JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Synthesis and Antifeedant Activity of New Oxadiazolyl 3(2*H*)-Pyridazinones

SONG CAO,[†,‡] XUHONG QIAN,*[,§] GONGHUA SONG,[†,‡] BING CHAI,[†,‡] AND ZHISHENG JIANG[||]

Institute of Pesticides and Pharmaceuticals, East China University of Science and Technology, P.O. Box 544, 130 Meilong Road, Shanghai 200237, P. R. China, State Key Laboratory of Fine Chemicals, Dalian University of Technology, Dalian 116012, P. R. China, Institute of Elemento-Organic Chemistry, Nankai University, Tianjing 300071, P. R. China, and Shanghai Key Laboratory of Chemical Biology, Shanghai 200237, P. R. China

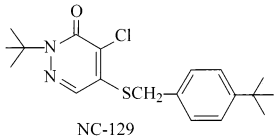
A total of 20 new compounds containing the oxadiazolyl 3(2*H*)-pyridazinone moiety were synthesized. The structures of all the compounds were confirmed by ^{1}H NMR, IR, MS, and elemental analysis. Their insect antifeedant activities against Asiatic corn borer *Ostrinia furnacalis* (Guenee) were examined and compared with commercial azadirachtin. The compounds exhibited significant levels of activity. The feeding deterrency values of **IIIa,j** were 57% and 51% at 500 mg/kg concentration, respectively.

KEYWORDS: Syntheses; oxadiazolyl 3(2*H*)-pyridazinones; antifeedant activity

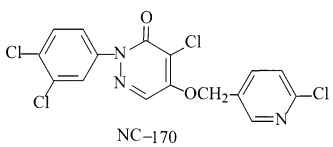
INTRODUCTION

2,5-Disubstituted-1,3,4-oxadiazoles were shown to inhibit chitin synthesis in *Drosophila* and *Musca domestica* both in vitro and in vivo studies (*1*). But those compounds' limited solubility in polar solvents made them commercially unattractive (*2*−*4*). Our group has always been interested in synthetic work for new 1,3,4-oxadiazoles, and we have concentrated on the promotion of solubility of 1,3,4-oxadiazoles and their insecticidal activity. Some new oxadiazoles which we have synthesized showed good improved solubility and insecticidal activity. Quantitative structure−activity relationships indicated that the introduction of a group that increases the value of the lipophilicity would improve the insecticidal activity of oxadiazole (*5*−*7*).

Pyridazinones have been used in numerous applications in the fungal, weed, and insect control sectors of agriculture. Four commercial products for insect control, NC-129, NC-170, NC-184, and NC-196, were developed from this series (*8*). For



NC-129



NC−170

example, NC-129 is a new acaricide which provides excellent control of mites and some insects including whiteflies, aphids, and thrips (*9*); NC-170 is a highly selective juvenoid, and it strongly inhibits metamorphosis in planthopper when topically applied to midpenultimate larvae (*10*). In this paper, we attached the oxadiazolyl moiety to 3(2*H*)-pyridazinones to enhance the solubility of the 1,3,4-oxadiazoles in polar solvents and hopefully improve the activity of the new pyridazinones (**Scheme 2**). A total of 20 new oxadiazolyl 3(2*H*)-pyridazinones were synthesized. The bioassay tests show that some compounds exhibited good antifeedant activity on the Asiatic corn borer *Ostrinia furnacalis* (Guenee). The feeding deterrency of **IIIa** was 57% at 500 mg/kg.

MATERIALS AND METHODS

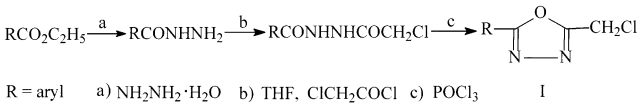
Experimental Chemistry. All melting points (mp) were obtained with an electrothermal digital apparatus made in Shanghai, P. R. China, and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WP-500SY (500 MHz) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (ppm) values. Infrared spectra were measured on a Nicolet FT-IR-20SX instrument using a potassium bromide (KBr) disk, scanning from 625 to 4000 cm^{-1}. Mass spectra were recorded under electron-impact (70 eV) condition using a Hitachi M80 instrument. Combustion analyses for elemental composition were made with an Italian MOD.1106 analyzer. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F_{254}), and spots were visualized with ultraviolet light.

