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Synthesis and Insecticidal Activities of Novel *N*-Sulfenyl-*N′*-*tert*-butyl-*N*,*N′*-diacylhydrazines. 1. *N*-Alkoxysulfenate Derivatives

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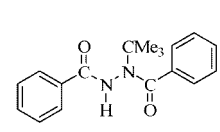
A series of novel *N*-alkoxysulfenyl-*N′*-*tert*-butyl-*N*,*N′*-diacylhydrazines were designed and synthesized as insect growth regulators by the key intermediates *N*-chlorosulfenyl-*N′*-*tert*-butyl-*N*,*N′*-diacylhydrazines, which were prepared for the first time. Compared to *N′*-*tert*-butyl-*N*,*N′*-diacylhydrazines, these *N*-alkoxysulfenyl derivatives displayed better solubility and improved hydrophobicities. The insecticidal activities of the new compounds were evaluated. The results of bioassays showed that the title compounds possessed a combination of strong stomach as well as contact poison property higher than the corresponding parent compounds. In particular, *N*-methoxysufenyl-*N′*-*tert*-butyl-*N*-4-ethylbenzoyl-*N′*-3,5-dimethylbenzoylhydrazide (**IIIf**) as a field testing candidate has higher stomach toxicities against oriental armyworm and beet armyworm than the corresponding parent compound **RH-5992**. Furthermore, the compound **IIIf** exhibits higher contact activities against oriental armyworm, Asian corn borer, tobacco cutworm, and cotton bollworm than **RH-5992**. The sulfenyl substituent was essential for high larvacidal activity.

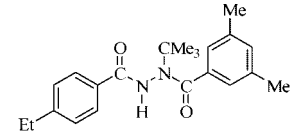
KEYWORDS: *N*-Sulfenate derivative; diacylhydrazine; RH-5992; stomach toxicity, contact toxicity; insecticidal activity; insect growth regulator

INTRODUCTION

Synthetic *N*-*tert*-butyl-*N*,*N*′-diacylhydrazines, discovered by Rohm and Haas Company in the mid-1980s, are a promising class of chemically and mechanistically novel insect control agents which have been found to work as nonsteroidal ecdysone agonists inducing, especially in *Lepidoptera*, precocious molting, leading to death (*1–5*). Among these compounds, *N*-*tert*-butyl-*N*,*N*′-dibenzoylhydrazine (**RH-5849**, **A**) was the first to be thoroughly investigated with regard to insecticidal effects and functional modes. *N*-*tert*-Butyl-*N*′−4-ethylbenzoyl-*N*-3,5-dimethylbenzoylhydrazide (tebufenozide; **RH-5992**, **B**) was the first to be commercialized as a leptidopteran-specific insecticide under the trade names Mimic, Confirm, and Romdan in several countries (*6, 7*). Because of the unique action mechanism, simple structure, low toxicity to vertebrates, and high insecticidal selectivity, diacylhydrazines have attracted considerable attention for decades (*8–12*). Recently, it has been reported that *N*′-benzoheterocyclecarbonyl-*N*-*tert*-butyl-3,5-dimethylbenzohydrazide analogues showed high insecticidal activities (*13–15*), of which **ANS-118** and **JS-118** represent successful examples. *N*′-*tert*-Butyl-*N*′-3,5-dimethylbenzoyl-*N*-5-methyl-6-chromanecarbohydrazide (Chromafenozide; **ANS-118**, **C**) has been commercialized as an insecticide under the trade name Matric (*16, 17*), and *N*′-*tert*-butyl-*N*′-(3,5-dimethylbenzoyl)-2,7-dimethyl-2,3-dihydrobenzofuran-6-carbohydrazide (**JS-118**, **D**) has been developing by the Jiangsu Institute of Agricultural Chemicals, P. R. China (*18, 19*).



A



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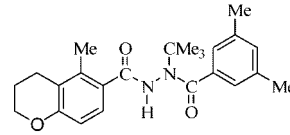

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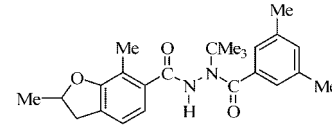

D

However, the preceding diacylhydraines have low solubility in water and limited solubility in common organic solvents.

