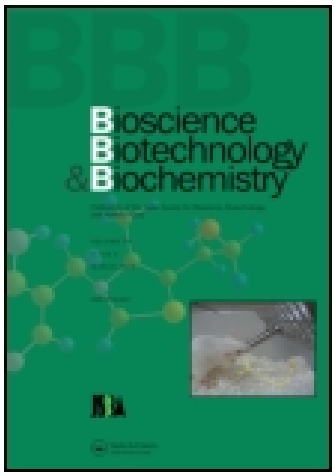

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Synthesis and Herbicidal Activity of Opened Hydantoin-ring Derivatives of Hydantocidin

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Note

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We synthesized three hydantocidin derivatives and evaluated their herbicidal activity in order to elucidate the role of the spirohydantoin system at the anomeric center of hydantocidin. With application to foliage at 1000 ppm, only α-ureidoamide 14 demonstrated activity, the remaining compounds being found to be inactive.

Key words: hydantocidin; ureidoribofuranose; *N*-aminocarbonyl-2-deoxy-β-D-*ribo*-hexulofuranosonamide; 2-ureido-D-*ribo*-hexulofuranosonamide

We have been investigating the structure–activity relationship of hydantocidin (**1**) because of its potent herbicidal activity without any toxicity to mammals. Our previous studies on the sugar part have revealed that all three hydroxy groups were necessary for the activity, while the oxygen atom in the furanose ring was not needed for the activity. On the other hand, to investigate the role of the hydantoin part, we prepared several spiro-heterocyclic analogues, but did not found a hydantocidin derivative whose herbicidal activity was superior to that of **1**.[1] We therefore designed simple derivatives to examine the effect of the spiro-ring system of **1** on herbicidal activity; one derivative was ureide-ribofuranose (**2**), which seemed to be a flexible compound having all functionalities as in **1**, except for a carbonyl group at *C*9. The second one was allophanoyl derivative (**3**), in which the allophanoyl moiety is extended from the α-side of the furanose ring. The third one was α-ureidoamide (**4**), in which both a urea and an amide group exist on the anomeric carbon (Fig.).

The reaction of **5**[2] with TMSNCO afforded the corresponding ureido derivative, which was directly treated with benzyl chloroformate to give **6** in 70% yield (Scheme 1). Heating **6** with Dowex 50W, followed by hydrogenolysis of the benzyloxycarbonyl moiety with 5% Pd/C under H_2 furnished ureido-ribofuranose **7** as a *ca.* 1:2 mixture of anomeric diastereomers by ^{1}H-NMR analysis. Preparation of allophanoyl derivative **3** began from **8**[3] (Scheme 2). Lewis acid-induced *C*-glycosidation[4] of **8** with TMSCN in the presence of TMSOTf afforded **9** and **10** in 21% and 26% yields, respectively. The assignments of **9** and **10** are based on the observation of *C*1–*C*2 proton couplings; $J = 5.6$ Hz for **9** and $J = 2.0$ Hz for **10**, indicating that **9** possesses a *cis* geometry between these protons.[5] All attempts to improve the yield and stereoselectivity by using other Lewis acids and/or other solvents have been fruitless. Hydrolysis of the cyanide group in **9** with hydrogen peroxide gave the amide, whose *C*6 hydroxy group was reprotected as a benzyl ether. Treatment of this benzyl ether with oxalyl chloride and by bubbling gaseous ammonia provided **11** in 38% yield from **9**. Removal of the protecting groups was accomplished by the same procedure at that used in the preparation of **2** to produce **3** in 44% yield from **11**. A diastereomeric mixture of α-aminoamide **12**[6] was converted to a ureido derivative by treating with PMBNCO, affording **13** in 69% yield (Scheme 3). Oxidative cleavage of the PMB group in **13** with CAN, which was followed by treating with Dowex 50W and then by heating in MeOH with 5% Pd/C under H_2 to give α-ureido-amido **14** in 16% yield from **13**, isolated as a *ca.* 3:1 ratio of a diastereomeric mixture by an HPLC analysis.