Synthesis. From different starting esters, monoacylhydrazines, *N*,*N*′-diacylhydrazines, and asymmetrical 2,5-disubstituted-1,3,4-oxadiazoles were prepared (**Scheme 1**). All the key intermediate 5-aryl-2-(chloromethyl)-1,3,4-oxadiazoles (**I**) were prepared by the cyclodehydration of *N*-(chloroacetyl)-*N*′- aroylhydrazines in boiling $POCl_3$ (*11*). The final compounds have been obtained by O- and S-alkylation of 2-*tert*-butyl-

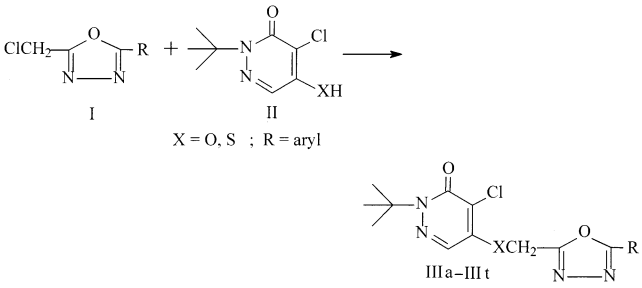
* To whom correspondence should be addressed. E-mail: xhqian@ecust.edu.cn; xhqian@dlut.edu.cn.
[†] East China University of Science and Technology.
[‡] Shanghai Key Laboratory of Chemical Biology.
[§] Dalian University of Technology.
[||] Nankai University.

10.1021/jf0208029 CCC: $25.00
Published on Web 12/07/2002

Scheme 1. General Synthetic Route for 5-Aryl-2-(chloromethyl)-1,3,4-oxadiazoles (**I**)



Scheme 2. General Synthetic Route for the Final Compounds **IIIa**–**t**



4-chloro-5-hydroxy (or mercapto)-3(2*H*)-pyridazinones (**II**) with 5-aryl-2-(chloromethyl)-1,3,4-oxadiazoles (**I**) at 80 °C in the presence of a phase transfer catalyst (TBAB, tetrabutylammonium bromide) and powdered K_2CO_3 in DMF (**Scheme 2**). It is a convenient and useful method for the preparation of the title compounds.

Bioassays. The neem extracts "Azadirachtin", an enriched and formulated product (containing 3 mg of azadirachtin mL^{-1}) extracted from ground neem seed kernels, was obtained from Yunnan Chemical Ind. Ltd. (Kunming, P. R. China). Compounds **IIIa**−**t** were compared with Azadirachtin using a feeding bioassay. All the compounds were tested using fifth-instar larvae of the Asiatic corn borer *Ostrinia furnacalis* (Guenee). The newly moulted fifth instar larvae were maintained on artificial diet containing the test compounds, with untreated diet as control (*12*).

Dite-Choice Test. Certain amounts of pure **IIIa,e-l** and Azadirachtin (3 mg of azadirachtin mL^{-1}) were dissolved in acetone and added to the ingredients of the diet prior to preparation. All compounds were tested with diets containing 500 mg/kg **IIIa,e**−**l** and Azadirachtin. Five replicates were prepared for this concentration with 10 fifth-instar larvae in each replicate. Control diets were prepared in a similar way but with only solvent. After 24 h, the deterrency index (%) for each treatment was calculated as the following:

$$\text{deterrency index (\%)} = [(C - T)/(C + T)] \times 100$$

Here C and T are the amounts of control and treated diets eaten, respectively.

Effect on Growth of Larvaes. The effect of compounds on weight gain was further assessed using fifth-instar larvae with a diet-choice test. Treated and untreated diets were prepared as previously described. Three concentrations of **IIIa,j** and Azadirachtin were selected. Batches of 10 of the larvae of Asiatic corn borer which had been starved for 4−6 h and weighed were then applied to each diet. Each batch of larvae was reweighed after 5 days. Controls were treated as above, and each treatment was replicated five times.

Synthesis of 2-*tert*-Butyl-4-chloro-5-hydroxy-3(2*H*)-pyridazinone (13, 14). A mixture of 2-*tert*-butyl-4,5-dichloro-3(2*H*)-pyridazinone (5 mmol), KOH (15 mmol), and glycol (20 mL) was stirred at 130 °C for 5 h. After cooling, it was poured into water, acidified with concentrated HCl (10 mL). The white solid was collected, washed, and dried (yield 92%), mp 218−220 °C.

