Pesticidal Activities of Some 3-Aryl-4-methylpyrazolo[3,4-*b*][1,5]benzodiazepines and 4-Aryl-2-imino-5-methyl-1,3-thiazino[4,5-*b*][1,5]benzodiazepines

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A number of 3-aryl-4-methylpyrazolo[3,4-*b*][1,5]benzodiazepines and 4-aryl-2-imino-5-methyl-1,3-thiazino[4,5-*b*][1,5]benzodiazepines have been synthesized from 3-(arylmethylene)-4-methyl-1,5-benzodiazepin-2-one by cyclocondensation with hydrazine hydrate and thiourea in basic medium, respectively. All of the compounds were evaluated for their insecticidal and fungistatic activities, and the results are compared with the standard insecticide Propoxure and the standard fungicide Maneb. Some structure–activity relationships are discussed on the basis of screening data.

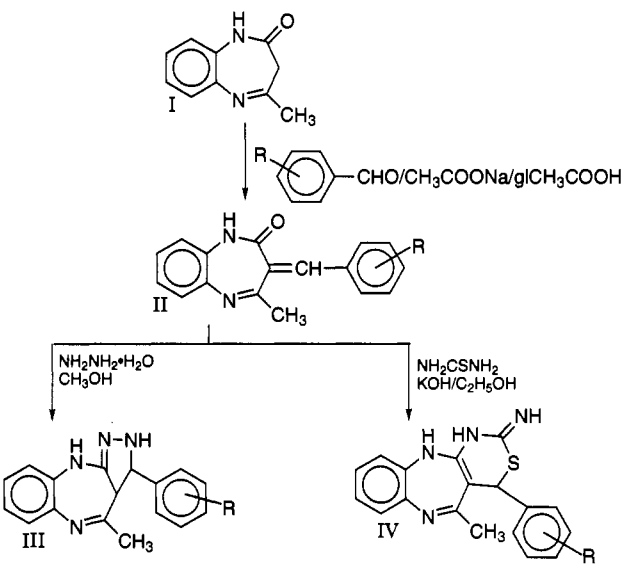
Keywords: *Pyrazolo[3,4-b][1,5]benzodiazepines; thiazino[4,5-b][1,5]benzodiazepines; insecticidal and fungistatic activities*

The medicinal value of benzodiazepines is well documented; for examples, sedative and transquilizing effects (Alhadeff, 1977; Tamura, 1981), antihypertensive effects (Atwal, 1987; Mendelson et al., 1982), and treatment for peptic ulcer (Feng et al., 1984). However, only a few reports have been found regarding the pesticidal properties of this ring; for example, 1,5-benzodiazepin-2-ones have been reported to have pesticidal properties (Clifford et al., 1976). Similarly 1,3-thiazine derivatives exhibit insecticidal (Hollowood et al., 1986), fungicidal (Khan and Giri, 1992), and anthelminthic (Canjolle et al., 1989) activities. Likewise, pyrazole derivatives exhibit herbicidal (Yanai and Honma, 1986) activity. In view of these findings and with the hope of achieving new compounds with enhanced biocidal activities, we decided to unite the 1,5-benzodiazepine nucleus with 1,3-thiazine and pyrazoline nuclei within a molecular framework for the possibility that the title compounds might have potential as insecticides and/or fungicides.

The reaction sequence leading to the formation of the title compounds is given in Scheme 1. The required 4-methyl-1,5-benzodiazepin-2-one (**I**) has been prepared (Kulkarni and Thakar, 1976). Condensation of **I** with aromatic aldehydes under Knoevenagal conditions furnished their corresponding arylmethylene benzodiazepinones (**II**). The cyclocondensation of these arylmethylenes with hydrazine hydrate or thiourea in basic medium furnished the title compounds **III** and **IV**, respectively.

The structural assignments of the synthesized compounds were based on elemental analyses, and IR, ^{1}H NMR, and mass spectral data (Tables 1 and 2).

Scheme 1



EXPERIMENTAL PROCEDURES

Melting points were determined in open glass capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer 157 spectrophotometer with a KBr disk (ν_{max} in cm^{-1}), ^{1}H NMR spectra were recorded on a Varian EM-360L (90 MHz) spectrometer (chemical shift in δ) in $CDCl_3$ and DMSO-d_6 using TMS as the internal reference, and mass spectra were recorded on a JEOL JMS-D 300 instrument.

4-Methyl-1,5-benzodiazepin-2-one (I). A mixture of *o*-phenylenediamine (0.1 M) and ethyl acetoacetate (0.1 M) in acidified methanol was refluxed for 3 h, cooled, and poured into water. The precipitated solid was filtered, washed, and recrystallized from aqueous ethanol; mp, 140 °C. The data for **I** agreed well with the analytical data already reported (Kulkarni and Thakar, 1976).