The results of the herbicidal tests on **3**, **7**, and **14** are summarized in Table. Ureido-amide derivative **14** demonstrated activity at 1000 ppm equal to that of **1**, although **3**, which has the same functional groups as **1** except for the spiro-ring system at the anomeric position, had only slight activity. The results of the bioassay indicate the possibility that both functional groups at the anomeric position of D-ribofuranose, which connects the amide

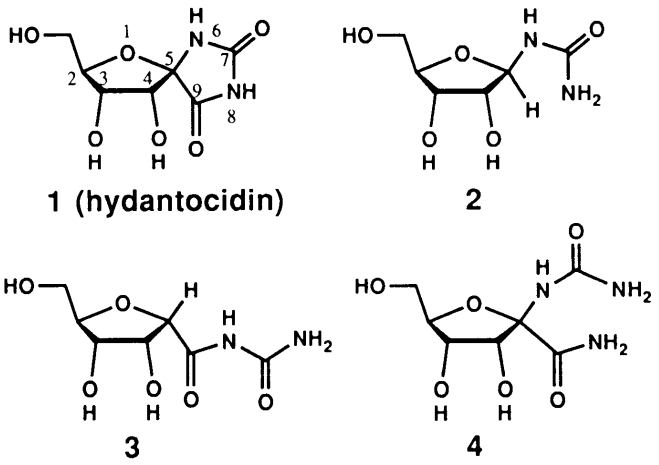
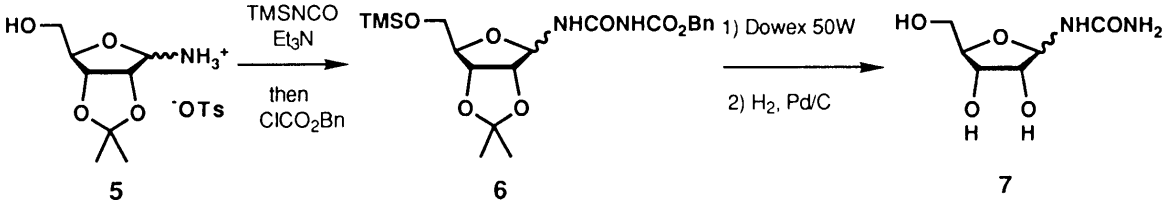
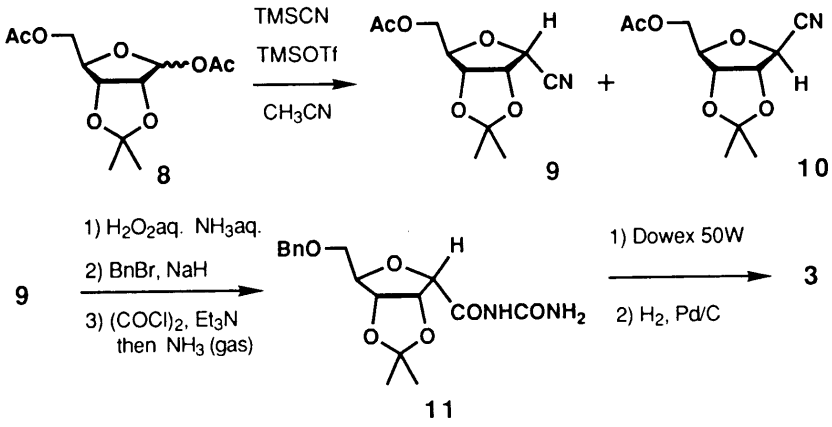


Fig.

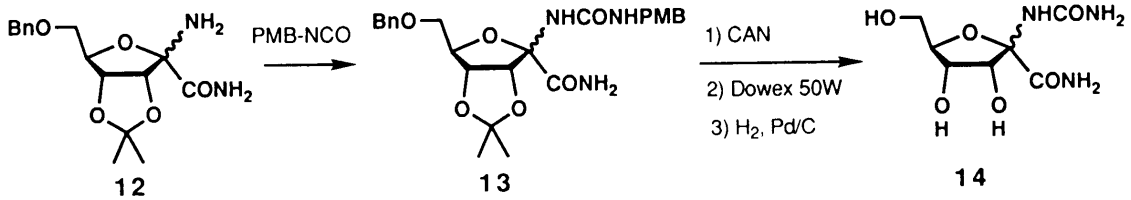


Scheme 1

Abbreviations: Bn, benzyl; CAN, ceric ammonium nitrate; PMB, *p*-methoxybenzyl; PMBNCO, *p*-methoxybenzyl isocyanate; TMSNCO, trimethylsilyl isocyanate; TMSOTf, trimethylsilyl triflate.