Synthesis of 2-*tert*-Butyl-4-chloro-5-mercapto-3(2*H*)-pyridazinone. To a stirred solution of 2-*tert*-butyl-4,5-dichloro-3(2*H*)-pyridazinone (5 mmol) in ethanol (20 mL) at 0 °C was added dropwise NaSH (30%, 10 mmol). After the addition was completed, the reaction mixture was stirred for 2 h. The mixture was acidified with concentrated HCl (10 mL). The yellow solid was collected, washed, and dried (yield 90%), mp 112−113 °C.

General Synthetic Procedure for 5-Aryl-2-(chloromethyl)-1,3,4-oxadiazoles (I). The mixture of the *N*-chloroacetyl-*N*′-aroylhydrazine (5 mmol) and $POCl_3$ (10 mL) was refluxed for 3 h. After being cooled to room temperature, it was poured slowly into an ice and water mixture. The resulting precipitate was filtered out, washed, dried, and recrystallized from ethanol to produce the pure oxadiazole **I** (*11*). ^{1}H NMR, MS, and mp for the typical compounds: 5-(4-chlorophenyl)-2-(chloromethyl)-1,3,4-oxadiazole, δ 4.78 (s, 2H, CH_2), 7.50 (d, 2H, Ar H), 8.04 (d, 2H, Ar H), MS m/z = 228 (M^+, 23), 139 (100), mp 81−82 °C; 5-(4-dichloro-5-fluorophenyl)-2-(chloromethyl)-1,3,4-oxadiazole, δ 4.80 (s, 2H, CH_2), 7.65 (d, 1H, Ar H), 7.87 (d, 1H, Ar H), MS m/z = 280 (M^+, 16), 191(100), mp 100−101 °C; 5-(3,5-dimethylphenyl)-2-(chloromethyl)-1,3,4-oxadiazole, δ 2.41 (s, 6H, $2CH_3$), 4.78 (s, 2H, CH_2), 7.19 (s, 1H, Ar H), 7.70 (d, 2H, Ar H), MS m/z = 222 (M^+, 27), 133 (100), mp 79−80 °C.

General Synthetic Procedure for 2-*tert*-Butyl-4-chloro-5-[5′-aryl-2′-(1′,3′,4′-oxdiazolyl)methoxy (or methylmercapto)]-3(2*H*)-pyridazinones (IIIa−t). A mixture of 2-*tert*-butyl-4-chloro-5-hydroxy (or mercapto)-3(2*H*)-pyridazinone (**II**) (2.5 mmol), anhydrous potassium carbonate (8 mmol), tetrabutylammonium bromide (0.2 mmol), and dry DMF (5 mL) was stirred at 90 °C (X = O) or 40 °C (X = S) for 0.5 h. To the mixture was added 5-aryl-2-(chloromethyl)-1,3,4-oxadiazole (**I**) (2.5 mmol) and dry DMF (5 mL). The reaction mixture was stirred at 90 °C (X = O) or 40 °C (X = S) for 2−4 h. After cooling, the mixture was treated with water (30 mL) and extracted with chloroform (3 × 15 mL). The organic layer was washed with water, dried over $MgSO_4$, and concentrated. The residue was chromatographed over a column of silica gel and eluted with petroleum ether (60−90 °C)−ethyl acetate = 2:1 (v/v). The desired product was determined by TLC. The preparative and spectral data of **IIIa**−**t** are listed in **Table 1** *Data for* **IIIa***:* ^{1}H NMR δ 1.65 (s, 9H, $(CH_3)_3C$), 5.55 (s, 2H, CH_2), 7.97 (s, 1H, Py H), 7.54 (m, 3H, Ar H), 8.08 (d, 2H, Ar H); IR (KBr, cm^{-1}) ν 1650 (C═O); MS m/z = 361 ($[M + 1]^+$, 12), 325 (20), 304 (40), 268 (37), 159 (71), 105 (100). Anal. Calcd for $C_{17}H_{17}ClN_4O_3$: C, 56.59; H, 4.75; N, 15.52. Found: C, 56.46; H, 4.72; N, 15.66.

Data for **IIIb***:* ^{1}H NMR δ 1.65 (s, 9H, $(CH_3)_3C$), 5.58 (s, 2H, CH_2), 7.96 (s, 1H, Py H), 8.29 (d, 2H, Ar H), 8.42 (d, 2H, Ar H); IR (KBr, cm^{-1}) ν 1660 (C═O); MS m/z = 406 ($[M + 1]^+$, 24), 350 (51), 150 (87), 56 (100), 41 (54). Anal. Calcd for $C_{17}H_{16}ClN_5O_5$: C, 50.32; H, 3.97; N, 17.26. Found: C, 50.02; H, 4.13; N, 17.62.

