

Synthesis of 3-Aminohydantoinyl-1,2-benzothiazine Derivatives

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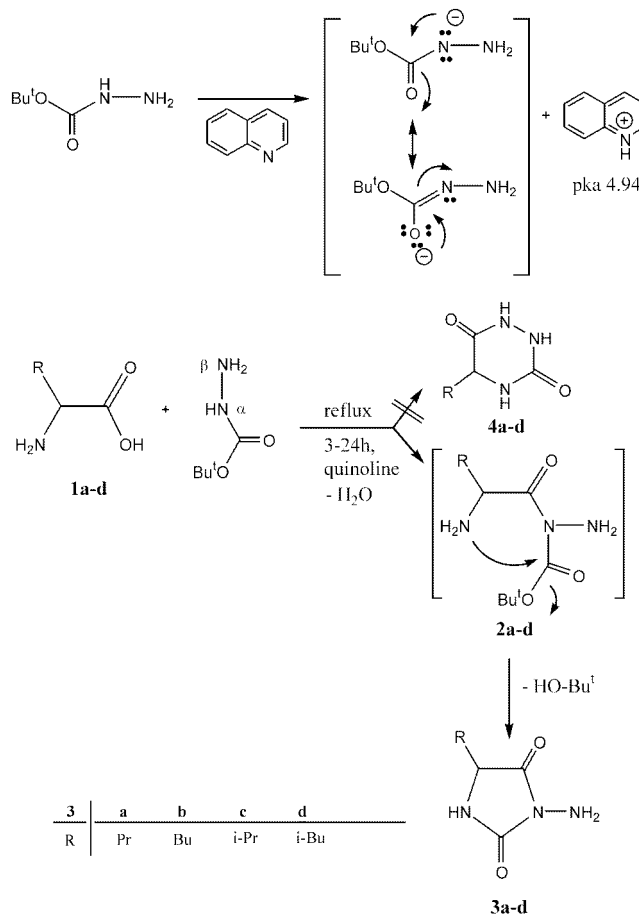
Since 1,2-benzothiazine was synthesized for the first time by Braun,¹ several synthetic methods of 4-hydroxy-1,2-benzothiazines were developed by Abe *et al.*² and these compounds have been investigated continuously because of biological and pharmacological properties. Recently, several 1,2-benzothiazines such as droxicam,³ ampiroxican,⁴ meloxicam,⁵ lornoxicam⁶ have been developed as nonsteroidal anti-inflammatory drugs (NSAIDs), years after piroxicam was introduced on the market in 1971.⁷

Previously, we have reported the syntheses of some new 1,2-benzothiazine derivatives^{8,9} and 1-amino-2-thioxohydantoin.¹⁰ By the application of these methods, 1,2-benzothiazine derivatives with 3-aminohydantoin moiety were prepared. Here, we report the synthesis of several new 3-aminohydantoinyl-1,2-benzothiazine derivatives and propose another mechanism of the cyclization to the hydantoin.

3-Aminohydantoin **3a-d** were prepared through cyclization of the condensation products **2a-d** that were formed by heating amino acids and *tert*-butyl carbazate in quinoline according to the method of Lalezari.¹¹ Even though L-amino acids were applied, the products were racemized. We used the quinoline that was freshly distilled under vacuum after standing with potassium hydroxide for a few days because the success of this reaction depends on the water content of quinoline. The yields of compounds (**3a-d**) were about 86-96% and those were identified using NMR. Because *tert*-butyl carbazate was often sublimated as white solid in the condenser, it was important to react the amino acids with excess (twofold mol %) *tert*-butyl carbazate. The generated byproduct, *tert*-butyl alcohol was removed during refluxing over the Dean-Stark apparatus.

Compounds **7a-c** were synthesized according to the method as described in the previous report.⁸ 6-Halo (Cl, Br) substituted saccharins **5b-c** were synthesized through the process of chlorosulfonation, ammonolysis and oxidation of *p*-halotoluene. 1,2-Benzothiazine derivatives **7a-c** were synthesized through Gabriel-Colman rearrangement after condensation of sodium halo (or H)saccharin with methyl chloroacetate. 7-Halo (or H)-1,2-benzothiazine-3-carboxamide derivatives **8a-j** were synthesized through the condensation of 7-halo(or H)-4-hydroxy-2H-1,2-benzothiazine-3-carboxylic acid methyl ester 1,2-dioxides (**7a-c**) with 3-amino-5-alkylimidazolidine-2,4-diones (**3a-d**) in xylene as shown in Scheme 2.