Scheme 2



Scheme 3

Table Herbicidal Activity of **3**, **7**, and **14** at 1000 ppm by Foliar Treatment[a]

Compound	A	B	C	D	E	F	G	H	I	J
3	0	0	0	0	1	2	1	0	0	0
7	0	0	0	0	0	0	0	0	0	0
14	5	5	-	5	5	5	5	4	5	4
1	5	5	5	5	5	5	5	5	5	5

[a] See ref. 1; ten days after the 3-leaf stage of the weeds had been treated, the herbicidal activity against each weed was visually evaluated by the following ratings: 5, 95–100% of control (plant growth inhibition); 4, 80–94% of control; 3, 50–79% of control; 2, 30–49% of control; 1, 10–29% of control; 0, 0–9% of control.

Plants: A, barnyardgrass; B, crabgrass; C, fall panicum; D, green foxtail; E, Johnsongrass; F, black nightshade; G, cocklebur; H, tall morning glory; I, ragweed; J, velvetleaf; -, not examined.

group and the nitrogen atom of the urea group, are important for activity. The finding that **14** has herbicidal activity comparable to that of **1** opens the way for a new conversion of **1** in the search for potent herbicides.

Experimental

1-Deoxy-1-ureido-D-ribofuranose (**7**). TMSNCO (0.45 ml) was added to a solution of **5** (1.08 g, 3.0 mmol) and Et_3N (2.1 ml) in CH_2Cl_2 (25 ml) at r.t. After 3 h, $ClCO_2Bn$ (0.47 ml) was added, this being followed by stirring for 90 min. The mixture was partitioned between aq. NH_4Cl and Et_2O, and the organic extracts were evaporated and purified with silica gel chromatography (hexane/EtOAc = 3 : 1) to give **6** (0.92 g, 70%) as a colorless syrup. IR ν_{max} ($CHCl_3$): 3430, 3010, 1740, 1705, 1530 cm^{-1}; NMR ($CDCl_3$) δ: 8.79 (0.7H, d, J = 9.0 Hz), 8.49 (0.3H, d, J = 9.0 Hz), 7.39–7.34 (3H, m), 7.21–7.20 (1H, m), 5.85 (0.7H, dd, J = 9.0, 4.5 Hz), 5.79 (0.3H, dd, J = 9.0, 1.9 Hz), 5.18 (1.4H, ABq, J = 12.2 Hz), 5.14 (0.6H, s), 4.80 (0.7H, d, J = 6.0 Hz), 4.69 (0.7H, dd, J = 6.0, 4.5 Hz), 4.67 (0.3H, d, J = 6.0 Hz), 4.59 (0.3H, dd, J = 6.0, 1.9 Hz), 4.30 (0.3H, m), 4.16–4.14 (0.7H, m), 3.77–3.62 (2H, m), 1.62 (2.1H, s), 1.53 (0.9H, s), 1.41 (2.1H, s), 1.34 (0.9H, s), 0.15 (6.3H, s), 0.13 (2.7H, s). *Anal.* Found: C, 54.55; H, 6.88; N, 6.07%. Calcd. for $C_{20}H_{30}N_2O_7Si$: C, 54.78; H, 6.90; N, 6.39%. A mixture of **6** (0.66 g, 1.5 mmol) and Dowex 50W (1.5 g) in MeOH (10 ml)–H_2O (6 ml) was heated at 60 C for 6 h, and then filtered. The filtrate was concentrated to afford a colorless syrup (0.45 g, 91%). NMR (CD_3OD) δ: 7.41–7.31 (5H, m), 5.66 (0.75H, d, J = 4.8 Hz), 5.43 (0.25H, d, J = 4.4 Hz), 5.18 (2H, s), 4.13–4.07 (1H, m), 3.95–3.81 (2H, m), 3.76–3.60 (2H, m), 3.58–3.51 (1H, m). A mixture of the triol (0.24 g, 0.74 mmol) and 5% Pd/C (0.2 g) in MeOH (100 ml) was heated at 40 C under H_2 (3 atm) for 3 h, filtered, and then concentrated. The residue was treated in a Dianion CHP-20 column (H_2O) to give **7** (0.10 g, 86%) as a colorless syrup. IR ν_{max} (KBr): 3400, 2930, 1670, 1610, 1530, 1400, 1330 cm^{-1}; NMR (CD_3OD) δ: 5.52 (0.7H, d, J = 4.1 Hz), 5.26 (0.3H, d, J = 5.6 Hz), 4.11–3.98 (1H, m), 3.88–3.50 (4H, m). *Anal.* Found: C, 37.22; H, 6.21; N, 14.30%. Calcd. for $C_6H_{12}N_2O_5$: C, 37.49; H, 6.30; N, 14.58%.