Data for **IIIc***:* ^{1}H NMR δ 1.65 (s, 9H, $(CH_3)_3C$), 2.45 (s, 3H, CH_3), 5.55 (s, 2H, CH_2), 7.39−7.90 (m, 4H, Ar H), 7.98 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1630 (C═O); MS m/z = 374 (M^+, 13), 282 (12), 119 (100), 91 (40), 56 (34). Anal. Calcd for $C_{18}H_{19}ClN_4O_3$: C, 57.68; H, 5.11; N, 14.95. Found: C, 57.45; H, 5.11; N, 15.22.

Data for **IIId**: ^{1}H NMR δ 1.65 (s, 9H, $(CH_3)_3C$), 2.40 (s, 6H, $2CH_3$), 5.54 (s, 2H, CH_2), 7.20 (s, 1H, Ar H), 7.69 (s, 2H, Ar H), 7.98 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1630 (C═O); MS m/z = 388 (M^+, 2.5), 187 (13), 133 (100), 105 (24). Anal. Calcd for $C_{19}H_{21}ClN_4O_3$: C, 58.69; H, 5.44; N, 14.41. Found: C, 58.77; H, 5.48; N, 14.41.

Data for **IIIe***:* ^{1}H NMR δ 1.65 (s, 9H, $(CH_3)_3C$), 2.45 (s, 3H, CH_3), 5.53 (s, 2H, CH_2), 7.34 (d, 2H, Ar H), 7.97 (d, 2H, Ar H), 7.99 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1660 (C═O); MS m/z = 374 (M^+, 7), 282 (12), 282 (11), 173 (22), 119 (100), 91 (22), 56 (22). Anal. Calcd for $C_{18}H_{19}ClN_4O_3$: C, 57.68; H, 5.11; N, 14.95.

Found: C, 57.58; H, 5.04; N, 14.93.

Data for **IIIf***:* ^{1}H NMR δ 1.65 (s, 9H, $(CH_3)_3C$), 5.55 (s, 2H, CH_2), 7.23 (m, 2H, Ar H), 8.00 (s, 1H, Py H), 8.10 (m, 2H, Ar H); IR (KBr, cm^{-1}) ν 1670 (C═O); MS m/z = 379 ($[M + 1]^+$, 4), 321 (20), 177 (25), 123 (100), 57 (33). Anal. Calcd for $C_{17}H_{16}ClFN_4O_3$: C, 53.90; H, 4.26; N, 14.79. Found: C, 53.85; H, 4.15; N, 14.86.

Data for **IIIg***:* ^{1}H NMR δ 1.26−1.29 (t, 3H, CH_3), 1.64 (s, 9H, $(CH_3)_3C$), 2.74 (q, 2H, CH_2), 5.54 (s, 2H, CH_2), 7.35 (d, 2H, Ar H), 8.00 (d, 2H, Ar H), 7.98 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1640 (C═O); MS m/z = 389 ($[M + 1]^+$, 6), 297 (15), 187 (31), 133 (100), 77 (8), 56 (30). Anal. Calcd for $C_{19}H_{21}ClN_4O_3$: C, 58.69; H, 5.44; N, 14.41. Found: C, 58.66; H, 5.44; N, 14.47.

Data for **IIIh***:* ^{1}H NMR δ 1.65 (s, 9H, $(CH_3)_3C$), 5.55 (s, 2H, CH_2), 7.52 (d, 2H, Ar H), 8.02 (d, 2H, Ar H), 8.03 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1640 (C═O); MS m/z = 394 (M^+, 10), 336 (15), 303 (11), 193 (32), 140 (100), 57 (38). Anal. Calcd for $C_{17}H_{16}Cl_2N_4O_3$: C, 51.66; H, 4.08; N, 14.18. Found: C, 51.50; H, 3.95; N, 14.18.

