Synthesis and Herbicidal Activity of Hydantocidin Analogues: Modification of the Carbonyl Groups in Spirohydantoin

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Syntheses of two carbonyl derivatives of hydantocidin 1, a potent, naturally occurring herbicide, and their herbicidal activity are described. Spiromidazolidinone 2, the descarbonyl compound at C9, was prepared by employing reductive demethylsulfurization with tri-n-butyltin hydride as the key step. Another derivative, spiromidazolinone 10, was obtained from α-azidoamide 8 and benzyl isocyanate via the az-a-Wittig reaction. 2 had lost almost all herbicidal activity, whereas 10 retained herbicidal activity against such dicotyledonous weeds as ragweed and cocklebur, but lost activity against monocotyledonous weeds. These results imply the possibility that proper modification of the carbonyl group at C7 of the parent compound would afford hydantocidin analogues possessing crop selectivity.

Our continuous investigation on the structure-herbicidal activity relationship of hydantocidin 1, the first naturally occurring spironucleoside, resulted in the synthesis of several analogues of hydantocidin diastereomers, deoxy derivatives, and carbocyclic nucleosides to elucidate the role of the sugar part of the natural product. All the diastereomers and deoxy derivatives, except the 5-epimer, were found to be inactive, indicating that the integrity of three hydroxy groups in the sugar part are required to retain the activity. In contrast, the carbocyclic analogue showed herbicidal activity when applied to the foliage of weeds at 1000 ppm.

On the other hand, the role of the spirohydantoin ring, which could be responsible for the interaction with a target site in plants, has not been clarified in spite of the synthesis of two analogues; a spirosuccinimide analogue, in which an amide nitrogen atom was replaced with a carbon atom, showed herbicidal activity, and a spirodihydrouracil analogue, in which a methylene group was inserted at the anomeric position, had no biological activity.

In order to evaluate the role of the two carbonyl groups in the hydantoin ring of the parent molecule, we designed spiromidazolidinone 2 and spiromidazolinone 3 (Fig.). Removal of the carbonyl group at C9 would bring about a conformational change at the anomerica position and thus eliminate the interaction ability with a certain receptor in plants. The H-NMR analysis of the natural compound revealed that the hydrogen bond between the carbonyl group at C9 and the hydroxy group at C3 resulted in the stereoconformation at the anomeric position being rigidly fixed in endo form in a solution. Alternatively, we could find out the influence of hydantoin ring modifications by replacing the other carbonyl group at C7 with an imine group. We describe here the synthesis and herbicidal activity of each of these analogues.

Materials and Methods

All melting point (mp) data were determined with Yanaco micro-melting point apparatus and are uncorrected. 1H-NMR spectra (270 MHz) were recorded with a JEOL GX-270 spectrometer, IR spectra with a JASCO A-102 spectrometer, and mass spectra with a JEOIL-JMS-D300 spectrometer. Optical rotation was measured by a JASCO DIP-360 polarimeter, and Merck Kieselgel 60 was used for silica gel column chromatography.

Materials and Methods

(2R,3S,4R,5S)-6-Benzoyloxycarbonyl-2-benzoxymethyl-9-hydroxy-3,4-isopropylidenedioxy-8-(4-methoxybenzyl)-1-oxa-6,8-diazaspiro[4.4]nonane-7-one (5). A solution of diol 4 (1 g, 1.8 mmol) and 2,2-dimethoxypropane (0.56 g, 5.4 mmol) in 1,4-dioxane (28 ml) was stirred at 50°C in the presence of p-toluenesulfonic acid monohydrate (0.10 g) for 50 min. The reaction mixture was diluted with EtOAc, washed with brine, dried, and concentrated. The residue was purified by silica gel chromatography (n-hexane/EtOAc = 5/1) to give an acetonide, (2R,3S,4R,5S)-6-benzyloxycarbonyl-2-benzoxymethyl-3,4-isopropylidenedioxy-8-(4-methoxybenzyl)-1-oxa-6,8-diazaspiro[4.4]nonane-7,9-dione (0.89 g, 83%), as a colorless oil.