N-Aminocarbonyl-2-deoxy-β-D-ribo-hexulofuranosonamide (**3**). TMSOTf (0.18 ml) was added to a solution of **8** (0.52 g, 1.9 mmol) and TMSCN (0.80 ml) in CH_3CN (6 ml) at −20 C, and the mixture was stirred for 2 h. The mixture was poured into aq. NH_4Cl and extracted with EtOAc. The organic layers were evaporated and purified by chromatography on silica gel (hexane/EtOAc = 3 : 1) to afford **9** (98 mg, 21%) as a colorless solid and its epimer **10** (0.12 g, 26%) as a colorless oil. For **9**: mp 74–75 C; $[\alpha]_D^{25}$ −44.3 (c = 0.79, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3550, 2950, 2250, 1740 cm^{-1}; NMR ($CDCl_3$) δ: 4.92 (1H, t, J = 5.6 Hz), 4.87 (1H, d, J = 5.6 Hz), 4.72 (1H, dd, J = 5.6, 2.0 Hz), 4.45 (1H, dd, J = 4.0, 2.0 Hz), 4.22 (1H, d, J = 12.3, 4.0 Hz), 4.15 (1H, dd, J = 12.3, 4.0 Hz), 2.10 (3H, s), 1.64 (3H, s), 1.26 (3H, s). *Anal.* Found: C, 54.60; H, 6.14; N, 5.61%. Calcd. for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81%. For **10**: $[\alpha]_D^{25}$ −26.8 (c = 1.43, $CHCl_3$); IR ν_{max} ($CHCl_3$): 3550, 3000, 2250 cm^{-1}; NMR ($CDCl_3$) δ: 5.08 (1H, dd, J = 6.0, 2.0 Hz), 4.82 (1H, dd, J = 6.0, 1.2 Hz), 4.76 (1H, d, J = 2.0 Hz), 4.51 (1H, td, J = 3.7, 1.2 Hz), 4.30 (1H, dd, J = 12.1, 3.7 Hz), 4.17 (1H, dd, J = 12.1, 3.7 Hz), 2.16 (3H, s), 1.52 (3H, s), 1.36 (3H, s). *Anal.* Found: C, 54.45; H, 6.55; N, 5.95%. Calcd. for $C_{11}H_{15}NO_5$: C, 54.77; H, 6.27; N, 5.81%. NH_4OH (25% in H_2O, 7.4 ml) was added to a mixture of **9** (1.29 g, 5.3 mmol) and H_2O_2 (30% in H_2O, 1.2 ml) in MeOH (16 ml) at 0 C, and it was maintained at r.t. for 2 h. After concentration, silica gel chromatography (EtOAc/MeOH = 10 : 1) of the residue gave a colorless solid (0.79 g, 68%). mp 103–105 C; NMR ($CDCl_3$) δ: 6.59 (1H, br. d), 5.80 (1H, br. d), 5.04 (1H, dd, J = 5.6, 4.4 Hz), 4.76 (1H, dd, J = 5.6, 1.0 Hz), 4.62 (1H, t, J = 4.4 Hz), 4.31 (1H, m), 3.74 (1H, dd, J = 11.7, 3.8 Hz), 3.67 (1H, dd, J = 11.7, 5.6 Hz), 1.49 (3H, s), 1.33 (3H, s). NaH (55 wt% in oil, 0.33 g) was added to a solution of the foregoing solid (0.82 g, 3.8 mmol) in a mixture of THF (13 ml) and DMF (3 ml) at 0 C. After 15 min, BnBr (0.50 ml) was added, the mixture then being stirred for 5.5 h, quenched with aq. NH_4Cl and extracted with EtOAc. The extracts were evaporated and chromatographed on silica gel (EtOAc) to give a benzyl ether (0.88 g, 76%) as a colorless solid. mp 105–106 C; NMR ($CDCl_3$) δ: 7.40–7.27