Table 1. Experimental Data and Reaction Conditions for **IIIa–t**

compd	X	R	reacn time (h)	reacn temp (°C)	mp (°C)	yield (%)
IIIa	O	C_6H_5	3.5	85	187–188	71
IIIb	O	C_6H_4(4-NO_2)	3	80	215–216	64
IIIc	O	C_6H_4(3-CH_3)	3.5	85	146–147	64
IIId	O	C_6H_3[3,5-$(CH_3)_2$]	3.5	85	189–190	61
IIIe	O	C_6H_4(4-CH_3)	3.5	85	177–178	72
IIIf	O	C_6H_4(4-F)	3	85	159–160	70
IIIg	O	C_6H_4(4-C_2H_5)	3.5	85	157–158	72
IIIh	O	C_6H_4(4-Cl)	3	85	149–150	69
IIIi	O	C_6H_4(4-OCH_3)	4	90	165–167	74
IIIj	O	C_6H_4(3-F)	3	85	149–150	68
IIIk	O	C_6H_4(2-F)	3	85	167–168	65
IIIl	O	C_6H_4(2,4-di-Cl-5-F)	3	85	161–162	59
IIIm	S	C_6H_5	2	50	174–176	45
IIIn	S	C_6H_4(4-F)	1.5	45	122–123	50
IIIo	S	C_6H_4(3-F)	1.5	45	154–156	60
IIIp	S	C_6H_4(2-F)	1.5	45	148–149	63
IIIq	S	C_6H_4(4-Cl)	1.5	45	170–172	61
IIIr	S	C_6H_3[3,5-$(CH_3)_2$]	2	50	134–135	53
IIIs	S	C_6H_4(3-CH_3)	2	50	139–140	48
IIIt	S	C_6H_4(4-NO_2)	1.5	40	181–182	39

Data for **IIIi**: ^{1}H NMR δ 1.65 (s, 9H, $(CH_3)_3C$), 2.09 (s, 3H, CH_3O), 5.54 (s, 2H, CH_2), 7.02 (d, 2H, Ar H), 8.02 (d, 2H, Ar H), 8.03 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1640 (C=O); MS m/z = 390 (M^+, 8), 354 (7), 189 (26), 135 (100), 77 (4), 92 (4), 56 (12). Anal. Calcd for $C_{18}H_{19}ClN_4O_4$: C, 55.32; H, 4.90; N, 14.34. Found: C, 55.18; H, 5.04; N, 14.37.

Data for **IIIj**: ^{1}H NMR δ 1.66 (s, 9H, $(CH_3)_3C$), 5.56 (s, 2H, CH_2), 7.29−7.90 (m, 4H, Ar H), 7.97 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1640 (C=O); MS m/z = 378 (M^+, 34), 321 (57), 286 (32), 177 (66), 123 (100), 57 (45). Anal. Calcd for $C_{17}H_{16}ClFN_4O_3$: C, 53.90; H, 4.26; N, 14.79. Found: C, 53.70; H, 4.26; N, 15.00.

Data for **IIIk**: ^{1}H NMR δ 1.65 (s, 9H, $(CH_3)_3C$), 5.58 (s, 2H, CH_2), 7.26−8.09 (m, 4H, Ar H), 7.98 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1650 (C=O); MS m/z = 378 (M^+, 5), 321 (10), 286 (50), 177 (57), 123 (100), 57 (12). Anal. Calcd for $C_{17}H_{16}ClFN_4O_3$: C, 53.90; H, 4.26; N, 14.79. Found: C, 53.51; H, 4.34; N, 14.76.

Data for **IIIl**: ^{1}H NMR δ 1.65 (s, 9H, $(CH_3)_3C$), 5.59 (s, 2H, CH_2), 7.70 (d, 1H, Ar H), 7.88 (d, 1H, Ar H), 7.95 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1640 (C=O); MS m/z = 447 (M^+, 1), 392 (21), 245 (27), 191 (100), 57 (93), 41 (47). Anal. Calcd for $C_{17}H_{14}Cl_3FN_4O_3$: C, 45.61; H, 3.15; N, 12.52. Found: C, 45.63; H, 3.23; N, 12.63.

Data for **IIIm**: ^{1}H NMR δ 1.65 (s, 9H, $(CH_3)_3C$), 4.48 (s, 2H, CH_2), 7.51 (m, 3H, Ar H), 8.00 (s, 1H, Py H), 8.04 (d, 2H, Ar H); IR (KBr, cm^{-1}) ν 1670 (C=O); MS m/z = 376 (M^+, 4), 341 (25), 285 (100), 105 (20). Anal. Calcd for $C_{17}H_{17}ClN_4O_2S$: C 54.18; H 4.55; N 14.87. Found: C 54.49; H 4.72; N 15.06.