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Scheme 1. General Synthetic Route for Compound **III**

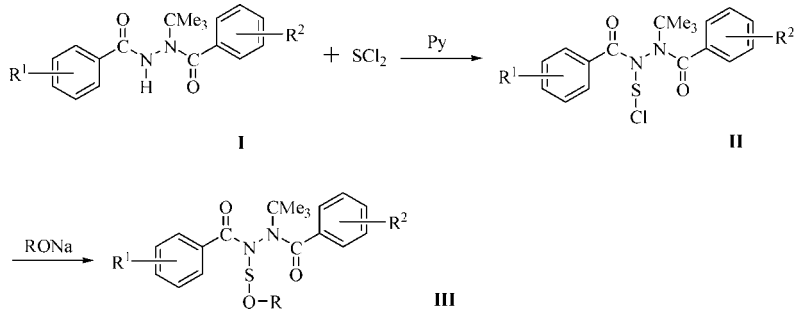


Table 1. Physical Properties and Elemental Analyses of the Compounds **IIIa–u**

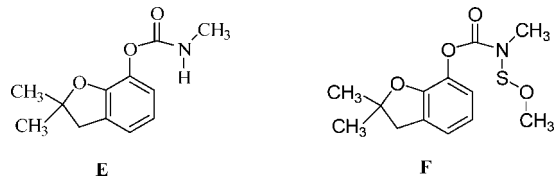
						elem anal. (%, calc)		
compd	R	R^1	R^2	mp (°C)	yield (%)	C	H	N
IIIa	methyl	H	H	122–125	29.6	63.38 (63.66)	6.13 (6.19)	7.90 (7.82)
IIIb	ethyl	H	H	oil	19.5	64.53 (64.49)	6.34 (6.49)	7.61 (7.52)
IIIc	*n*-propyl	H	H	oil	70.0	65.20 (65.26)	6.54 (6.78)	7.47 (7.25)
IIId	*i*-propyl	H	H	83–85	18.5	65.41 (65.26)	6.95 (6.78)	7.46 (7.25)
IIIe	*t*-butyl	H	H	126–128	45.3	66.07 (65.97)	6.93 (7.05)	7.26 (6.99)
IIIf	methyl	Et	3,5-Me_2	74–76	56.6	66.51 (66.64)	7.24 (7.29)	6.77 (6.76)
IIIg	ethyl	Et	3,5-Me_2	83–85	77.0	67.17 (67.26)	7.57 (7.53)	6.71 (6.54)
IIIh	*n*-propyl	Et	3,5-Me_2	oil	53.8	67.77 (67.84)	7.45 (7.74)	6.40 (6.33)
IIIi	*i*-propyl	Et	3,5-Me_2	91–93	72.2	67.88 (67.84)	7.72 (7.74)	6.49 (6.33)
IIIj	*n*-butyl	Et	3,5-Me_2	oil	29.7	68.20 (68.39)	7.80 (7.95)	5.99 (6.13)
IIIk	*i*-butyl	Et	3,5-Me_2	oil	50.7		479.2343 (479.2339)[a]	
IIIl	*t*-butyl	Et	3,5-Me_2	123–125	76.6	68.42 (68.39)	7.93 (7.95)	6.20 (6.13)
IIIm	*n*-pentyl	Et	3,5-Me_2	43–45	40.7	68.85 (68.90)	8.11 (8.14)	5.85 (5.95)
IIIn	*t*-pentyl	Et	3,5-Me_2	94–96	49.8	68.72 (68.90)	8.11 (8.14)	6.01 (5.95)
IIIo	benzyl	Et	3,5-Me_2	75–76	36.0	70.90 (70.99)	7.09 (6.98)	5.69 (5.71)
IIIp	2-phenethyl	Et	3,5-Me_2	90–92	43.7	71.61 (71.40)	7.07 (7.19)	5.58 (5.55)
IIIq	2-fluoroethyl	Et	3,5-Me_2	96–98	61.2	64.40 (64.55)	7.07 (7.00)	6.30 (6.27)
IIIr	2,2,2-trifluoroethyl	Et	3,5-Me_2	86–88	56.7	59.70 (59.74)	6.01 (6.06)	5.96 (5.81)
IIIs	2-methoxyethyl	Et	3,5-Me_2	77–79	46.3	65.31 (65.47)	7.38 (7.47)	6.18 (6.11)
IIIt	2-ethoxyethyl	Et	3,5-Me_2	oil	56.6		495.2292 (495.2288)[a]	
IIIu	methyl	*b*	3,5-Me_2	60–62	37.0	65.79 (65.76)	7.04 (7.06)	5.95 (6.14)

[a] The value of HRMS. [b] R^1 is identical to the corresponding substituents of the parent compound (**JS-118**).