\[ \text{[\text{x}]_2^\text{D} = +6.6 \ (c = 2.76, \text{CHCl}_3) \] \] 1NMR (CDCl3): δ: 7.39-7.27 (12H, m), 6.82 (2H, d, J = 8.6 Hz), 5.25 (2H, ABq, J = 12.3 Hz), 5.23 (1H, d, J = 6.7 Hz), 4.72-4.64 (2H, m), 4.61 (2H, ABq, J = 14.5 Hz), 4.53 (2H, ABq, J = 12.4 Hz), 3.77 (3H, s), 3.58 (2H, d, J = 5.6 Hz), 1.57 (3H, s), 1.27 (3H, s), MS m/z: 602 (M+) 587, 558, 467, 439, 361, 233, 162, 121, 92. Analysis: Found: C, 65.62; H, 5.89; N, 6.40. Calcd. for C30H28N4O6: C, 65.77; H, 5.69; N, 4.65%.

Sodium borohydride (15 mg, 0.42 mmol) was added to a cold (0°C) solution of the above spirohydantoin (50 mg, 0.083 mmol) in methanol (2 ml). After being stirred at room temperature for 40 min, the reaction mixture was poured into 0.5N HCl and extracted with EtOAc. The combined organic layers were dried, evaporated, and purified by chromatography on silica gel (n-hexane/EtOAc = 4/1) to afford hemiacetal 5 (46 mg, 91%) as a colorless oil.
\[ \text{H}_2\text{O}_2 + 2\text{e}^- (c=0.34, \text{MeOH}; \text{IR } \text{vs}(\text{CHCl}_3): 3500, 1780, 1720, 1105 \text{ cm}^{-1}; \text{NMR (CDCl}_3): 7.4-7.24 (12H, m), 6.85 (2H, d, J = 8.4 Hz), 5.23 (2H, ABq, J = 12.5 Hz), 5.18 (1H, d, J = 12.1 Hz), 5.00 (1H, d, J = 6.4 Hz), 4.75 (1H, dd, J = 6.4, 4.8 Hz), 4.65 (1H, d, J = 14.9 Hz), 4.50 (2H, ABq, J = 12.5 Hz), 4.22 (1H, d, J = 14.9 Hz), 4.22-4.18 (1H, m), 3.79 (9H, C(s)), 3.32 (1H, C(s)), 3.21 (3H, s), 1.25 (3H, s); MS m/z: 604 (M^+) \), 469, 452, 277, 234, 162, 131. \]

(2R,3S,4R,5S)-6-Benzoylcarbonyl-2-benzylmethyl-3,4-isoproplidenedioxy-8-(4-methoxybenzyl)-5-methylthio-1-oxa-6,8-diazaaspiro[4.4]nonan-7-one (6). A solution of hemiacetal 5 (0.10 g, 0.16 mmol) in dichloromethane (2 ml) was added to a solution of tri-n-butylphosphine (0.33 g, 1.6 mmol) and dimethyl sulfoxide (0.15 g, 1.6 mmol) in dichloromethane (2 ml), and it was stirred at room temperature for 28 h. The reaction mixture was partitioned between EtOAc and brine, and the organic extracts were dried and evaporated. The residue was subjected to silica gel chromatography (n-hexane/EtOAc = 1/1) to give thiocarbonyl 6 (6.45 mg, 43%) and its epimer (7%, 43%) as colorless oils.