Data for **IIIn**: ^{1}H NMR δ 1.65 (s, 9H, $(CH_3)_3C$), 4.92 (s, 2H, CH_2), 7.36 (m, 2H, Ar H), 8.11 (m, 2H, Ar H), 8.21 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1670 (C=O); MS m/z = 394 (M^+, 4), 359 (25), 303 (100), 123 (30). Anal. Calcd for $C_{17}H_{16}ClFN_4O_2S$: C, 51.71; H, 4.08; N, 14.19. Found: C, 51.85; H, 4.15; N, 14.79.

Data for **IIIo**: ^{1}H NMR δ 1.58 (s, 9H, $(CH_3)_3C$), 4.41 (s, 2H, CH_2), 7.41−7.77 (m, 4H, Ar H), 7.92 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1680 (C=O); MS m/z = 394 (M^+, 6), 359 (28), 303 (100), 123 (26). Anal. Calcd for $C_{17}H_{16}ClFN_4O_2S$: C, 51.71; H, 4.08; N, 14.19. Found: C, 51.90; H, 4.26; N, 15.00.

Data for **IIIp**: ^{1}H NMR δ 1.64 (s, 9H, $(CH_3)_3C$), 4.47 (s, 2H, CH_2), 7.26−8.09 (m, 4H, Ar H), 7.98 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1630 (C=O); MS m/z = 394 (M^+, 5), 359 (30), 303 (100), 123 (24). Anal. Calcd for $C_{17}H_{16}ClFN_4O_2S$: C, 51.71; H, 4.08; N, 14.19. Found: C, 51.51; H, 4.34; N, 14.76.

Data for **IIIq**: ^{1}H NMR δ 1.64 (s, 9H, $(CH_3)_3C$), 4.47 (s, 2H, CH_2), 7.50 (d, 2H, Ar H), 7.98 (d, 2H, Ar H), 7.99 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1660 (C=O); MS m/z = 410 (M^+, 5), 375 (27), 319 (100), 139 (32). Anal. Calcd for $C_{17}H_{16}Cl_2N_4O_2S$: C, 49.64; H, 3.92; N, 13.62. Found: C, 49.50; H, 3.95; N, 13.88.

Data for **IIIr**: ^{1}H NMR δ 1.63 (s, 9H, $(CH_3)_3C$), 2.39 (s, 6H, $2CH_3$), 5.54 (s, 2H, CH_2), 7.27 (s, 1H, Ar H), 7.63 (s, 2H, Ar H), 8.23 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1670 (C=O); MS m/z = 404 (M^+, 2.5), 369 (20), 313 (100), 133 (25), 105 (14). Anal. Calcd for $C_{19}H_{21}ClN_4O_2S$: C, 56.36; H, 5.23; N, 13.84. Found: C, 56.77; H, 5.48; N, 13.41.

Data for **IIIs**: ^{1}H NMR δ 1.64 (s, 9H, $(CH_3)_3C$), 2.44 (s, 3H, CH_3), 4.47 (s, 2H, CH_2), 7.36−7.86 (m, 4H, Ar H), 8.00 (s, 1H, Py H); IR (KBr, cm^{-1}) ν 1650 (C=O); MS m/z = 390 (M^+, 13), 299 (100), 119 (16), 56 (10). Anal. Calcd for $C_{18}H_{19}ClN_4O_2S$: C, 55.31; H, 4.90; N, 14.33. Found: C, 55.64; H, 5.11; N, 14.73.

Data for **IIIt**: ^{1}H NMR δ 1.66 (s, 9H, $(CH_3)_3C$), 4.50 (s, 2H, CH_2), 7.99 (s, 1H, Py H), 8.14 (d, 2H, Ar H), 8.36 (d, 2H, Ar H); IR (KBr, cm^{-1}) ν 1640 (C=O); MS m/z = 421 (M^+, 24), 366 (51), 330 (100), 150 (20). Anal. Calcd for $C_{17}H_{16}ClN_5O_4S$: C, 48.40; H, 3.82; N, 16.60. Found: C, 48.68; H, 4.00; N, 16.90.

RESULTS AND DISCUSSION

Bioassay. Bioassay tests show that the growth and development of the fifth-instar larvae of the Asiatic corn borer fed with the treated diets was deterred and those compounds caused the formation of half-sized and sterile adults. Likewise, food intake and weight gain ceased dramatically as compared to controls. It can be deduced that the decrease in weight gain and feeding in the larva of Asiatic corn borer treated with **III** may result from ecdysonergic activity of the compound.