Moreover, they have poor hydrophilicity and cuticular penetration; thus, they have low contact toxicity. These disadvantages impede their field application (*20–22*).

The activity spectrum of a pesticide is often determined by the physical properties of the compound, and it is possible to develop a new insecticide with improved biological properties by attaching an appropriate functional group to an insecticide. Moreover, the physical properties of an insecticidal compound may be manipulated to obtain products with other selected types of activity by proper selection of the derivatizing moiety (*22*, *23*). For example, the *N*-methoxysulfenyl derivative (**F**) of carbofuran displayed an insecticidal activity comparable to that of carbofuran (**E**) with a much lower mammalian toxicity (*24*, *25*).

Encouraged by these reports, we developed an idea that the



E **F**

introduction of an alkoxysulfenyl substituent into *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines by substituting the hydrogen on the *N*′ atom could improve biological properties and suffer shortcomings. Therefore, in a search for new insect growth regulators with improved profiles, we designed and synthesized a series of novel *N*-alkoxysulfenyl-*N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines (**III**) as shown in **Scheme 1**.

MATERIALS AND METHODS

Instruments. The title compounds were synthesized under a nitrogen atmosphere. ^{1}H NMR spectra were obtained at 300 MHz using a Bruker AV300 spectrometer or at 400 MHz using a Varian Mercury Plus400 spectrometer in $CDCl_3$ solution with tetramethylsilane as the internal standard. Chemical shift values (δ) were given in ppm. Elemental analyses were determined on a Yanaca CHN Corder MT-3 elemental analyzer. HRMS data was obtained on a FTICR-MS instrument (Ionspec 7.0T). The melting points were determined on an X-4 binocular microscope melting point apparatus (Beijing Tech Instruments Co., Beijing, China) and were uncorrected. Yields were not optimized.

General Synthesis. All anhydrous solvents were dried and purified by standard techniques just before use. *N*′-*tert*-Butyl-*N*,*N*′-diacylhydrazines (**I**) were synthesized by the literature method (*3*, *21*). Sulfur dichloride was prepared by the reaction of sulfur monochloride with chlorine (*26*). Pyridine was distilled over sodium hydroxide pellets and kept dry by storing over the same reagent.

General Synthetic Procedure for II. To a magnetically stirred and cooled (−20 °C) solution of sulfur dichloride (0.83 g, 8 mmol) in dichloromethane (15 mL) was added dropwise a solution of pyridine (0.63 g, 8 mmol) in dichloromethane (5 mL). After addition was complete, the reaction mixture was stirred below −15 °C for 15 min. Then, a solution of *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines (**I**) (7 mmol) in dichloromethane (5 mL) was added, and the resulting mixture was stirred at room temperature for 4 h. The solvent was removed in vacuo to afford a viscous residue, and then petroleum ether (60–90 °C (20 mL) was added. The mixture was stirred at −10 °C for 15 min and then filtered to remove the pyridinium chloride. The filtrate was directly used for the next step without further purification.