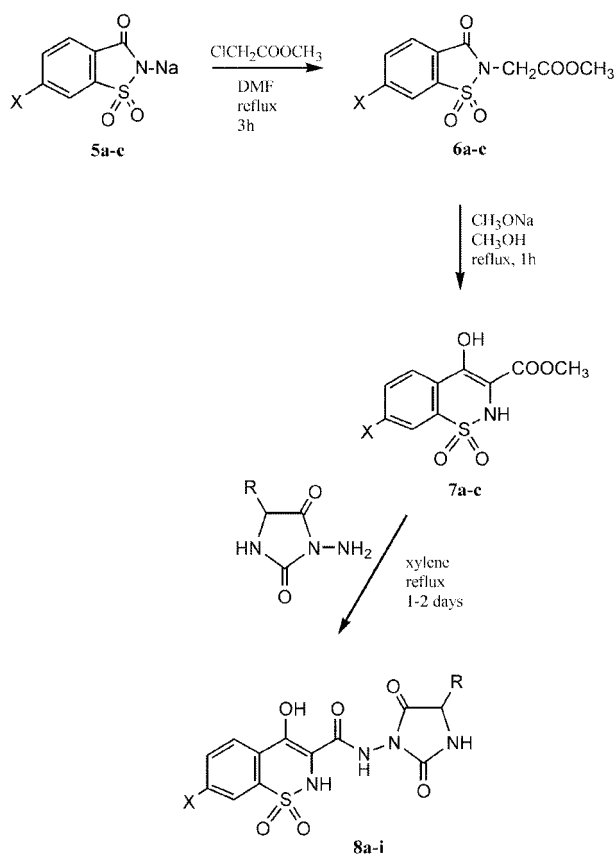
The reaction mechanism of the formation of the 3-amino-



Scheme 1

hydantoin (**3a-d**) involves the amidation and cyclization between α -amino acid and *tert*-butyl carbazate. One molecule of *tert*-butanol is generated from intermediate **2a-d** by the intramolecular nucleophilic attack of amino group to the electron deficient carbonyl carbon of ester. In general, compounds **3a-d** can be easily formed because *tert*-butoxyl group is very good leaving group. The cyclization products of amino acids and *tert*-butyl carbazate were found to be 3-aminohydantoin (**3a-d**) rather than hexahydro-1,2,4-triazine-3,6-diones (**4a-d**).

Even though Lalezari¹¹ proposed a possible reaction mechanism of the formation of the 3-aminohydantoin, we propose another possible mechanism outlined in Scheme 1. According to our opinion, the driving force of this reaction is the nucleophilic attack of α -nitrogen of *tert*-butyl carbazate



8	a	b	c	d	e
X	H	Cl	Cl	Cl	Cl
R	i-Pr	Pr	Bu	i-Pr	i-Bu

8	f	g	h	i
X	Br	Br	Br	Br
R	Pr	Bu	i-Pr	i-Bu

Scheme 2

to the carbon of carboxyl group of amino acid.

The proton of α -nitrogen of *tert*-butyl carbazate is more acidic than the proton of β -nitrogen because of vicinal carbonyl group. The pKa of quinoline as solvent is 4.94 similar to 5.23 of pyridine. The basic quinoline is easier to accept a proton of α -nitrogen than a proton of β -nitrogen. As a result, the α -nitrogen of *tert*-butyl carbazate attacks carboxyl carbon of the amino acid. After then the primary amino group of unstable intermediate 2a-d attacks intramolecularly to the carbonyl carbon of ester and 3-aminohydantoin 3a-d are formed. This cyclization method from α -amino acids could be applicable to the preparation of various hydantoin.