We examined the effects of the changes of gross structure on the biological activity. Antifeedent activities of compounds **IIIa,e−l** are shown in **Tables 2** and **3**. Of the other 11 compounds **IIIb−d,m−t**, the deterrency indexes were not determined as the compounds showed attenuated biological activity at concentrations as high as 500 mg/kg. Exchanging the phenyl ring in **IIIa** with the various substituent groups on benzene led to drastically diminishing activity. The activity of substituted compounds depended upon the types and positions of substitution. By comparison of the antifeedent activities of the compounds **IIIa,e−l** and Azadirachtin (**Table 2**), it was found that their activities against the Asiatic corn borer were in the following order: Azadirachtin > **IIIa** > **IIIj** > **IIIf** > **IIIh** > **IIIk** > **IIIg** > **IIIi** > **IIIl** > **IIIe**. **IIIa** and **IIIe** were the most and least active compounds against the Asiatic corn borer, respectively, and **IIIa** was almost as active as Azadirachtin at 500 mg/kg. **IIIa,j** and Azadirachtin (>10 mg/kg) significantly reduced weight gain by the Asiatic corn borer in choice-diet bioassays (**Table 3**). The substituent effects were not generalized except for the following aspects. The effects of electron-withdrawing substituents such as halogens were more favorable

Table 2. Feeding Deterrency of **IIIa,e–l** and Azadirachtin to the Asiatic Corn Borer in the Diet-Choice Bioassay[a]

	compd (500 mg/kg)				
	IIIa	**IIIe**	**IIIf**	**IIIg**	**IIIh**
av deterrency index (%)	57.61 ± 3.94	4.28 ± 3.35	51.08 ± 9.02	40.18 ± 8.04	46.73 ± 10.04

	compd (500 mg/kg)				
	IIIi	**IIIj**	**IIIk**	**IIIl**	Azadirachtin
av deterrency index (%)	38.45 ± 7.66	51.67 ± 9.03	41.34 ± 5.45	35.16 ± 7.82	59.90 ± 9.96

[a] Mean and SE of the percentage of larvae calculated from 5 replicates of an initial number of 10 larvae each. Means followed by the same letter in the same column are not significantly different ($P > 0.05$).

Table 3. Effect of **IIIa,j** and Azadirachtin on Weight Gain by Fifth-Instar Larvae of the Asiatic Corn Borer: Choice-Diet Bioassay

	mean wt gain (mg) (mean ± SE)[a]			
treament (mg/kg of diet)	control	**IIIa**	**IIIj**	Azadirachtin
5	43.3 ± 20.8	42.3 ± 17.9	38.4 ± 18.6	22.0 ± 16.4
10		16.2 ± 9.1	22.6 ± 11.9	7.8 ± 6.9
20		6.6 ± 5.6	8.7 ± 4.5	1.2 ± 0.1

[a] Mean and SE of the percentage of larvae calculated from 5 replicates of an initial number of 10 larvae each. Means followed by the same letter in the same column are not significantly different ($P > 0.05$).

to activity than those of electron-donating alkyl and alkoxy groups. For example, *m*-methyl (**IIIc**) or 3,5-dimethyl (**IIId**) substituents in the phenyl ring showed reduced activity at 500 mg/kg concentration, whereas **IIIj** and **IIIf** are more active. Bulkier electron-withdrawing groups such as NO_2 displayed unfavorable activity. Compounds **IIIm−t** were designed to probe the effect of replacing the oxo bridge ($-OCH_2-$ group) with a mercapto bridge ($-SCH_2-$ group). To our surprise, replacement of the oxo bridge by a mercapto bridge led to a loss of biological activity, suggesting that the oxo bridge is critical to activity.

CONCLUSIONS

We combined the bioactive units of oxadiazole and pyridazinone to design and synthesize novel oxadiazolyl 3(2*H*)-pyridazinones. In general, the oxadiazolyl 3(2*H*)-pyridazinone derivatives have increased lipophilicity relative to the 2,5-disubstituted-1,3,4-oxadiazoles and are soluble in most organic solvents (about 200 g/L, ethanol, 25 °C). The bioassay showed that the new compounds possess antifeedent activities against the Asiatic corn borer. The symptoms of toxicity included weight loss, cessation of feed, and developmentally premature specimens. Some of **III**'s activities seem to be only a little weaker than that of the natural antifeedent azadirachtin. The electron-withdrawing substituents on the benzene ring such as halogens were more favorable to activity. Now, there is much current interest in natural azadirachtin's use as a pesticide for its potent antifeedant and growth regulatory effects against insects (*15*, *16*). The synthesis of azadirachtin is now almost complete, but its production on a commercial scale would not be viable for such a complex molecule. Though some of the **III** compounds possess only modest biological activity, we hope to find a potent simple structural antifeedant agent which can mimick the activity of the complex azadirachtin through structural modifications of our compounds.

