N-tert-Butyl-N´-(4-ethylbenzoyl)-3,5-dimethylbenzohydrazideの3,5-dimethylbenzoyl部分を変換した誘導体の合成と殺虫活性

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Original Article

Synthesis and Insecticidal Activity of 3,5-Dimethylbenzoyl Moiety Modified Analogues of *N-tert*-Butyl-*N'*-(4-ethylbenzoyl)-3,5-dimethylbenzohydrazide

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Fourteen analogues were synthesized by rationally modifying the 3,5-dimethylbenzoyl moiety of RH-5992, and evaluated for insecticidal activity against the common cutworm (*Spodoptera litura*). Although several derivatives showed good insecticidal activity, they were less active than RH-5992.

Key words: 20-hydroxyecdysone, RH-5992, tebufenozide, ecdysone agonist, insecticidal activity, common cutworm.

INTRODUCTION

20-Hydroxyecdysone (20E) is a major insect hormone that regulates insect metamorphosis and development.[1] Recently, a new class of compounds has been traced to the 20E agonists that initiate a precocious and incomplete molt. A class of *N'*-benzoyl-*N-tert*-butylbenzohydrazide (BTBH) analogues have been developed for use as new generation insect growth regulators (IGRs)[2–4] that mimic the action of 20E (Fig. 1). Among the BTBH analogues, *N-tert*-butyl-*N'*-(4-ethylbenzoyl)-3,5-dimethylbenzohydrazide (RH-5992; tebufenozide) is the first commercialized non-steroidal ecdysone agonist that is specific to insects and scarcely toxic to vertebrates.[5]

To develop novel insecticides, we focused on the clear structural difference between 20E and BTBH, and hypothesized that new BTBH derivatives with structural similarities to 20E would have stronger insecticidal activity.

The molting activity of ecdysone is closely dependent on its structure. The C20-C27 side chain plays a particularly important role in the activity. For example, rubrosterone, which does not have this side chain, shows very weak molting activity. Similarly, 22-deoxy-20-hydroxyecdysone and 22-iso-20-hydroxyecdysone show very weak activity and no activity, respectively (Fig. 1).[6]

Figure 2 is a hypothetical superimpositional model of the two compounds. According to this simple model, the side chain of 20E is superimposed on the 3-methyl group (or 5-methyl group) of the 3,5-dimethylphenyl moiety (B-ring). For a better fit onto the 20E template, we changed the 3,5-dimethylphenyl part to benzene-ring-reduced derivatives, 3-alkoxymethylphenyl derivatives, a 3-hydroxymethyphenyl derivative, 3-halomethylphenyl derivatives, a 3-formylphenyl derivative, a 3-vinylphenyl derivative and heterocyclic derivatives (Fig. 2).

In this paper we describe the preparation of fourteen new B-ring-modified RH-5992 analogues (**1**–**14**) and also their insecticidal activity against the common cutworm (*Spodoptera litura*).

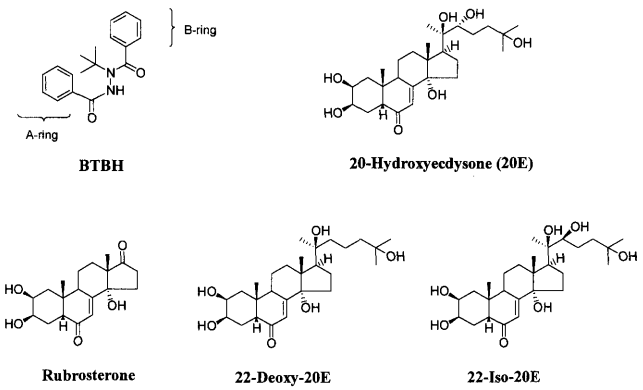

Fig. 1 Chemical structures of BTBH, 20E and analogues.

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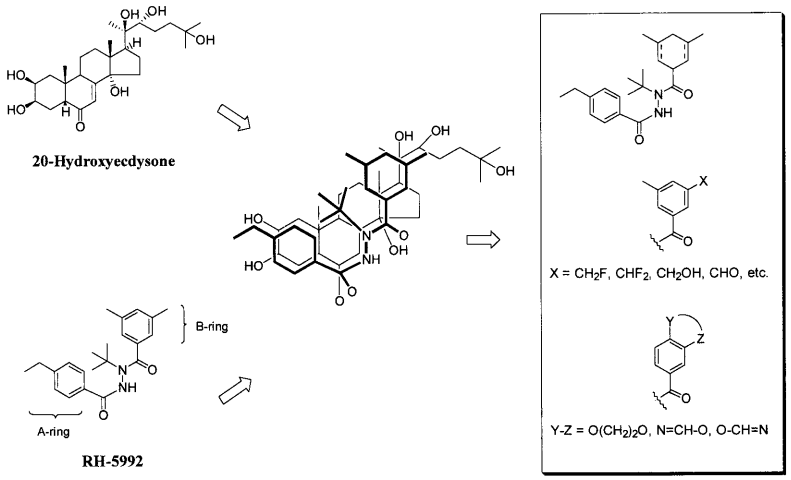


Fig. 2 Strategy for the modification of the B-ring.

MATERIALS AND METHODS

1. *General*

Melting points (mp) were measured with a Yanagimoto micromelting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured on a Varian EM 360A spectrometer at 200 MHz using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained with a JEOL JMS-D300 and a VG Auto Spec M mass spectrometer.

2. *Synthesis of Compounds*

Table 1 shows the compounds used in this study together with the data for instrumental analysis. Methods for the synthesis of each type of test compound are outlined in Figs. 3 and 4. The intermediary carboxylic acids and benzoic acids were prepared by the procedures shown in Fig. 5. Some typical procedures (compounds **1**, **6**–**10** and **I**–**XIII**) are described below (yields not optimized). Other compounds (**2**–**5** and **11**–**14**) were similarly prepared.