Table 2. ^{1}H NMR of Compounds **IIIa–u**

compd	δ (ppm)
IIIa	7.42–6.87 (m, 10H, Ph), 3.27 (s, 3H, OCH_3), 1.67 (s, 9H, $C(CH_3)_3$)
IIIb	7.45–6.78 (m, 10H, Ph), 3.48 (m, 1H, CH_2), 3.15 (m, 1H, CH_2), 1.60 (s, 9H, $C(CH_3)_3$), 0.84 (t, $^3J_{HH}$ = 7.6 Hz, 3H, CH_2CH_3)
IIIc	7.41–6.84 (m, 10H, Ph), 3.45 (m, 1H, OCH_2), 3.07 (m, 1H, OCH_2), 1.67 (d, 9H, $C(CH_3)_3$), 1.26 (m, 2H, CH_2CH_3), 0.66 (m, 3H, CH_2CH_3)
IIId	6.77–7.44 (m, 10H, Ph), 3.44–3.36 (m, 1H, CH), 1.68 (s, 9H, $C(CH_3)_3$), 1.04 (d, 3H, $^3J_{HH}$ = 6.0 Hz, $CH(CH_3)_2$), 0.63 (d, 3H, $^3J_{HH}$ = 6.0 Hz, $CH(CH_3)_2$)
IIIe	7.49–6.73 (m, 10H, Ph), 0.90 (s, 9H, $OC(CH_3)_3$), 1.68 (s, 9H, $NC(CH_3)_3$)
IIIf	7.26–6.85 (m, 7H, Ph), 3.31 (s, 3H, OCH_3), 2.63 (q, $^3J_{HH}$ = 7.6 Hz, 2H, $PhCH_2CH_3$), 2.24 (s, 6H, $Ph(CH_3)_2$), 1.65 (s, 9H, $C(CH_3)_3$), 1.20 (t, $^3J_{HH}$ = 7.6 Hz, 3H, $PhCH_2CH_3$)
IIIg	7.26–6.83 (m, 7H, Ph), 3.65–3.54 (m, 1H, OCH_2), 3.34–3.24 (m, 1H, OCH_2), 2.62 (q, 2H, $^3J_{HH}$ = 7.6 Hz, $PhCH_2CH_3$), 2.24 (s, 6H, $PH(CH_3)_2$), 1.65 (s, 9H, $C(CH_3)_3$), 1.20 (t, $^3J_{HH}$ = 7.6 Hz, 3H, $PhCH_2CH_3$), 0.92 (t, $^3J_{HH}$ = 7.0 Hz, 3H, OCH_2CH_3)
IIIh	7.26–6.83 (m, 7H, Ph), 3.54–3.44 (m, 1H, OCH_2), 3.19–3.09 (m, 1H, OCH_2), 2.62 (q, $^3J_{HH}$ = 7.6 Hz, 2H, $PhCH_2CH_3$), 2.24 (s, 6H, $Ph(CH_3)_2$), 1.65 (s, 9H, $C(CH_3)_3$), 1.33–1.22 (m, 2H, $CH_2CH_2CH_3$), 1.20 (t, 3H, $^3J_{HH}$ = 7.6 Hz, $PhCH_2CH_3$), 0.67 (t, 3H, $^3J_{HH}$ = 7.2 Hz, $CH_2CH_2CH_3$)
IIIi	7.26–6.79 (m, 7H, Ph), 3.52–3.40 (m, 1H, CH), 2.63 (q, $^3J_{HH}$ = 7.6 Hz, 2H, $PhCH_2CH_3$), 2.24 (s, 6H, $Ph(CH_3)_2$), 1.66 (s, 9H, $C(CH_3)_3$), 1.18 (t, $^3J_{HH}$ = 7.6 Hz, 3H, $PhCH_2CH_3$), 1.04 (d, $^3J_{HH}$ = 6.0 Hz, 3H, $CH(CH_3)_2$), 0.65 (d, $^3J_{HH}$ = 6.0 Hz, 3H, $CH(CH_3)_2$)
IIIj	7.25–6.83 (m, 7H, Ph), 3.58–3.47 (m, 1H, OCH_2), 3.21–3.10 (m, 1H, OCH_2), 2.63 (q, $^3J_{HH}$ = 7.6 Hz, 2H, $PhCH_2CH_3$), 2.24 (s, 6H, $PH(CH_3)_2$), 1.65 (s, 9H, $C(CH_3)_3$), 1.28–1.18 (m, 5H, $PhCH_2CH_3$ and $CH_2CH_2CH_2CH_3$), 1.15–1.02 (m, 2H, $CH_2CH_2CH_2CH_3$), 0.74 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_2(CH_2)_2CH_3$)
IIIk	7.08 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ph), 6.99 (s, 3H, Ph), 6.86 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ph), 3.34–3.23 (m, 1H, OCH_2), 2.99–2.89 (m, 1H, OCH_2), 2.63 (q, $^3J_{HH}$ = 7.5 Hz, 2H, $PhCH_2CH_3$), 2.25 (s, 6H, $Ph(CH_3)_2$), 1.66 (s, 9H, $C(CH_3)_3$), 1.53–1.42 (m, 1H, $CH_2CH(CH_3)_2$), 1.20 (t, $^3J_{HH}$ = 7.5 Hz, 3H, $PhCH_2CH_3$), 0.69 (d, $^3J_{HH}$ = 6.6 Hz, 3H, $CH_2CH(CH_3)_2$), 0.62 (d, $^3J_{HH}$ = 6.6 Hz, 3H, $CH_2CH(CH_3)_2$)
IIIl	7.26–6.74 (m, 7H, Ph), 2.62 (q, $^3J_{HH}$ = 7.6 Hz, 2H, $PhCH_2CH_3$), 2.19 (s, 6H, $Ph(CH_3)_2$), 1.67 (s, 9H, $NC(CH_3)_3$), 1.20 (t, 3H, $PhCH_2CH_3$), 0.91 (s, 9H, $OC(CH_3)_3$)