(5H, m), 6.54 (1H, br.d), 5.90 (1H, br.d), 5.03 (1H, dd, J=5.7, 4.8 Hz), 4.80 (1H, dd, J=5.7, 0.8 Hz), 4.69 (1H, dd, J=4.8 Hz), 4.51 (2H, ABq, J=11.9 Hz), 3.61 (1H, dd, J=10.5, 3.0 Hz), 3.55 (1H, dd, J=10.5, 3.6 Hz), 1.47 (3H, s), 1.32 (3H, s). Oxalyl chloride (0.08 ml) was added to a solution of the benzyl ether (0.15 g, 0.5 mmol) in $ClCH_2CH_2Cl$ (4 ml) at 70°C. After 2 h, Et_3N (0.08 ml) was added and the mixture was heated at 70°C for 2 h. Gaseous NH_3 was bubbled through the mixture for 1 h at r.t., before the mixture was acidified and extracted with EtOAc. The extracts were concentrated and chromatographed on silica gel (hexane/EtOAc = 1 : 1) to afford **11** (0.13 g, 74%) as a colorless solid. mp 175–177°C; $[\alpha]_D^{25}$ −72.6 (c = 0.46, $CHCl_3$); IR ν_{max} (KBr): 3370, 3240, 2980, 1700, 1670 cm^{-1}; NMR ($CDCl_3$) δ: 8.47 (1H, br.d), 8.06 (1H, br.d), 7.40–7.25 (5H, m), 5.18 (1H, br.d), 5.03 (1H, dd, J=5.4, 4.7 Hz), 4.83 (1H, d, J=5.4 Hz), 4.77 (1H, d, J=4.7 Hz), 4.49 (2H, ABq, J=11.8 Hz), 4.40 (1H, t, J=2.6 Hz), 3.66 (1H, dd, J=10.5, 2.6 Hz), 3.57 (1H, dd, J=10.5, 2.6 Hz), 1.45 (3H, s), 1.31 (3H, s). *Anal.* Found: C, 57.96; H, 6.28; N, 7.81%. Calcd. for $C_{17}N_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00%. A mixture of **11** (0.48 g, 1.38 mmol) and Dowex 50W (1.4 g) in MeOH (10 ml)–H_2O (10 ml) was heated at 60°C for 18 h. After filtration, the filtrate was concentrated to give a colorless solid (0.20 g, 46%). mp 133–134°C; NMR (CD_3OD) δ: 7.38–7.25 (5H, m), 4.59 (2H, s), 4.54 (1H, d, J=3.8 Hz), 4.35 (1H, t, J=3.8 Hz), 4.15 (1H, ddd, J=8.4, 4.8, 2.0 Hz), 4.12 (1H, dd, J=8.4, 3.8 Hz), 3.78 (1H, dd, J=10.9, 2.0 Hz), 3.64 (1H, dd, J=10.9, 4.8 Hz). A mixture of this diol (0.15 g, 0.48 mmol) and 5% Pd/C (0.2 g) in MeOH (100 ml) was heated at 55°C under H_2 (4 atm) for 6 h. The mixture was filtered and concentrated to give **3** (0.10 g, 95%) as a colorless solid. mp 180–183°C; $[\alpha]_D^{25}$ −39.6 (c = 0.77, water); IR ν_{max} (KBr): 3000, 1710, 1690 cm^{-1}; NMR (CD_3OD) δ: 4.55 (1H, d, J=4.0 Hz), 4.37 (1H, t, J=4.0 Hz), 4.13 (1H, dd, J=8.1, 4.0 Hz), 4.05 (1H, ddd, J=8.1, 4.6, 2.4 Hz), 3.85 (1H, dd, J=12.2, 2.4 Hz), 3.62 (1H, dd, J=12.2, 4.6 Hz). *Anal.* Found: C, 37.98; H, 5.45; N, 12.42%. Calcd. for $C_7H_{12}N_2O_6$: C, 38.19; H, 5.49; N, 12.72%.