2.1 *N′-tert-Butyl-4-ethylbenzohydrazide (I)*

A portion of 4-ethylbenzoyl chloride was obtained by reacting 4-ethylbenzoic acid (3.0 g, 20 mmol) with thionyl chloride, and then the product was dissolved in dichloromethane (15 ml). The solution of 4-ethylbenzoyl chloride in dichloromethane (5 ml) was added dropwise to a stirred suspension of *tert*-butylhydrazine hydrochloride (2.49 g, 20 mmol) and sodium hydroxide (2.0 g, 48 mmol) in dichloromethane (30 ml) and water (10 ml) in an ice bath. After stirring overnight at room temperature, ethyl acetate (150 ml) was added to the reaction mixture. The organic layer was washed successively with water (100 ml) and with brine (100 ml), then dried over magnesium sulfate. Finally, the solvent was evaporated, and the residue was purified by silica-gel column chromatography (*n*-hexane/ethyl acetate=4/1, v/v) to give 1.87 g (43%) of **I** as crystals. mp 120–122 °C. ^{1}H NMR δ ($CDCl_3$) ppm: 1.16 (9H, s), 1.25 (3H, t, J=7.7 Hz), 2.70 (2H, q, J=7.7 Hz), 7.28 (2H, dd, J=6.4 & 1.8 Hz), 7.70 (2H, dd, J=6.4 & 1.8 Hz).

2.2 *N-tert-Butyl-N′-(4-ethylbenzoyl)-1,4-dihydro-3,5-dimethylbenzohydrazide (1)*

A portion of 3,5-dimethyl-1,4-dihydrobenzoyl chloride was obtained by reacting the corresponding benzoic acid (400 mg, 2.6 mmol) with thionyl chloride then the product was dissolved in dichloromethane (1 ml). The solution was added dropwise to a stirred mixture of **I** (560 mg, 2.5 mmol), triethylamine (315 mg, 3.1 mmol), and dichloromethane (3 ml) in an ice bath. After stirring of the mixture at room temperature for 3 hr, ethyl acetate (100 ml) was added. The organic layer was washed successively with water (50 ml) and brine (50 ml), and then dried over sodium sulfate. The solvent was evaporated, and the residue was purified by silica-gel column chromatography (*n*-hexane/ethyl acetate=4/1, v/v) to give 260 mg (29%) of **1** as crystals (Table 1).

2.3 *N-tert-Butyl-N′-(4-ethylbenzoyl)-3-hydroxymethyl-5-methylbenzohydrazide (6)*

Hydrogen fluoride-pyridine (HF=70%, 1 ml) was added dropwise to a stirred solution of *N-tert*-butyl-*N′*-(4-ethylbenzoyl)-3-*tert*-butyldimethylsililoxymethyl-5-methylbenzohydrazide (**5**) (638 mg, 1.32 mmol) in acetonitrile (5 ml) in an ice bath. The reaction mixture was stirred for 10 min at room temperature, poured into ice water (50 ml), and extracted with ethyl acetate (50 ml×3). The organic layer was washed successively with a saturated sodium hydrogen carbonate solution (50 ml), water (50 ml) and brine (50 ml), then dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was purified by silica-gel column chromatography (*n*-hexane/ethyl acetate=4/1, v/v) to give 486 mg (100%) of **6** as crystals (Table 1).

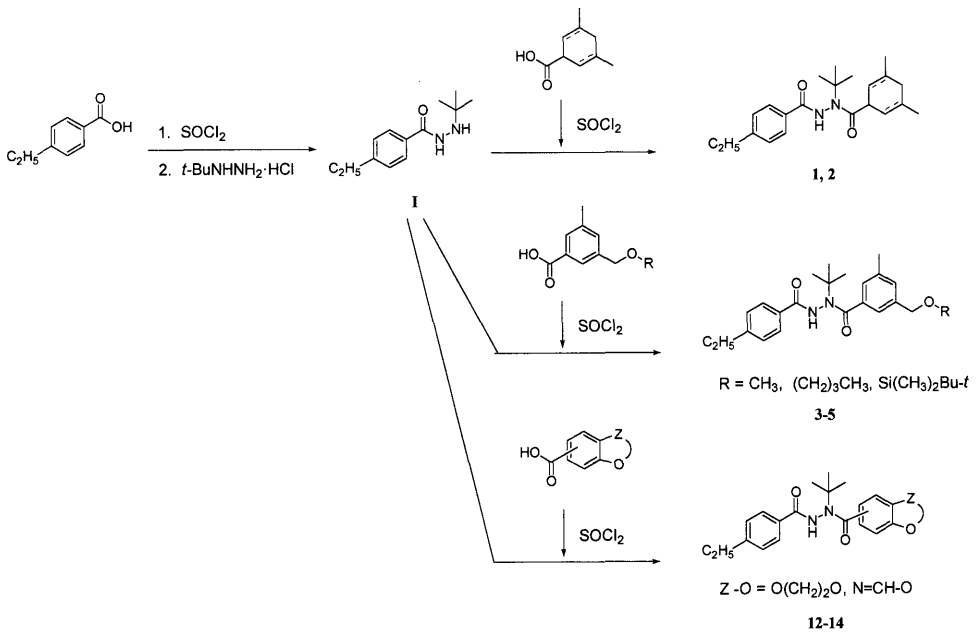


Fig. 3 Methods for the synthesis of BTBH analogues (**1**–**5** and **12**–**14**).