IIIm	7.08 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ph), 6.99 (s, 3H, Ph), 6.84 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ph), 3.59–3.46 (m, 1H, OCH_2), 3.22–3.10 (m, 1H, OCH_2), 2.63 (q, $^3J_{HH}$ = 7.5 Hz, 2H, $PhCH_2CH_3$), 2.25 (s, 6H, $Ph(CH_3)$), 1.66 (s, 9H, $C(CH_3)_3$), 1.34–0.96 (m, 9H, $PhCH_2CH_3$ and $CH_2(CH_2)_3CH_3$), 0.80 (t, $^3J_{HH}$ = 7.2 Hz, 3H, $CH_2(CH_2)_3CH_3$)
IIIn	7.10–6.67 (m, 7H, Ph), 2.63 (q, $^3J_{HH}$ = 7.5 Hz, 2H, $PhCH_2CH_3$), 2.20 (s, 6H, $Ph(CH_3)_3$), 1.67 (s, 9H, $C(CH_3)_3$), 1.31–1.10 (m, 5H, $PhCH_2CH_3$ and $C(CH_3)_2CH_2CH_3$), 0.86 (s, 3H, $C(CH_3)_2CH_2CH_3$), 0.78 (s, 3H, $C(CH_3)_2CH_2CH_3$), 0.70 (t, $^3J_{HH}$ = 7.5 Hz, 3H, $C(CH_3)_2CH_2CH_3$)
IIIo	7.28–7.19 (m, 3H, Ph), 7.12 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ph), 6.99 (s, 3H, Ph), 6.94–6.81 (m, 4H, Ph), 4.58 (d, $^2J_{HH}$ = 11.4 Hz, 1H, OCH_2), 4.09 (d, $^2J_{HH}$ = 11.4 Hz, 1H, OCH_2), 2.66 (q, $^3J_{HH}$ = 7.5 Hz, 2H, $PhCH_2CH_3$), 2.22 (s, 6H, $Ph(CH_3)_2$), 1.69 (s, 9H, $C(CH_3)_3$), 1.24 (t, $^3J_{HH}$ = 7.5 Hz, 3H, $PhCH_2CH_3$)
IIIp	7.24–6.79 (m, 12H, Ph), 3.80–3.67 (m, 1H, OCH_2), 3.44–3.32 (m, 1H, OCH_2), 2.70–2.52 (m, 4H, $PhCH_2CH_3$ and OCH_2CH_3), 2.24 (s, 6H, $Ph(CH_3)_3$), 1.60 (s, 9H, $C(CH_3)_3$), 1.20 (t, $^3J_{HH}$ = 7.5 Hz, 3H, $PhCH_2CH_3$)
IIIq	7.15–6.80 (m, 7H, Ph), 4.27 (t, $^3J_{HH}$ = 4.2 Hz, $^2J_{HF}$ = 47.4 Hz, 1H, FCH_2), 4.12 (t, $^3J_{HH}$ = 4.2 Hz, $^2J_{HF}$ = 47.4 Hz, 1H, FCH_2), 3.80–3.61 (m, 1H, OCH_2), 3.47–3.27 (m, 1H, OCH_2), 2.64 (q, $^3J_{HH}$ = 7.5 Hz, 2H, $PhCH_2CH_3$), 2.25 (s, 6H, $Ph(CH_3)_2$), 1.66 (s, 9H, $C(CH_3)_3$), 1.21 (t, J = 7.5 Hz, 3H, $PhCH_2CH_3$)
IIIr	7.18–6.84 (m, 7H, Ph), 3.79–3.60 (m, 1H, OCH_2), 3.44–3.26 (m, 1H, OCH_2), 2.65 (q, $^3J_{HH}$ = 7.5 Hz, 2H, $PhCH_2CH_3$), 2.26 (s, 6H, $Ph(CH_3)_2$), 1.64 (s, 9H, $C(CH_3)_3$), 1.21 (t, $^3J_{HH}$ = 7.5 Hz, 3H, $PhCH_2CH_3$)
IIIs	7.09 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ph), 6.99 (s, 3H, Ph), 6.85 (d, $^3J_{HH}$ = 7.8 Hz, 2H, Ph), 3.71–3.60 (m, 1H, $SOCH_2$), 3.34–3.24 (m, 1H, $SOCH_2$), 3.21 (s, 3H, OCH_3), 3.19 (t, $^3J_{HH}$ = 4.8 Hz, 2H, CH_3OCH_2), 2.63 (q, $^3J_{HH}$ = 7.5 Hz, 2H, $PhCH_2CH_3$), 2.25 (s, 6H, $Ph(CH_3)_2$), 1.66 (s, 9H, $C(CH_3)_3$), 1.20 (t, $^3J_{HH}$ = 7.5 Hz, 3H, $PhCH_2CH_3$)
IIIt	7.08 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ph), 6.99 (s, 3H, Ph), 6.86 (d, $^3J_{HH}$ = 8.1 Hz, 2H, Ph), 3.72–3.61 (m, 1H, $SOCH_2$), 3.39–3.27 (m, 3H, $SOCH_2$ and OCH_2CH_3), 3.23 (t, $^3J_{HH}$ = 7.5 Hz, 2H, $SOCH_2CH_2$), 2.63 (q, $^3J_{HH}$ = 7.5 Hz, 2H, $PhCH_2CH_3$), 2.24 (s, 6H, $Ph(CH_3)_2$), 1.66 (s, 9H, $C(CH_3)_3$), 1.20 (t, $^3J_{HH}$ = 7.5 Hz, 3H, $PhCH_2CH_3$), 1.10 (t, $^3J_{HH}$ = 6.9 Hz, 3H, OCH_2CH_3)
IIIu	7.11–6.70 (m, 5H, Ph), 4.95–4.81 (m, 1H, $PhOCH(CH_3)CH_2$), 3.32–3.21 (m, 4H, OCH_3 and $PhCH_2$), 2.81–2.72 (m, 1H, $PhCH_2$), 2.26 (s, 6H, $Ph(CH_3)_2$), 1.66 (s, 9H, $C(CH_3)_3$), 1.57 (s, 3H, $PhCH_3$), 1.42 (d, $^3J_{HH}$ = 6.4 Hz, 3H, $PhOCH(CH_3)CH_2$)

