried (sodium sulfate) and concentrated to yield a semi-solid residue. This residue was crystallized from 1 ml. of chloroform with the addition of 5 ml. of hexane to give 1.0 mg. (2%) of solid, m.p. 212-217° dec. Thin layer chromatographic comparison (Brinkman 0.25 mm. pre-coated tlc plates, silica gel. F-254) and a mass spectrum ($M^+ = 337$; superimposable with a mass spectrum of authentic VIII) of this product showed it to be identical to a sample of authentic (2) VIII.

4-Isopropoxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic Acid 1,1-Dioxide (IXb).

A dark red solution of 300 mg. (1.0 mmole) of 3-acetyl-4-isopropoxy-2-methyl-2*H*-1,2-benzothiazine 1,1-dioxide (X) (4), 254 mg. (1.0 mmole) of iodine and 3 ml. of dry pyridine was heated on a steam bath for 7.5 hours. The reaction was then allowed to stand at room temperature for seven days. Concentration of the reaction produced a brown viscous oil, presumably the pyridinium salt, which was used in the next step without further purification. A solution of (1.0 mmole) of the crude pyridinum salt from the above reaction, 10 ml. of 10*M* potassium hydroxide and 1 ml. of water was heated at 150° for 1.5 hours. The reaction was then cooled, diluted with water and acidified with 3*N* hydrochloric acid. The acidic mixture was extracted three times with ether and the combined ether extracts washed with 250 ml. of saturated sodium bicarbonate. The basic aqueous layer was treated with charcoal, filtered and acidified with 3*N* hydrochloric acid. The aqueous acidic layer was extracted three times with ether, dried (sodium sulfate) and concentrated to an oil which slowly crystallized: 110 mg. (37% overall yield for the two steps); m.p. 152-154°; ir: 2.8 (OH) 5.95 (C=O).

Anal. Calcd. for $C_{13}H_{15}O_5NS$: C, 52.52; H, 5.09; N, 4.71. Found: C, 52.47; H, 5.00; N, 4.62.

4-Isopropoxy-2-methyl-*N*-(2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (XI).

To a solution of 40 mg. (0.135 mmole) of 4-isopropoxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylic acid 1,1-dioxide (IXb) in 1.5 ml. of dry tetrahydrofuran was added 14.2 mg. (0.142 mmole) of 2-aminothiazole in 0.5 ml. of dry tetrahydrofuran. After addition of 37 mg. (0.15 mmole) of *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) in 2 ml. of dry tetrahydrofuran, the reaction was stirred for 112 hours at room temperature

with additional 37 mg. portions of EEDQ added at the 16th and 40th hours. Concentration of the reaction to dryness on a rotary evaporator gave a semi-solid which was slurried in ether and filtered. The ether filtrate was concentrated to dryness, taken up in 20 ml. of methylene chloride and washed twice with 25 ml. of 0.5*N* hydrochloric acid and once with water. The dried methylene chloride layer was concentrated to a dark tan gum; mass spectrum $M.^+ = 379$ (calcd. 379). This crude material was carried on to the next step without further purification.

4-Hydroxy-2-methyl-*N*-(2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-Dioxide (VIII).

A solution of 20 mg. (0.053 mmole) of 4-isopropoxy-2-methyl-*N*-(2-thiazolyl)-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide (XI) and 1.0 ml. of 32% hydrobromic acid in acetic acid was stirred at room temperature for 0.5 hour. Upon heating the solution to 50°, a precipitate formed within 15 minutes. After heating at 90° for 10 minutes the suspension was cooled, the solids filtered, washed well with water and dried, yield 4.0 mg. (22%), m.p. 243° dec.; mass spectrum: $M.^+ = 337$ (superimposable with a mass spectrum of authentic (2) VIII). Mixture melting point with authentic product (m.p. 248° dec.) gave m.p. 242° dec. Thin layer chromatographic (9:1 acetone-hexane eluent using Brinkman 0.25 mm pre-coated tlc plates, silica gel, F-254) comparison of the product with authentic (2) material confirmed their identity.

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(10) Unpublished results from this laboratory indicate that mild hydrolysis of the methyl ester (m.p. 162-165°) (1) derived from IXa produces a new compound decomposing at 144-156° with rapid carbon dioxide evolution. This compound, presumably IXa, was not sufficiently stable to be correctly analyzed. Following decarboxylation, a compound was isolated and shown to be identical to 2-methyl-2*H*-1,2-benzothiazine-4(3*H*)one 1,1-dioxide (11).

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