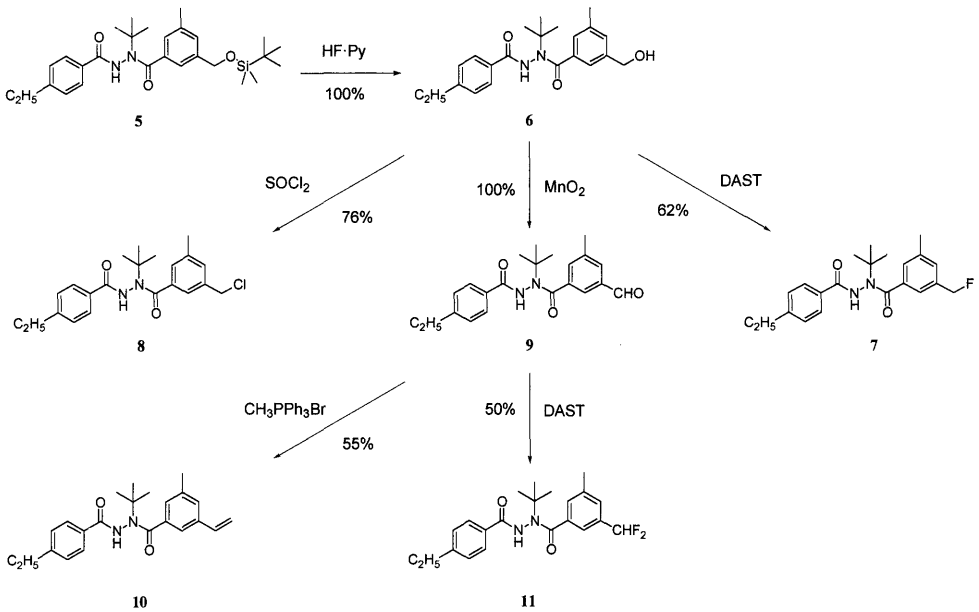


Fig. 4 Methods for the synthesis of BTBH analogues (**6**–**11**).

2.4 N-tert-Butyl-N′-(4-ethylbenzoyl)-3-fluoromethyl-5-methylbenzohydrazide (7)

Diethylaminosulfur trifluoride (DAST, 0.27 ml, 2.05 mmol) was added dropwise to a solution of compound **6** (302 mg, 0.82 mmol) in dichloromethane (3 ml) in an ice bath. The reaction mixture was stirred at 0°C for 30 min, poured into ice-water (50 ml), and extracted with ethyl acetate (30 ml×3). The organic layer was washed successively with water (50 ml), a saturated sodium hydrogen carbonate solution (50 ml) and brine (50 ml), and then dried over sodium sulfate. Finally, the solvent was evaporated, and the residue was purified by preparative TLC (*n*-hexane/ethyl acetate=4/1, v/v) to give 188 mg (62%) of **7** as crystals (Table 1).

2.5 N-tert-Butyl-N′-(4-ethylbenzoyl)-3-chloromethyl-5-methylbenzohydrazide (8)

Thionyl chloride (0.4 ml, 4.11 mmol) was added dropwise to a stirred solution of **6** (1.0 g, 2.71 mmol), dichloromethane (25 ml) and pyridine (0.31 ml, 3.8 mmol) in an ice bath. The reaction mixture was stirred

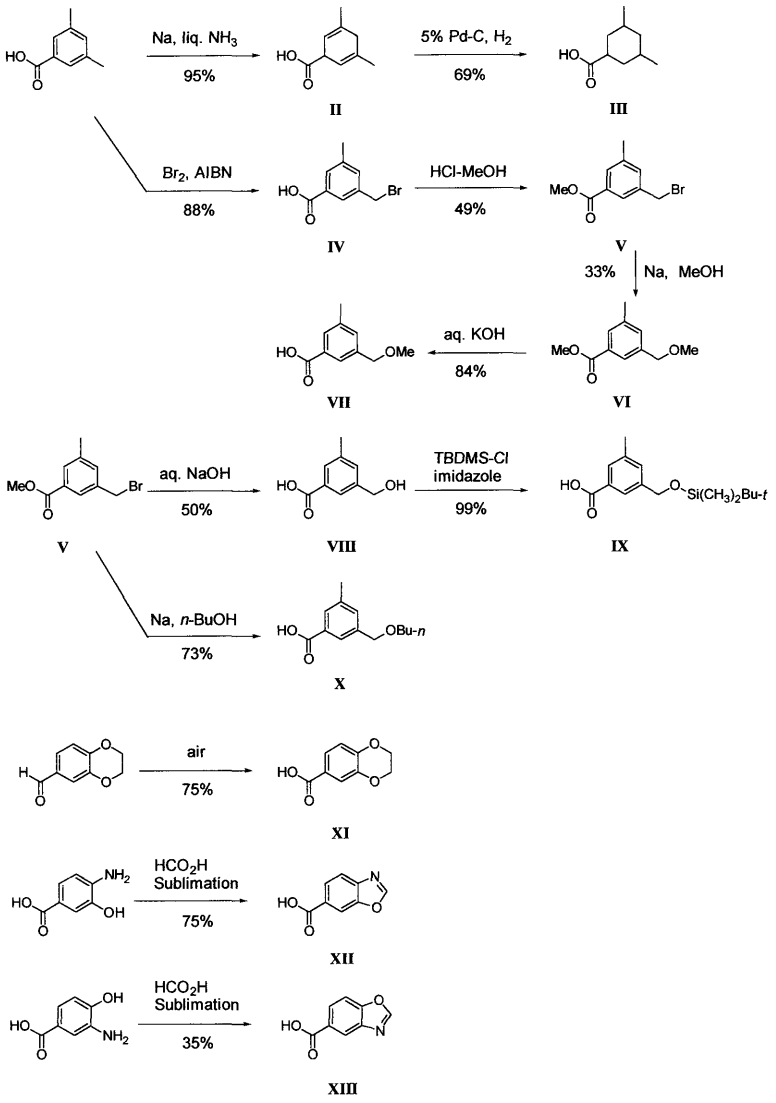


Fig. 5 Methods for the synthesis of intermediary carboxylic acids and benzoic acids (**II-XIII**).