We previously reported that 1-aminohydantoin¹⁰ and 3,5-substituted-1-aminohydantoin¹² were prepared by the condensation of aralkylthiocyanate with ethyl hydrazinoacetate hydrochloride (or ethyl 2-hydrazinopropionate monohydrochloride) in the presence of triethylamine. The intermediates, N-amino-N-ethoxycarbonylmethyl-N'-aralkylthioureas, which were formed during the reaction and could be

transformed into the appropriate 1-aminohydantoin, were isolated and characterized. This intermediates were formed because the proton of α -nitrogen (secondary amino group) of N-amino-N-ethoxycarbonylmethyl-N'-aralkylthioureas is more acidic than the proton of β -nitrogen (primary amino group). In this reaction, triethylamine was applied as a base and 1-aminohydantoin (5-membered ring) could be exclusively obtained instead of hexahydro-1,2,4-triazine-3,6-diones (6-membered ring). In principle, this reaction is same as the 3-aminohydantoin formation from α -amino acids (1a-d) and *tert*-butyl carbazate.

But Lalezari reported that primary amino group (β -nitrogen) initially attacks to the electron deficient carboxyl carbon of amino acid¹¹ and the intermediate is cyclized to an unstable diaziridinone. And then the primary amino group of intermediate attacks the carbonyl carbon of the diaziridinone.

Finally, novel 7-halo-4-hydroxy-2H-N-(5-alkyl-3-aminohydantoinyl)-1,2-benzothiazine-3-carboxamide 1,1-dioxides 8a-i were synthesized through the condensation of related 1,2-benzothiazine and 3-aminohydantoin. Compounds 8a-i were evaluated for analgesic and anti-inflammatory activities and exhibit a good activities.

Experimental Section

Chemicals were supplied by Aldrich, Sigma, Merck, and Tokyo Kasei. Melting points were determined in open capillary tubes on a Büchi 535 melting point apparatus and uncorrected. The NMR spectra were recorded using Gemini Varian 300 MHz NMR spectrometer. Chemical shift values were reported in parts per million on the scale in deuteriochloroform or dimethyl- d_6 sulfoxide with tetramethylsilane as the internal standard. The NMR spin multiplicities were indicated by the symbols: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). IR spectra were recorded on a Perkin-Elmer 16F PC FT-IR spectrometer using NaCl discs.

General procedure for the synthesis of 5-alkyl-3-aminohydantoin derivatives (3a-d). L-Amino acid (0.036 mole) and *tert*-butyl carbazate (0.072 mole) were refluxed for about 5-10 hrs in distilled quinoline (80 mL) using Dean-Stark apparatus until the disappearance of the starting material. The reaction mixture was cooled and ether (90 mL) was poured into the mixture. The precipitated solid by adding slowly with *n*-hexane (270 mL) was filtered and recrystallized from 2-propanol-water.

Yield 86-96%

General procedure for the synthesis of 7-substituted (or nonsubstituted) 4-hydroxy-2H-1,2-benzothiazine-3-carboxylic acid methyl ester 1,1-dioxide derivatives (7a-c). A solution of sodium methoxide was prepared from sodium (1.065 mol) in absolute methanol. To the cooled solution in an ice-bath 7a-c (0.15 mol) was added immediately as powder. Color changes from yellow to orange. After a few minutes, the mixture was refluxed for 1h. The orange slurry was poured into ice-cold concentrated hydrochloric acid (100 mL). The mixture was cooled in an ice bath. The

precipitate was filtered off, washed with water and the residue was recrystallized from diluted methanol.

Yield 55-85%

General procedure for the synthesis of 3-aminohydantoinyl-1,2-benzothiazine derivatives (8a-i). 4-Hydroxy-2H-1,2-benzothiazine-3-carboxylic acid methyl ester 1,2-dioxides (0.004 mole) and 5-alkyl-3-aminohydantoin (0.0056 mole) were refluxed for about 24 hrs in xylene (15 mL) in a Dean-stark apparatus until the disappearance of the starting material. The reaction mixture was allowed to cool to room temperature, evaporated to decrease volume of xylene to 1/3. The cooled reaction mixture was filtered to yield a pale yellow solid after washing with ethyl acetate. The crude solid was recrystallized from methanol.