General Synthetic Procedure for the Target Compounds IIIa–u. To a suspension of sodium hydride (8 mmol) in anhydrous xylene (20 mL) was added dropwise alcohol at room temperature. The reaction mixture was warmed to about 70 °C, stirring was continued for 2 h, and the mixture was then cooled to −10 °C. The above filtrate of *N*-chlorosulfenyl diacylhydrazine (**II**) was added dropwise, the resulting mixture was stirred at room temperature for 4 h and filtered, and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on a silica gel using petroleum ether (60–90 °C) and ethyl acetate as the eluent to afford the title compounds **IIIa–u**.

Biological Assay. All bioassays were performed on representative test organisms reared in the laboratory. The bioassay was repeated at 25 ± 1 °C according to statistical requirements. Assessments were made on a dead/alive basis, and mortality rates were corrected using Abbott's formula (*27*). Evaluations are based on a percentage scale of 0–100 in which 0 = no activity and 100 = total kill.

Stomach Toxicity against Oriental Armyworm (*Mythimna separata*). The stomach toxicities of the title compounds **IIIa–u** and the parent compounds **I** against Oriental armyworm were evaluated by foliar application using the reported procedure (*22*, *28*, *29*). For the foliar armyworm tests, individual corn leaves were placed on moistened pieces of filter paper in Petri dishes. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with 10 fourth-instar Oriental armyworm larvae. Percentage mortalities were evaluated 4 days after treatment. Each treatment was performed three times. For comparative purposes, the parent compounds, **RH-5849**, **RH-5992**, and **JS-118**, were tested under the same conditions.

Table 3. Stomach Toxicities against Oriental Armyworm of Compounds **IIIa–u** and Parent Compounds

	larvicidal activity (%) at conc (mg kg^{-1})					
compd	100	50	25	10	5	2.5
IIIa		100	100	0		
IIIb	100	85	0			
IIIc		90	50	10		
IIId		100	100	10		
IIIe		100	100	10		
IIIf			100	100	100	**100**
IIIg		100	100	100	100	70
IIIh		100	100	100	90	**80**
IIIi		100	100	100	100	50
IIIj		100	100	100	100	**90**
IIIk					100	**80**
IIIl		100	100	100	70	60
IIIm					100	**100**
IIIn					80	70
IIIo					90	70
IIIp					90	50
IIIq					100	70
IIIr					100	**90**
IIIs					90	70
IIIt					100	**90**
IIIu						80
RH-5849		100	70	0		
RH-5992				100	95	**55**
JS-118					100	90