for 1 hr at room temperature, poured into ice water (150 ml), and extracted with ethyl acetate (50 ml×3). The organic layer was washed successively with water (50 ml), saturated sodium hydrogen carbonate solution (50 ml) and brine (50 ml), and then dried over sodium sulfate. After the solvent has evaporated, the residue was purified by silica-gel column chromatography (*n*-hexane/ethyl acetate=4/1, v/v) to give 800 mg (76%) of **8** as crystals (Table 1).

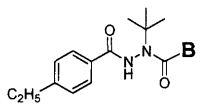
*2.6 N-tert-Butyl-N′-(4-ethylbenzoyl)-3-formyl-5-methylbenzohydrazide (**9**)*

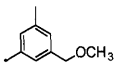
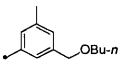
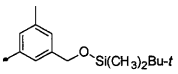
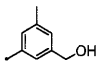
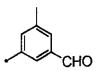
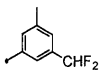
A mixture of **6** (1.0 g, 2.71 mmol), chloroform (20 ml) and manganese (IV) dioxide (4.73 g) was refluxed for 1.5 hr. The reaction mixture was filtered through a Celite® pad and the solvent was removed in vacuo. The residue was purified by silica-gel column chromatography (*n*-hexane/ethyl acetate=4/1, v/v) to give 0.99 g (100%) of **9** as an amorphous solid (Table 1).

*2.7 N-tert-Butyl-N′-(4-ethylbenzoyl)-3-methyl-5-vinylbenzohydrazide (**10**)*

A mixture of oil-free sodium hydride (16 mg, 0.65 mmol), dimethyl sulfoxide (DMSO, 3 ml) and methyltriphenylphosphonium bromide (624 mg, 1.74 mmol) was stirred at room temperature for 20 min under a nitrogen atmosphere. After the addition of **9** (205 mg, 0.56 mmol), the reaction mixture was stirred at room temperature for 1.5 hr, poured into ice-water (70 ml), and extracted with ethyl acetate (50 ml×3). The organic layer was washed successively with water (50 ml) and brine (50 ml), then dried over sodium sulfate. Finally, the solvent was evaporated, and the residue was purified by silica-gel column chromatography (*n*-hexane/ethyl acetate=4/1, v/v) to give 112 mg (55%) of **10** as an amorphous solid (Table 1).

Table 1 Structure and characterization data for the BTBH analogues.