(2R,3S,4S,5R)-6-Benzoylcarbonyl-2-benzylmethyl-3,4-isoproplidenedioxy-8-(4-methoxybenzyl)-1-oxa-6,8-diazaaspiro[4.4]nonan-7-one (7). A diastereomeric mixture of thiocarbonyl (60.0 mg, 0.16 mmol) in toluene (3 ml) was added to a mixture of tri-butyltin hydride (0.72 g, 2.4 mmol) and AIBN (50 mg) in toluene (7 ml), and it was heated at 100°C for 1 h. The reaction mixture was quenched with water and extracted with EtOAc. The organic layers were washed with water and brine, prior to drying and solvent evaporation. Silica gel chromatography (n-hexane/EtOAc = 5/1) of the residue afforded spiroximidazole 7 (72.75 mg, 75%) as a colorless oil.

\[ \text{H}_2\text{O}_2 + 17.3 (c=1.12, \text{MeOH}; \text{IR } \text{vs}(\text{CHCl}_3): 1780, 1740 \text{ cm}^{-1}; \text{NMR (CDCl}_3): \delta: 7.4-7.21 (12H, m), 6.86 (2H, d, J = 8.53 Hz), 5.23 (2H, ABq, J = 12.5 Hz), 4.98 (1H, d, J = 6.9 Hz), 4.96 (1H, d, J = 14.9 Hz), 4.70 (1H, s), 4.68 (1H, t, J = 6.8 Hz), 4.53 (2H, ABq, J = 12.1 Hz), 4.41 (1H, dd, J = 6.8, 6.4 Hz), 4.46 (1H, d, J = 14.9 Hz), 3.79 (3H, s), 3.61 (1H, d, J = 10.5 Hz), 4.33 (5H, s), 3.53 (4H, s), 2.00 (3H, s), 1.55 (3H, s); MS m/z: 634 (M^+), 588, 453, 343, 287, 211, 122, 95. HRMS m/z (%): Calcd for C_{38}H_{37}N_{10}O_{12}: 634.2349. Found: 634.2349.

(2R,3S,4R,5S)-6-Benzoylcarbonyl-2-benzylmethyl-3,4-isoproplidenedioxy-8-(4-methoxybenzyl)-1-oxa-6,8-diazaaspiro[4.4]nonan-7-one (7). A solution of spiroximidazole 7 (0.10 g, 0.17 mmol) in acetonitrile (6 ml) was added in one portion to a solution of ceric ammonium nitrate (1.4 g, 2.6 mmol) in water (3 ml). The resulting yellow mixture was stirred at room temperature for 20 min, quenched by adding of brine, and extracted with EtOAc. The organic extracts were washed with saturated aqueous solution, dried, and evaporated. The residue was chromatographed on silica gel (n-hexane/EtOAc = 4/1) to provide (2R,3S,4R,5S)-6-benzoylcarbonyl-2-benzylmethyl-3,4-isoproplidenedioxy-8-(4-methoxybenzyl)-1-oxa-6,8-diazaaspiro[4.4]nonan-7-one (53 mg, 51%) as a colorless oil.

\[ \text{H}_2\text{O}_2 + 13.4 (c=0.35, \text{MeOH}; \text{IR } \text{vs}(\text{CHCl}_3): 2900, 1750 \text{ cm}^{-1}; \text{NMR (CDCl}_3): \delta: 7.4-7.3 (10H, m), 5.22 (2H, ABq, J = 12.5 Hz), 5.09 (1H, s), 5.02 (1H, d, J = 6.4 Hz), 4.73 (1H, dd, J = 6.4, 4.8 Hz), 4.51 (2H, ABq, J = 12.1 Hz), 4.15 (1H, dd, J = 7.2, 4.8 Hz), 3.95 (1H, d, J = 10.9 Hz), 3.56 (1H, dd, J = 10.1, 7.2 Hz), 3.50 (1H, dd, J = 10.1, 7.2 Hz), 1.37 (1H, d, J = 10.9 Hz); MS m/z: 468 (M^+), 424, 333, 227, 175, 107, 91. \]
Synthesis of Two Analogues of Hydantocidin

Scheme 1.

Scheme 2.