Table 4. Stomach Toxicities against Beet Armyworm of Compounds **IIIf** and **RH-5992**

				toxic ratio	
compd	$y = a + bx$	LC_{50} (mg/L)	LC_{90} (mg/L)	LC_{50}	LC_{90}
IIIf	$y = 3.6670 + 0.9614x$	24.354	524.29	3.4	5.1
RH-5992	$y = 3.3604 + 0.8534x$	83.420	2648.6	1	1

Table 5. Contact Toxicities against Oriental Armyworm of Compounds **IIIf** and **RH-5992**

	LD_{50}	LD_{90}		toxic ratio	
compd	(μg per larva)	(μg per larva)	$y = a + bx$	LD_{50}	LD_{90}
IIIf	0.0195	0.0479	$y = -0.899 + 3.271x$	141	154
RH-5992	0.0275	0.0739	$y = -0.813 + 2.976x$	100	100

Stomach Toxicity against Beet Armyworm (*Spodoptera exigua*). The stomach toxicities of the title compound **IIIf** and the corresponding parent compound **RH-5992** against beet armyworm were tested by the leaf-dip method using the reported procedure (*30, 31*). Leaf discs (5 cm × 3 cm) were cut from fresh cabbage leaves and then were dipped into the test solution for 3 s. After air-drying, the treated leaf discs were placed individually into boxes (80 cm^3). Each dried treated leaf disc was infested with five third-instar beet armyworm larvae. Percentage mortalities were evaluated 3 days after treatment. Leaves treated with water and acetone were provided as controls. Each treatment was performed three times. For comparative purposes, the parent compound, **RH-5992**, was tested under the same conditions.

Contact Toxicity against Oriental Armyworm (*Mythimna separata*). The contact toxicities of the title compound **IIIf** and the corresponding parent compound **RH-5992** against Oriental armyworm were tested by topical application using the reported procedure (*31, 32*). The compounds were dissolved in acetone to test at varying concentrations. For each fourth-instar larva of Oriental armyworm, 0.306 μL of tested dilution was applied on the thoracic tergite with a platinum loop. After treatment, the insects were then transferred to their standard rearing conditions. Mortalities were calculated 96 h after treatment, and LD_{50} and LD_{90} values were established. Each treatment was performed three times. Acetone alone served as a control, and **RH-5992** was used as a positive control sample.

Contact Toxicity against Tobacco Cutworm (*Spodoptera litura*), Asian Corn Borer (*Ostrinia furnacalis*), and Cotton Bollworm (*Helicoverpa armigera*). The contact toxicities of the title compound **IIIf** and the corresponding parent compound **RH-5992** against tobacco cutworm, Asian corn borer, and cotton bollworm were tested by topical application using the reported procedure (*31, 33, 34*). The compounds were dissolved in acetone to prepare five to seven concentrations. For each fourth-instar larva, 1 μL of tested dilution was applied on the thoracic tergite with an automatic microapplicator (Robbins Scientific, America). Acetone alone served as a control, and **RH-5992** was used as a positive control sample. Usually, 40 insects per dose were tested, and each treatment was replicated four times. After treatment, the insects were returned to their standard rearing conditions. Mortalities were calculated 48 h after treatment, and LD_{50} values (the median lethal dose) were established.

RESULTS AND DISCUSSION

Synthesis. *N*-Alkoxysulfenyl-*N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines **IIIa–u** were synthesized as shown in **Scheme 1**. *N*-Chlorosulfenyl-*N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines (**II**) were prepared for the first time by the reaction of sulfur dichloride with *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines (**I**) in the presence of pyridine. The key intermediates **II** without further purification were reacted with sodium alkoxy to give the title compounds **IIIa–u**. We found that the title compounds **III** have better solubility than the parent compound **I** in organic solvents such as methylene dichloride, chloroform, toluene, xylene, petroleum ether, etc., which should make them easier to apply in the field. Moreover, compared to the parent compounds **I**, the hydrophobicities of the title compounds **III** were obviously improved. The physical properties and elemental analyses of the title compounds **IIIa–u** are listed in **Table 1**, and their ^{1}H NMR data are listed in **Table 2**.