Compound No.	B	mp (℃)	HRMS (M^+) (*m*/*z*) Calcd	Found	[^{1}H]NMR ($CDCl_3$) (ppm)
1		250-253	354.2307	354.2308	1.27 (3H, t, *J* = 7.6 Hz), 1.50 (9H, s), 1.57 (3H, s), 1.73 (3H, s), 2.27 (2H, m), 2.72 (2H, q, *J* = 7.6 Hz), 3.93 (1H, m), 5.39 (2H, d, *J* = 2.3 Hz), 7.30 (2H, d, *J* = 8.1 Hz), 7.69 (2H, d, *J* = 8.1 Hz)
2		201-203	358.2620	358.2619	0.57 (1H, q, *J* = 12.2 Hz), 0.84-0.90 (6H, m), 0.98-1.20 (2H, m), 1.27 (3H, t, *J* = 8.1 Hz), 1.25-1.40 (1H, m), 1.48 (9H, s), 1.52-1.77 (3H, m), 2.47-2.60 (1H, m), 2.73 (2H, q, *J* = 8.1 Hz), 7.32 (2H, d, *J* = 8.1 Hz), 7.69 (2H, d, *J* = 8.1 Hz), 7.84 (1H, s)
3		119-121	382.2256	382.2256	1.19 (3H, t, *J* = 7.6 Hz), 1.59 (9H, s), 2.26 (3H, s), 2.62 (2H, q, *J* = 7.6 Hz), 3.25 (3H, s), 4.33 (1H, d, *J* = 11.0 Hz), 4.37 (1H, d, *J* = 11.0 Hz), 7.00-7.30 (7H, m), 7.75 (1H, br s)
4		73-77	424.2726	424.2727	0.89 (3H, t, *J* = 7.1 Hz), 1.19 (3H, t, *J* = 7.6 Hz), 1.20-1.60 (4H, m), 1.59 (9H, s), 2.26 (3H, s), 2.62 (2H, q, *J* = 7.6 Hz), 3.33 (2H, t, *J* = 6.4 Hz), 4.37 (1H, d, *J* = 11.0 Hz), 4.39 (1H, d, *J* = 11.0 Hz), 7.07-7.30 (7H, m), 7.72 (1H, s)
5		amorphous	482.2965	482.2965	0.02 (3H, s), 0.04 (3H, s), 0.90 (9H, s), 1.19 (3H, t, *J* = 7.6 Hz), 1.59 (9H, s), 2.26 (3H, s), 2.62 (2H, q, *J* = 7.6 Hz), 4.61 (1H, d, *J* = 14.0 Hz), 4.62 (1H, d, *J* = 14.0 Hz), 7.05-7.30 (7H, m), 7.70 (1H, s)
6		173-175	368.2100	368.2101	1.15 (3H, t, *J* = 7.6 Hz), 1.59 (9H, s), 2.17 (3H, s), 2.48 (1H, br s), 2.56 (2H, q, *J* = 7.6 Hz), 4.35 (1H, d, *J* = 14.0 Hz), 4.36 (1H, d, *J* = 14.0 Hz), 6.96 (1H, s), 6.99 (2H, d, *J* = 8.2 Hz), 7.12 (2H, s), 7.28 (2H, d, *J* = 8.2 Hz), 8.83 (1H, br s)
7		188-192	370.2057	370.2057	1.19 (3H, t, *J* = 7.6 Hz), 1.59 (9H, s), 2.26 (3H, s), 2.62 (2H, q, *J* = 7.6 Hz), 5.25 (1H, dd, *J* = 47.6 & 12.0 Hz), 5.26 (1H, dd, *J* = 47.6 & 12.0 Hz), 7.10 (1H, s), 7.12 (2H, d, *J* = 8.2 Hz), 7.26 (2H, s), 7.28 (2H, d, *J* = 8.2 Hz), 7.92 (1H, s)
8		175-177	386.1761	386.1760	1.18 (3H, t, *J* = 7.6 Hz), 1.59 (9H, s), 2.22 (3H, s), 2.61 (2H, q, *J* = 7.6 Hz), 4.45 (2H, s), 7.05-7.15 (3H, m), 7.20-7.30 (4H, m), 8.07 (1H, br s)
9		amorphous	366.1943	366.1944	1.17 (3H, t, *J* = 7.6 Hz), 1.62 (9H, s), 2.32 (3H, s), 2.60 (2H, q, *J* = 7.6 Hz), 7.08 (2H, d, *J* = 8.0 Hz), 7.32 (2H, d, *J* = 8.0 Hz), 7.56 (1H, s), 7.61 (1H, s), 7.74 (1H, s), 8.41 (1H, br s), 9.82 (1H, s)
10		amorphous	364.2151	364.2152	1.19 (3H, t, *J* = 7.6 Hz), 1.60 (9H, s), 2.24 (3H, s), 2.62 (2H, q, *J* = 7.6 Hz), 5.20 (1H, d, *J* = 10.8 Hz), 5.69 (1H, d, *J* = 17.6 Hz), 6.60 (1H, dd, *J* = 17.6 & 10.8 Hz), 7.07-7.18 (4H, m), 7.22-7.33 (3H, m), 7.79 (1H, s)
11		165-167	388.1962	388.1963	1.20 (3H, t, *J* = 7.7 Hz), 1.60 (9H, s), 2.31 (3H, s), 2.63 (2H, q, *J* = 7.7 Hz), 6.55 (1H, t, *J* = 56.4 Hz), 7.15 (2H, d, *J* = 8.1 Hz), 7.23 (1H, s), 7.29 (2H, d, *J* = 8.1 Hz), 7.42 (2H, s), 7.73 (1H, s)
12		151-153	382.1893	382.1892	1.18 (3H, t, *J* = 7.2 Hz), 1.57 (9H, s), 2.65 (2H, q, *J* = 7.2 Hz), 4.19 (4H, s), 6.74 (1H, d, *J* = 8.8 Hz), 7.02 (2H, dd, *J* = 8.8 & 2.2 Hz), 7.18 (2H, d, *J* = 8.4 Hz), 7.38 (2H, d, *J* = 8.4 Hz), 7.71 (1H, s)
13		197-200	365.1739	365.1740	1.13 (3H, t, *J* = 7.6 Hz), 1.61 (9H, s), 2.55 (2H, q, *J* = 7.6 Hz), 7.03 (2H, d, *J* = 8.2 Hz), 7.30 (2H, d, *J* = 8.2 Hz), 7.43 (1H, d, *J* = 8.4 Hz), 7.60 (1H, dd, *J* = 8.4 & 1.5 Hz), 7.89 (1H, d, *J* = 1.5 Hz), 8.06 (1H, s), 8.48 (1H, s)
14		194-197	365.1739	365.1740	1.15 (3H, t, *J* = 7.6 Hz), 1.62 (9H, s), 2.58 (2H, q, *J* = 7.6 Hz), 7.07 (2H, d, *J* = 8.2 Hz), 7.30 (2H, d, *J* = 8.2 Hz), 7.46 (1H, d, *J* = 8.4 Hz), 7.61 (1H, dd, *J* = 8.4 & 1.5 Hz), 7.91 (1H, d, *J* = 1.5 Hz), 8.05 (1H, s), 8.14 (1H, br s)

2.8 3,5-Dimethyl-1,4-dihydrobenzoic acid (II)[7]

Sodium (5.0 g, 0.22 mol) was added to a stirred solution of 3,5-dimethylbenzoic acid (5.0 g, 0.033 mol) in dry ether (50 ml) and dry liquid ammonia (200 ml) in a dry ice-ethanol bath. The resulting solution was stirred for 2 hr and quenched with ammonium chloride (12.0 g, 0.22 mol). The ammonia was evaporated under a stream of nitrogen, the residue was acidified with 6 N hydrochloric acid, the aqueous solution was extracted with dichloromethane (50 ml×3), and the organic layer was washed with brine (50 ml). The combined extracts were dried over sodium sulfate and concentrated in vacuo to give 4.75 g (95%) of **II** as crystals. mp 107–109°C. ^{1}H NMR δ ($CDCl_3$) ppm: 1.76 (6H, s), 2.50 (2H, d, J=8.0 Hz), 3.70–3.82 (1H, m), 5.49–5.55 (2H, m).