LITERATURE CITED

(1) Cunn, B. M. Synthesis and activity of agrochemicals. Thesis, University of Central Florida, 1985.
(2) Dow Chemical Co. Oral insecticide for manure insect control. Jpn. Kokai Tokkyo Koho 8085506, 1980.
(3) Edwards, L. H. Insecticidal 5-thiocarbamoyl-1,3,4-oxadiazoles. U.S. Patent 4500539, 1985.
(4) Simmons, K. A.; Halling, B. P. 2-(2′-Nitrophenyl)-1,3,4-oxadiazoles. Synthesis and biological activity. *ACS Symp., Synth. Chem. Agrochem.* **1991**, *443*, 236−246.
(5) Qian, X.; Zhang R. Syntheses and Insecticidal Activities of Novel 2,5-Disubtituted-1,3,4-oxadizoles. *J. Chem. Technol. Biotechnol.* **1996**, *67*, 124−130.
(6) Shi, W.; Qian X.; Zhang R.; Song G. Synthesis and Quantitative Structure−Activity Relationships of New 2,5-Disubstituted-1,3,4-oxadiazoles. *J. Agric. Food Chem.* **2001**, *49*, 124−130.
(7) Shi, W.; Qian X.; Zhang R.; Song G. Syntheses and insecticidal activities of novel 2-fluorophenyl-5-aryl/cyclopropyl-1,3,4-oxadizoles. *J. Fluorine Chem.* **2000**, *106*, 173−179.
(8) Miyake, T.; Igarashi, S.; Ishii, S.; Ogura, T.; Haruyama, H. NC-196, a new systemic juvenile hormone mimic; its practical performance as a control agent of the brown plant-hopper, *Nilaparvata lugens. Brighton Crop Prot. Conf.-Pests Dis.* **1994**, (1), 59−66.
(9) Hirata, K.; Kudo, M.; Miyake, T.; Kawamura, Y.; Ogura, T. NC-129-a new acaricide. *Brighton Crop Prot. Conf.-Pests Dis.* **1988,** (1), 41−8.
(10) Miyake, T.; Haruyama H.; Ogura T.; Mitsui T.; Sakurai A. Effects of a new juvenile hormone mimic, NC-170, on metamorphosis and diapause of the small brown planthopper, *Laodelphax striatellus*. *J. Pestic. Sci.* (*Int. Ed*.) 1992, *17* (1), 75−82.
(11) Vakula, R. T.; Srinivasan R. V. 1,3,4-Oxa(thia)diazoles: Part VIII—Synthesis & Reactivity of 5-Aryl-2-chloromethyl-1,3,4-oxadiazoles. *Indian J. Chem.* 1973, *11*, 732−734.
(12) Xie, Y. S.; Fields, P. G.; Isman, M. B. Repellency and toxicity of azadirachtin and neem concentrates to three stored-product beetles. *J. Econ. Entomol.* **1995**, *88* (4), 1024−1031.
(13) Taniguchi, M.; Baba, M.; Ochiai, Y.; Hirose, M.; Hirata, K. Preparation of insecticidal pyridazinone derivatives. CA 1270830, 1990.
(14) Ogura, T.; Kawamura, Y.; Baba, M.; Ishii, S. Pyridazinone derivatives and their insecticidal, acaricidal, nematocidal and fungicidal compositions. EP 199281, 1986.
(15) Verkerk R. H. J.; Wright D. J. Biological Activity of Neem Seed Kernel Extracts and Synthetic Azadirachtin against Larvae of *Plutella xylostella* L. *Pestic. Sci.* **1993**, *37*, 83−91.
(16) Isman, M. B. Growth Inhibitory and Antifeedant Effects of Azadirachtin on Six Noctuids of Regional Economic Importance. *Pestic. Sci.* **1993**, *38*, 57−63.

Received for review July 23, 2002. Revised manuscript received September 30, 2002. Accepted October 2, 2002.

JF0208029