4-Hydroxy-2H-N-(5-isopropyl-3-aminohydantoinyl)-1,2-benzothiazine-3-carboxamide 1,1-dioxide 8a. Yield 1.11 g (73%), mp 287-289 °C (dec). Recrystal solvent: methanol. IR (NaCl, cm^{-1}) 3370 (NH), 3130 (NH), 3021 (aromatic), 1741 (CO), 1377 (SO_2); $^1\text{H NMR}$ (DMSO-d_6) δ 11.03 (s, 1H, NH), 9.83 (s, 1H, NH), 8.58 (s, 1H, OH), 7.88-7.81 (m, 4H, C_6H_4), 4.21 (d, $J = 5.4$ Hz, 1H, CH), 2.12-2.09 (m, 1H, CH), 1.02 (d, $J = 6.9$ Hz, 3H, CH_3), 0.79 (d, $J = 6.9$ Hz, 3H, CH_3).

7-Chloro-4-hydroxy-2H-N-(5-propyl-3-aminohydantoinyl)-1,2-benzothiazine-3-carboxamide 1,1-dioxide 8b. Yield 51%, mp 286-288 °C (dec), Recrystal solvent: methanol. IR (NaCl, cm^{-1}) 3240 (NH), 3130 (NH), 3010 (aromatic), 1720 (CO), 1380 (SO_2), 730 (C-Cl); $^1\text{H NMR}$ (DMSO-d_6) δ 11.07 (s, 1H, NH), 8.61 (s, 1H, OH), 8.05-7.91 (m, 3H, $\text{C}_6\text{H}_3\text{Cl}$), 4.30 (t, $J = 6.1$ Hz, 1H, CH), 1.75-1.57 (m, 2H, CH_2), 1.42-1.40 (m, 2H, CH_2), 0.92 (t, $J = 7.1$ Hz, 3H, CH_3).

7-Chloro-4-hydroxy-2H-N-(5-butyl-3-aminohydantoinyl)-1,2-benzothiazine-3-carboxamide 1,1-dioxide 8c. Yield 56%, mp 266-268 °C (dec). Recrystal solvent: methanol. IR (NaCl, cm^{-1}) 3190 (NH), 3020 (aromatic), 1720 (CO), 1380 (SO_2), 730 (C-Cl); $^1\text{H NMR}$ (DMSO-d_6) δ 11.05 (s, 1H, NH), 8.60 (s, 1H, OH), 8.07-7.95 (m, 3H, $\text{C}_6\text{H}_3\text{Cl}$), 4.30 (t, $J = 5.8$ Hz, 1H, CH), 1.73-1.72 (m, 2H, CH_2), 1.64-1.59 (m, 2H, CH_2), 1.32-1.27 (m, 2H, CH_2), 0.87 (t, $J = 6.8$ Hz, 3H, CH_3).

7-Chloro-4-hydroxy-2H-N-(5-isopropyl-3-aminohydantoinyl)-1,2-benzothiazine-3-carboxamide 1,1-dioxide 8d. Yield 83%, mp 272-274 °C (dec). Recrystal solvent: methanol. IR (NaCl, cm^{-1}) 3300 (NH), 3040 (aromatic), 1725 (CO), 1380 (SO_2), 725 (C-Cl); $^1\text{H NMR}$ (DMSO-d_6) δ 11.07 (s, 1H, NH), 8.58 (s, 1H, OH), 8.07-7.95 (m, 3H, $\text{C}_6\text{H}_3\text{Cl}$), 4.20 (d, $J = 5.9$ Hz, 1H, CH), 2.12-2.10 (m, 1H, CH), 1.02 (d, $J = 6.9$ Hz, 3H, CH_3), 0.89 (d, $J = 6.9$ Hz, 3H, CH_3).