2.9 3,5-Dimethylcyclohexanecarboxylic acid (III)

A mixture of compound **II** (1.0 g, 6.7 mmol), palladium carbon (5%, 0.1 g), and ethanol (30 ml) was transferred to a 250 ml Parr hydrogenation flask. The flask was purged and filled with H_2 three times then left under a H_2 atmosphere at 40 psi with shaking for 4 hr. The reaction mixture was filtered through a Celite® pad and the solvent was removed in vacuo. Recrystallization of the residue from ethanol and water provided 0.70 g (69%) of **III** as an amorphous solid. ^{1}H NMR δ ($CDCl_3$) ppm: 0.58 (1H, q, J=12.0 Hz), 0.92 (6H, d, J=4.0 Hz), 0.95–2.70 (8H, m).

2.10 3-Bromomethyl-5-methylbenzoic acid (IV)

A mixture of 3,5-dimethylbenzoic acid (20.0 g, 0.13 mol) and 2,2′-azobisisobutyronitrile (AIBN, 2.19 g, 0.013 mol) in carbon tetrachloride (400 ml) was heated to a reflux temperature and a solution of bromine (25.5 g, 0.16 mol) in carbon tetrachloride (50 ml) was gradually added to the refluxing solution over a 2.5 hr period. The reaction mixture was refluxed for an additional 4 hr, and cooled to room temperature, then extracted with dichloromethane (200 ml×3). The organic layer was washed successively with a saturated sodium hydrogen carbonate solution (200 ml), water (200 ml) and brine (200 ml), then dried over sodium sulfate. After the solvent had evaporated, the residue was recrystallized from ethanol and water to give 26.8 g (88%) of **IV** as crystals. mp 143–146°C. ^{1}H NMR δ ($CDCl_3$) ppm: 2.43 (3H, s), 4.51 (s, 2H), 7.45–7.98 (3H, m).

2.11 Methyl 3-bromomethyl-5-methylbenzoate (V)

A solution of **IV** (26.8 g, 0.117 mol) in 10% hydrogen chloride-methanol solution (100 ml) was stirred at room temperature for 12 hr. The methanol was evaporated, and the residue was diluted with ethyl acetate (500 ml). The organic solution was washed successively with water (200 ml×3) and brine (200 ml), then dried over sodium sulfate. The solvent was evaporated, and the residue was purified by silica-gel column chromatography (*n*-hexane/ethyl acetate=7/1, v/v) to give 14.0 g (49%) of **V** as an amorphous solid. ^{1}H NMR δ ($CDCl_3$) ppm: 3.94 (3H, s), 4.52 (2H, s), 4.62 (3H, s), 7.63 (1H, s), 7.99–8.03 (2H, m).

2.12 Methyl 3-methoxymethyl-5-methylbenzoate (VI)

Sodium (0.51 g, 22 mmol) was added to a stirred solution of **V** (1.0 g, 4.1 mmol) in methanol (20 ml) at room temperature. The mixture was refluxed for 2 hr, then concentrated *in vacuo*. The resulting residue was poured into ice-water, and the mixture was extracted with ethyl acetate (50 ml×3). The organic layer was washed successively with water (50 ml) and brine (50 ml), then dried over sodium sulfate. After the solvent had evaporated, the residue was purified by silica-gel column chromatography (*n*-hexane/ethyl acetate=7/1, v/v) to give 265 mg (33%) of **VI** as an oil. ^{1}H NMR δ ($CDCl_3$) ppm: 2.40 (3H, s), 3.40 (3H, s), 3.91 (3H, s), 4.46 (2H, s), 7.36 (1H, s), 7.80 (2H, s).

2.13 3-Methoxymethyl-5-methylbenzoic acid (VII)

A solution of **VI** (550 mg, 3.81 mmol) in dioxane (2 ml) and ethanol (2 ml) was added to a suspension of 2 N potassium hydroxide solution (2 ml), and the mixture was refluxed for 1 hr. The reaction mixture was poured into ice-water and washed with ether (30 ml×3). The aqueous layer was acidified with 6 N hydrochloric acid and extracted with ethyl acetate (50 ml×3). The organic layer was washed successively with water (50 ml) and brine (50 ml), then dried over magnesium sulfate. The solvent was evaporated, and the residue was purified by silica-gel column chromatography (*n*-hexane/ethyl acetate=2/1, v/v) to give 414 mg (84%) of **VII** as an amorphous solid. ^{1}H NMR δ ($CDCl_3$) ppm: 2.43 (3H, s), 3.42 (3H, s), 4.49 (2H, s), 7.44 (1H, s), 7.87 (2H, s).

2.14 3-Hydroxymethyl-5-methylbenzoic acid (VIII)

A mixture of **V** (41.7 g, 0.18 mol) and sodium hydroxide (15.6 g, 0.39 mol) in water (150 ml) was refluxed for 2 hr. After cooling, water and 6 N hydrochloric acid were added to cause precipitation. The precipitate was collected by filtration, washed with water and dried to give 16.2 g (50%) of **VIII** as an amorphous solid. ^{1}H NMR δ (DMSO-d_6) ppm: 2.33 (3H, s), 4.53 (2H, s), 5.30 (1H, br s), 7.30–7.90 (3H, m).