Bioassay. *Stomach Toxicity against Oriental Armyworm (Mythimna separata).* **Table 3** shows the stomach toxicities of *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines and their *N*-alkoxysulfeny derivatives **III** against oriental armyworm. The results indicate that the title compounds **III** have excellent stomach toxicities against oriental armyworm and that some of the title compounds **III** exhibit higher larvicidal activities than the corresponding parent compounds. For example, the larvicidal activities of **IIIa**, **IIId**, and **IIIe** were 100% at 25 mg kg^{-1}, whereas the corresponding parent compound **RH-5849** caused 70% mortality at this concentration; and the larvicidal activities of **IIIf**, **IIIh**, **IIIj**, **IIIk**, **IIIm**, **IIIr**, and **IIIt** at 2.5 mg kg^{-1} were 100%, 80%, 90%, 80%, 100%, 90%, and 90%, respectively, as compared with 55% mortality of the corresponding parent compound **RH-5992** at the same concentration. In particular, **IIIf** stood out as the best and was sent for advanced field testing. We found that

Table 6. Contact Toxicities against Asian Corn Borer, Tobacco Cutworm, and Cotton Bollworm of Compounds **IIIf** and **RH-5992**

	IIIf		**RH-5992**		
	y = a + bx	LD_{50}(ug/g)	y = a + bx	LD_{50}(ug/g)	toxic ratio
Asian corn borer	$y = 1.6368 + 2.0348x$	44.961	$y = 3.1305 + 1.0539x$	59.414	1.6
tobacco cutworm	$y = 2.4481 + 2.1164x$	16.061	$y = 1.5124 + 1.2813x$	527.12	**32.8**
cotton bollworm	$y = -1.8340 + 3.6571x$	73.907	$y = 0.2223 + 1.5321x$	1311.9	**17.8**

compound **IIIf** is highly active in the field, comparable to the case in laboratory tests, which will be the subject of a subsequent publication.

Stomach Toxicity against Beet Armyworm (Spodoptera exigua). **Table 4** shows the stomach toxicities of the field testing candidate **IIIf** and the corresponding parent compound **RH-5992** against beet armyworm. LC_{50} is the median lethal concentration, and LC_{90} is the lethal concentration at 90%. The results indicated that the stomach toxicity of **IIIf** against beet armyworm was 3.4-fold higher than that of **RH-5992** from the value of LC_{50} and 5.1-fold higher from the value of LC_{90}.

The results of the stomach toxicities of the title compounds **III** against oriental armyworm and beet armyworm implied that the introduction of the *N*-alkoxysulfenate was essential for the larvacidal activity, and the changes in physical properties might account for the improvement of larvicidal activities.

Contact Toxicity against Oriental Armyworm (Mythimna separata). **Table 5** shows the contact toxicities of the field testing candidate **IIIf** and the corresponding parent compound **RH-5992** against oriental armyworm. The results indicated that **IIIf** has higher contact activity than **RH-5992**.

Contact Toxicity against Tobacco Cutworm (Spodoptera litura), Asian Corn Borer (Ostrinia furnacalis), and Cotton Bollworm (Helicoverpa armigera). **Table 6** shows the contact toxicities of the field testing candidate **IIIf** and the corresponding parent compound **RH-5992** against Asian corn borer, tobacco cutworm, and cotton bollworm. The results indicated that **IIIf** has higher contact activities than **RH-5992**, especially toward tobacco cutworm and cotton bollworm, 32.8 times and 17.8 times, respectively. This could be explained by the marked changes of the physical properties, particularly the decrease of the polarity and the increase of the lipophilicity, both of which lead to the enhancement of cuticular penetration and body assimilation.

In summary, a series of novel *N*-alkoxysulfenyl-*N*′-*tert*-butyl-*N*,*N*′-dyacylhydrazines were designed and synthesized as insect growth regulators from the key intermediates *N*-chlorosulfenyl-*N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines, which were prepared for the first time. Compared to *N*′-*tert*-butyl-*N*,*N*′-diacylhydrazines, these *N*-alkoxysulfeny derivatives displayed better solubility and improved hydrophobicities. The results of bioassays showed that the title compounds possessed a combination of strong stomach as well as contact poison properties higher than those of the corresponding parent compounds. In particular, *N*-methoxysufenyl-*N*′-*tert*-butyl-*N*-4-ethylbenzoyl-*N*′-3,5-dimethylbenzoylhydrazide (**IIIf**) as a field testing candidate has higher stomach toxicities against oriental armyworm and beet armyworm than the corresponding parent compound **RH-5992**. Furthermore, the compound **IIIf** exhibits higher contact activities against oriental armyworm, Asian corn borer, tobacco cutworm, and cotton bollworm than **RH-5992**. The sulfenyl substituent was essential for highlarvacidal activity.

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