7-Chloro-4-hydroxy-2H-N-(5-isobutyl-3-aminohydantoinyl)-1,2-benzothiazine-3-carboxamide 1,1-dioxide 8e. Yield 80%, mp 283-285 °C (dec). Recrystal solvent: methanol. IR (NaCl, cm^{-1}) 3295 (NH), 3020 (aromatic), 1720 (CO), 1380 (SO_2), 720 (C-Cl); $^1\text{H NMR}$ (DMSO-d_6) δ 11.04 (s, 1H, NH), 8.68 (s, 1H, OH), 8.09-7.95 (m, 3H, $\text{C}_6\text{H}_3\text{Cl}$), 4.30 (t, $J = 5.4$ Hz, 1H, CH), 1.86-1.82 (m, 2H, CH_2), 1.64-1.47 (m, 2H, CH_2), 0.93 (d, $J = 7.2$ Hz, 6H, $\text{CH}_3 \times 2$).

7-Bromo-4-hydroxy-2H-N-(5-propyl-3-aminohydantoin-

yl)-1,2-benzothiazine-3-carboxamide 1,1-dioxide 8f. Yield 73%, mp 288-291 °C (dec). Recrystal solvent: methanol. IR (NaCl, cm^{-1}) 3240 (NH), 3130 (NH), 3010 (aromatic), 1720 (CO), 1380 (SO_2), 730 (C-Br); $^1\text{H NMR}$ (DMSO-d_6) δ 11.07 (s, 1H, NH), 8.61 (s, 1H, OH), 8.09-7.91 (m, 3H, BrC_6H_3), 4.30 (t, $J = 5.4$ Hz, 1H, CH), 1.75-1.57 (m, 2H, CH_2), 1.42-1.37 (m, 2H, CH_2), 0.92 (t, $J = 7.2$ Hz, 3H, CH_3).

7-Bromo-4-hydroxy-2H-N-(5-butyl-3-aminohydantoinyl)-1,2-benzothiazine-3-carboxamide 1,1-dioxide 8g. Yield 64%, mp 286-287 °C (dec). Recrystal solvent: methanol. IR (NaCl, cm^{-1}) 3190 (NH), 3130 (NH), 3010 (aromatic), 1720 (CO), 1380 (SO_2), 730 (C-Br); $^1\text{H NMR}$ (DMSO-d_6) δ 11.09 (s, 1H, NH), 8.60 (s, 1H, OH), 8.07-7.95 (m, 3H, BrC_6H_3), 4.30 (t, $J = 5.4$ Hz, 1H, CH), 1.79-1.55 (m, 2H, CH_2), 1.32-1.29 (m, 2H, CH_2), 0.87 (t, $J = 7.2$ Hz, 3H, CH_3).

7-Bromo-4-hydroxy-2H-N-(5-isopropyl-3-aminohydantoinyl)-1,2-benzothiazine-3-carboxamide 1,1-dioxide 8h. Yield 86%, mp 283-285 °C (dec), Recrystal solvent: methanol. IR (NaCl, cm^{-1}) 3300 (NH), 3130 (NH), 3010 (aromatic), 1725 (CO), 1380 (SO_2), 725 (C-Br); $^1\text{H NMR}$ (DMSO-d_6) δ 11.07 (s, 1H, NH), 8.58 (s, 1H, OH), 8.10-7.92 (m, 3H, BrC_6H_3), 4.12 (d, $J = 5.4$ Hz, 1H, CH), 2.19-2.06 (m, 1H, CH), 1.02 (d, $J = 7.2$ Hz, 3H, CH_3), 0.89 (d, $J = 7.2$ Hz, 3H, CH_3).

7-Bromo-4-hydroxy-2H-N-(5-isobutyl-3-aminohydantoinyl)-1,2-benzothiazine-3-carboxamide 1,1-dioxide 8i. Yield 56%, mp 297-298 °C (dec), Recrystal solvent: methanol. IR (NaCl, cm^{-1}) 3295 (NH), 3130 (NH), 3010 (aromatic), 1720 (CO), 1475 (SO_2), 720 (C-Br); $^1\text{H NMR}$ (DMSO-d_6) δ 11.08 (s, 1H, NH), 8.68 (s, 1H, OH), 8.09-7.95 (m, 3H, BrC_6H_3), 4.30 (t, $J = 5.4$ Hz, 1H, CH), 1.84-1.82 (m, 1H, CH), 1.60-1.49 (m, 2H, CH_2), 0.92 (d, $J = 7.2$ Hz, 6H, $\text{CH}_3 \times 2$).

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