2.15 3-tert-Butyldimethylsilyloxymethyl-5-methylbenzoic acid (IX)

A mixture of **VIII** (0.77 g, 4.6 mmol), imidazole (0.95 g, 14 mmol), *tert*-butyldimethylsilyl chloride (2.10 g, 14 mmol) and DMF (5 ml) was refluxed for 3 hr. The reaction mixture was poured into ice-water and extracted with ethyl acetate (50 ml×3). The organic layer was washed successively with water (50 ml) and brine (50 ml), then dried over magnesium sulfate. After evaporation of the solvent, the residue was dissolved in methanol (6 ml) and THF (2 ml). The solution was added to potassium carbonate (0.3 g, 2.2 mmol) in water (1.5 ml) and stirred at room temperature for 30 min. The organic solvents were evaporated, and the residue was poured into an ice-cooled 6 N hydrochloric acid (130 ml). The mixture was extracted with ethyl acetate (100 ml×2) and washed successively with water (100 ml) and brine (100 ml), and then the extract was dried over sodium sulfate. Evaporation of the solvent gave 1.28 g (99%) of **IX** as an amorphous solid. ^{1}H NMR δ ($CDCl_3$) ppm: 0.12 (6H, s), 0.95 (9H, s), 2.42 (3H, s), 4.78 (2H, s), 7.40–7.90 (3H, m).

2.16 3-Buthoxymethyl-5-methylbenzoic acid (X)

Sodium (0.58 g, 25 mmol) was added to a solution of **V** (1.0 g, 4.1 mmol) in *n*-butyl alcohol (20 ml) at room temperature. The reaction mixture was stirred for 45 mim, poured into ice-water, and extracted with ethyl acetate (30 ml×2). The organic layer was washed successively with water (20 ml) and brine (40 ml), and then dried over magnesium sulfate. The solvent was evapor-

ated, and the residue was purified by silica-gel column chromatography (*n*-hexane/ethyl acetate=7/1, v/v) to give crude benzoate. A solution of the benzoate in dioxane (4 ml) and ethanol (2 ml) was added to a suspension of 2 N potassium hydroxide solution (4 ml), and the mixture was refluxed for 45 min. The reaction mixture was poured into ice-water and washed with ether (50 ml×3). The aqueous layer was acidified with 6 N hydrochloric acid and extracted with ethyl acetate (60 ml×3). The organic layer was washed successively with water (80 ml) and brine (80 ml), then dried over magnesium sulfate. Evaporation of the solvent gave 688 mg (73%) of **X** as an amorphous solid. ^{1}H NMR δ ($CDCl_3$) ppm: 0.93 (3H, t, J=7.1 Hz), 1.35–1.70 (4H, m), 2.42 (3H, s), 4.53 (s, 2H), 7.44 (1H, s), 7.86 (2H, d, J=5.4 Hz).

2.17 2,3-Dihydro-1,4-benzodioxine-6-carboxylic acid (XI)

Air was bubbled through a mixture of 2,3-dihydro-1,4-benzodioxine-6-carboxaldehyde (10.2 g, 62.1 mmol), tetrahydrofuran (100 ml), 10% sodium hydroxide solution (300 ml) and 10% palladium carbon (3.7 g) for 30 hr. The reaction mixture was filtered through a Celite® pad and the solvent was washed with diethyl ether (2×50 ml). The aqueous solution was acidified with 6 N hydrochloric acid and extracted with ethyl acetate (50 ml×3). The organic layer was washed with water (50 ml) and brine (50 ml). The combined extracts were dried over magnesium sulfate and concentrated in vacuo to give 8.34 g (75%) of **XI** as crystals. mp 134–136°C (lit.[8] mp 136°C). ^{1}H NMR δ ($CDCl_3$) ppm: 4.25–4.37 (4H, m), 6.92 (1H, d, J=8.8 Hz), 7.60–7.68 (2H, m).

2.18 Benzoxazole-6-carboxylic acid (XII)

A mixture of 4-amino-3-hydroxybenzoic acid (5.0 g, 33 mmol) and formic acid (85%, 15 ml) was refluxed for 2 hr. After cooling to room temperature, the reaction mixture was filtered and the collected solid was recrystallized from 50% DMF in water. The crude solid thus obtained was sublimed at 280–290°C under reduced pressure (16 mmHg) to give 4.0 g (75%) of **XII** as crystals. mp 240°C. ^{1}H NMR δ (DMSO-d_6) ppm: 7.92 (1H, d, J=8.5 Hz), 8.04 (1H, d, J=8.5 Hz), 8.31 (1H, s), 8.96 (1H, s).

2.19 Benzoxazole-5-carboxylic acid (XIII)

A mixture of 3-amino-4-hydroxybenzoic acid (5.0 g, 33 mmol) and formic acid (85%, 15 ml) was refluxed for 1.5 hr. The reaction mixture was cooled to room temperature, and passed through a filter, and then the collected solid was recrystallized from 50% of DMF in water. The crude solid thus obtained was sublimed at 280–290 °C under reduced pressure (16 mmHg). Recrystallization of the resulting white solid from ethanol provided 1.89 g (35%) of **XIII** as crystals. mp 225–228°C (lit.[9] 249°C). ^{1}H NMR δ (DMSO-d_6) ppm: 7.90 (1H, d, J=8.6 Hz), 8.08 (1H, dd, J=8.6 Hz and 1.5 Hz), 8.33 (1H, d, J=1.5 Hz), 8.89 (1H, s).

3. Biological Tests

3.1 Insects

Larvae of the common cutworm, *Spodoptera litura*, were reared on an artificial diet (Insecta LF, Nihon-Nosan Kogyo Co.) under standard laboratory conditions (25°C, 60% relative humidity, and a 16L-8D photoperiod).

3.2 Assay method for assessment of insecticidal activity

For leaf dipping experiments, test compounds were dissolved with acetone and diluted to the respective test concentrations with water. Freshly cut cabbage leaves were dipped in the respective test solutions for 20 sec. After air-drying, each treated leaf was placed into a clear plastic cup (9 cm in diameter), then ten third-instar *Spodoptera litura* larvae were released into the cup. Leaves treated with water and acetone were provided as controls. All assays were performed under the standard conditions specified above. Insecticidal activity was rated on a scale from 0 to 10, where 0=no effect, and 10=complete killing. Mortality was observed 5 days later. At least twenty larvae were used for each treatment.