Results and Discussion

Synthetic route to spiromiazidolinone 2 is presented in Scheme 1. Reaction of diol 4 with 2,2-dimethoxypropane gave a corresponding isopropylidenecetal, which was reduced with sodium borohydride at room temperature to afford hemiacetal 5 as a single stereoisomer in 76% yield from 4. Attempts at direct reduction of 5 with silylhydride and Lewis acids were unsuccessful due to other reactive functional groups in 5 such as an N,O-ketal, isopropylidene acetal, and carbonyl group. Stepwise reduction of 5 to spiromiazidolinone 7 was accomplished: Conversion of 5 to a thiaoacetol by treatment with tri-n-butylphosphine and dimethyl disulfide smoothly afforded thiaoacetol 6 as a 6:1 mixture of diastereomers after chromatographic purification. Radical demethylysulfurization of 6 with tri-n-butyltin hydride in the presence of azobisisobutyronitrile in toluene at 100 °C gave 7 in 75% yield. Sequential removal of the protecting groups of 7 was achieved as follows: oxidative removal of a p-methoxybenzyl group at N8 with ceric ammonium nitrate in acetonitrile-water, followed by treatment with p-toluene sulfonic acid at room temperature, afforded a corresponding diol compound. This diol compound was subjected to hydrogenolysis by heating at 55 °C in the presence of 5% Pd/C under H2 atmosphere in methanol to furnish decarbonyl analogue 2 in 18% yield from 7.

With spiromiazidolinone analogue 2 in hand, our attention turned to the synthesis of spiromiazidolinone analogue 3. In our planned synthesis, the spiromiazidolizone skeleton would evolve from -azido amide 8, which was prepared from t-fructose, through an iminophosphorane intermediate. Spiromiazidolinone ring construction from 8 was efficiently achieved by treating with benzyl isocyanate and tri-n-butylphosphine in THF at room temperature, affording spiromcompound 9 in 98% yield (Scheme 2). Acid hydrolysis of the isopropylidene group in 9 by heating with Dowex 50W (H+ form) in methanol–water gave a corresponding diol in a low yield (20%) due to the slow decomposition of 9 under these conditions, affording unknown compounds. Hydrogenolysis of the benzyl group in the sugar part of 9 was accomplished with 5% Pd/C under H2 atmosphere at 55 °C to give triol 10; however, further debenzylation at the nitrogen atom in the hydantoin ring did not occur even under forced conditions of heating at 80 °C under 8 kg/cm2 pressure of H2 atmosphere.

N-Benzyl compound 10 was tested for its herbicidal activity as well as spiromiazidolinone 2, the results being summarized in the Table. Compound 2 demonstrated slight weed control at 1000 ppm, while hydantocidin gave complete control under the same conditions, clearly indicating that the carbonyl group at C9 is required for activity. Surprisingly, compound 10, even though it has an attached benzyl group at the nitrogen atom, retained herbicidal activity against such dicotyledonous weeds as ragweed and cocklebur, but lost its activity against...
monocotyledonous weeds. These results support the possibility that modifying the carbonyl group at C7 of hydantocidin would give hydantoin analogues possessing crop selectivity, because hydantocidin possesses non-selective herbicidal activity.13

In summary, we prepared spiro compounds 2 and 10 as analogues of hydantocidin, involving 1) reductive demethylsulfurization with tri-n-butyltin hydride, and 2) efficient spiromiadazolinone annulation with α-azidoamide and benzyl isocyante via the aza-Wittig reaction as key steps. Spiromiadazolinone analogue 10, having a connected benzyl group, maintained herbicidal property against some dicotyledonous weeds, although spiroimidazolidinone 2 was found to be inactive. Further studies on the structure-herbicidal activity relationship of hydantocidin are now in progress.

Table Herbicidal Activity of Compounds 2 and 10 (1000 ppm)

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<th>Compound</th>
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A, barnyardgrass; B, crabgrass; C, fall panicum; D, green foxtail; E, Johnsonsgrass; F, black nightshade; G, cocklebur; H, tall morningglory; I, ragweed; J, velvetleaf.

References