2-Deoxy-2-ureido-D-ribo-hexulofuranosonamide (**14**). A solution of **12** (2.50 g, 7.76 mmol), PMBNCO (1.52 g), and Et_3N (0.20 ml) in THF (25 ml) was heated at 50°C for 1 h and then concentrated. The residue was recrystallizaed from *iso*-Pr_2O to give **13** (2.63 g, 69%) as a colorless solid. mp 200–202°C; NMR (CD_3OD) δ: 7.32–7.28 (5H, m), 7.17 (2H, d, J=8.4 Hz), 6.82 (2H, d, J=8.4 Hz), 4.83 (1H, dd, J=5.8, 2.0 Hz), 4.71 (1H, d, J=5.8 Hz), 4.50 (2H, s), 4.45 (1H, td, J=6.0, 2.0 Hz), 4.19 (2H, ABq, J=14.5 Hz), 3.74 (3H, s), 3.59 (2H, d, J=6.0 Hz), 1.47 (3H, s), 1.29 (3H, s). A solution of **13** (0.30 g, 0.62 mmol) in a mixture of CH_3CN (20 ml) and MeOH (40 ml) was added to a solution of CAN (5.1 g) in H_2O (10 ml) at r.t. After 20 min, the mixture was poured into water and extracted with EtOAc. The organic layers were evaporated and purified by TLC ($CHCl_3$/MeOH = 5 : 1) to give a colorless solid (0.20 g, 89%). mp 188–190°C; NMR (CD_3OD) δ: 7.27–7.44 (5H, m), 4.82 (1H, m), 4.72 (1H, d, J=6.4 Hz), 4.57 (2H, s), 4.46 (1H, td, J=6.0, 1.6 Hz), 3.61 (2H, d, J=6.0 Hz), 1.47 (3H, s), 1.29 (3H, s). A mixture of this compound (89 mg, 0.24 mmol) and Dowex 50W (0.30 g) in MeOH (3 ml)–H_2O (2 ml) was stirred at r.t. for 3 d. After filtration, the filtrate was concentrated to give 64 mg of a diol (81%) as a colorless oil. NMR (CD_3OD) δ: 7.38–7.28 (5H, m), 4.57 (2H, ABq, J=11.7 Hz), 4.28 (1H, d, J=4.4 Hz), 4.24–4.15 (2H, m), 3.59 (2H, d, J=4.8 Hz). A mixture of this diol (0.51 g, 1.57 mmol) and 5% Pd/C (0.25 g) in MeOH (250 ml) was stirred at 55°C under H_2 (3 atm) for 6 h and then filtered. The filtrate was concentrated and chromatographed on Dianion CHP-20 (H_2O) to give **14** (82 mg, 22%) as a colorless syrup. IR ν_{max} (KBr): 3500, 3050, 1780, 1730 cm^{-1}; NMR (CD_3OD) δ: 4.26–4.20 (1H, m), 4.18–4.15 (1H, m), 4.12–4.02 (1H, m), 3.69–3.55 (1H, m). *Anal.* Found: C, 35.45; H, 5.50%; N, 17.52. Calcd. for $C_7H_{13}N_3O_6$: C, 35.73; H, 5.57; N, 17.87%.

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