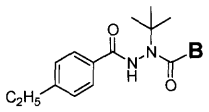
RESULTS AND DISCUSSION

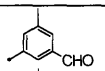
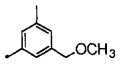
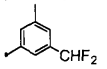
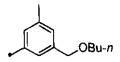
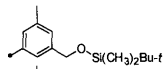
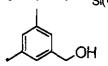
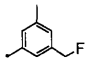
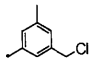
Table 2 shows the insecticidal activity of the fourteen newly synthesized compounds (**1**–**14**) and RH-5992 against the common cutworm.

Compound **1**, whose B-ring was reduced to a 3,5-dimethyl-2,5-cyclohexadienylcarbonyl group, showed reduced insecticidal activity. Compound **2**, which had a more reduced 3,5-dimethylcyclohexylcarbonyl group, was inactive. Shimizu *et al*. recently reported that aliphatic acyl derivatives of BTBH analogues have insecticidal activity against the rice stem borer (*Chilo suppressalis*). The corresponding B-ring-modified analogues of BTBH were less active than the other series of compounds, while the A-ring-modified ones (cf. hexanoyl derivative) retained hormonal and larvicidal activity.[10] Although 20E has no aromatic structure, the aromaticity of the B-ring of BTBH analogues is important for their insecticidal activity.

Compounds **3** to **11** are analogues in which one of the two methyl groups of the 3,5-dimethylbenzoyl moiety of RH-5992 is modified. The analogues **3** (CH_2OMe), **7** (CH_2F), **8** (CH_2Cl), **10** (vinyl) and **11** (CHF_2), in which the methyl groups of the B-ring are converted to more sterically hindered groups, showed strong insecticidal activity. In particular, fluoromethyl analogue **7** and difluoromethyl analogue **11** had almost the same activity as RH-5992. On the other hand, analogues **4** (CH_2-OBu-*n*) and **5** ($CH_2OSi(Me)_2Bu$-*t*), which have very

Table 2 Insecticidal activity of test compounds against the common cutworm.



Compound No.	B	Insecticidal activity* 200	50	12.5	3.1 ppm	Compound No.	B	Insecticidal activity* 200	50	12.5	3.1 ppm
1		10	10	4	-	**9**		0	-	-	-
2		1	0	-	-	**10**		10	7	1	-
3		9	5	-	-	**11**		10	10	8	-
4		0	-	-	-	**12**		0	-	-	-
5		0	-	-	-	**13**		1	-	-	-
6		0	-	-	-	**14**		5	-	-	-
7		10	10	5	-	**RH-5992**		10	10	10	3
8		7	1	-	-						

* Insecticidal activities were rated on a scale of 0 to 10; 0=no effect, 10=complete killing.

large groups on the B-rings, were inactive. Oxidation of a methyl group on the B-ring, such as in compound **6** (CH_2OH) or **9** (CHO), strongly diminished the activity. Benzoheterocyclic derivatives **12** (benzodioxane) and **13** (benzoxazole) were inactive, and another benzoxazole derivative (**14**) was almost inactive.

According to the hypothetical superimpositional model of 20E and BTBH analogues, the B-ring of RH-5992 was modified. Although several derivatives showed good insecticidal activity, they were less active than RH-5992, indicating that the superimpositional model did not work very well for this B-ring modification. Most structure-activity relationship studies on 20E and its derivatives suggested that there are three important regions, 2,3-$(OH)_2$ (X region), 6-keto-7-ene and 14α-OH (Y region), and 22-OH of the side chain (Z region).[6,11] The BTBH analogues and 20E have very different structures and can be superimposed on each other in a number of ways. For example, Qian[12] performed molecular modeling studies on the similarity between the three-dimensional structures of BTBH and 20E, and proposed a model in which the *tert*-butyl group of RH-5849 was superimposed on the C20 of 20E. On the other hand, Nakagawa *et al.*[13] analyzed SAR using CoMFA and proposed a model in which the A-ring (B-ring/Nakagawa) and two carbonyl oxygens of RH-5849 correspond to the 20 and 22-OH oxygens on the side chain of 20E. Other A-ring modifications based on the model are still under study.

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要　　約

N-tert-Butyl-*N′*-(4-ethylbenzoyl)-3,5-dimethylbenzohydrazide の 3,5-dimethylbenzoyl 部分を変換した誘導体の合成と殺虫活性

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横井進二，柳　幹夫，渡部哲夫

20-ヒドロキシエクダイソンテンプレートとの平面構造の重ね合わせモデルから，エクダイソンアゴニストである *N′*-benzoyl-*N-tert*-butylbenzohydrazide 類のひとつ RH-5992 の 3,5-dimethylbenzoyl 部分を変換した化合物を合成し，そのハスモンヨトウ 3 齢幼虫に対する殺虫活性を調べた．3,5-Dimethylbenzoyl 基のベンゼン環を還元したもの，3 位のメチル基を変換したものおよび 3, 4 位でヘテロ環を形成させたものをそれぞれ合成した．ベンゼン環の還元では還元が進むにつれて活性が低下消失した．3 位をフルオロメチル基やジフルオロメチル基としたものは比較的高い殺虫活性を保持したが，3 位のメチル基を酸化したものや，大きな置換基を導入したものの殺虫活性はほとんどなかった．3,5-dimethylbenzoyl 部分を含酸素縮合ヘテロ環へ変換した化合物は，ほとんど殺虫活性を示さなかった．