3-(Arylmethylene)-4-methyl-1,5-benzodiazepin-2-ones (IIa–g). A mixture of 4-methyl-1,5-benzodiazepin-2-one (0.01 M), an appropriate aromatic aldehyde (0.01 M), and anhydrous sodium acetate (0.012 M) was refluxed in glacial acetic acid for 3–4 h. The reaction mixture was poured into cold water, and the precipitated mass was filtered, washed

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Table 1. Melting Points, Yield, Molecular Formulas, and Elemental Analyses of II, III, and IV

compd	mp (°C)	yield (%)[a]	mol formula	found (%) (calcd) C	H	N
IIa	64–65	81	$C_{17}H_{14}N_2O$	77.80 (77.86)	5.24 (5.34)	10.82 (10.69)
IIb	55–56	69	$C_{17}H_{13}N_2OCl$	68.92 (68.80)	4.31 (4.38)	9.59 (9.44)
IIc	96–97	73	$C_{17}H_{13}N_2OCl$	68.94 (68.80)	4.49 (4.38)	9.56 (9.44)
IId	59–60	65	$C_{17}H_{12}N_2OCl_2$	61.76 (61.63)	3.72 (3.63)	8.54 (8.46)
IIe	59–62	65	$C_{19}H_{19}N_3O$	74.89 (74.75)	6.15 (6.23)	13.84 (13.77)
IIf	155	70	$C_{18}H_{16}N_2O$	78.20 (78.26)	5.71 (5.80)	10.01 (10.14)
IIg	172–173	76	$C_{18}H_{16}N_2O_2$	73.83 (73.97)	5.40 (5.48)	9.51 (9.59)
IIIa	105–106	78	$C_{17}H_{16}N_4$	73.82 (73.90)	5.89 (5.80)	20.21 (20.29)
IIIb	74–75	69	$C_{17}H_{15}N_4Cl$	65.81 (65.70)	4.89 (4.83)	18.13 (18.03)
IIIc	152–153	68	$C_{17}H_{15}N_4Cl$	65.79 (65.70)	4.96 (4.83)	18.17 (18.03)
IIId	176	81	$C_{17}H_{14}N_4Cl_2$	59.19 (59.13)	4.17 (4.06)	16.11 (16.23)
IIIe	110–112	72	$C_{19}H_{21}N_5$	71.34 (71.47)	6.63 (6.58)	21.98 (21.94)
IIIf	97–98	70	$C_{18}H_{18}N_4$	74.36 (74.48)	6.13 (6.21)	19.44 (19.31)
IIIg	82–83	81	$C_{18}H_{18}N_4O$	70.50 (70.59)	5.81 (5.88)	18.39 (18.30)
IVa	101–102	76	$C_{18}H_{16}N_4S$	67.63 (67.50)	5.09 (5.0)	17.65 (17.50)
IVb	115	84	$C_{18}H_{15}N_4SCl$	60.80 (60.93)	4.30 (4.23)	15.94 (15.80)
IVc	169	80	$C_{18}H_{15}N_4SCl$	60.83 (60.93)	4.29 (4.23)	15.72 (15.80)
IVd	58–60	70	$C_{18}H_{14}N_4SCl_2$	55.67 (55.53)	3.69 (3.60)	14.31 (14.40)
IVe	180	73	$C_{20}H_{21}N_5S$	66.28 (66.12)	5.71 (5.78)	19.20 (19.28)
IVf	121	67	$C_{19}H_{18}N_4S$	68.33 (68.26)	5.30 (5.39)	16.63 (16.77)
IVg	163–164	77	$C_{19}H_{18}N_4OS$	65.31 (65.14)	5.19 (5.14)	16.10 (16.0)

[a] Reported percent yield for the condensation step only.

Table 2. Spectral Data of III and IV

compd	IR (KBr) (cm^{-1}) C=N	NH	^1H NMR (DMSO-d_6) (δ)	MS/M^+ (m/z)
IIIa	1620	3260	1.9 (s, 3H, CH_3), 7.1–7.8 (m, 9H, ArH), 9.3 (b, 2H, NH)	276
IIIb	1620	3270	1.9 (s, 3H, CH_3), 7.0–7.8 (m, 8H, Ar–H) 9.4 (b, 2H, NH)	310, 312
IIIc	1615	3260	2.0 (s, 3H, CH_3), 7.0–7.9 (m, 8H, Ar–H) 9.5 (b, 2H, NH)	310, 312
IIId	1615	3260	1.9 (s, 3H, CH_3), 7.0–7.8 (m, 7H, Ar-H) 9.3 (b, 2H, NH)	344, 346, 348
IIIe	1610	3265	1.8 (s, 3H, CH_3), 2.8 (s, 6H, 2 × CH_3), 7.0–7.8 (m, 8H, Ar-H), 9.5 (b, 2H, NH)	319
IIIf	1620	3270	2.0 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 7.1–7.8 (m, 8H, Ar-H), 9.3 (b, 2H, NH)	290
IIIg	1615	3255	1.9 (s, 3H, CH_3), 3.8 (s, 3H, OCH_3), 7.1–7.7 (m, 8H, Ar-H), 9.2 (b, 2H, NH)	306
IVa	1610, 1635	3280	1.9 (s, 3H, CH_3), 7.0–7.8 (m, 9H, Ar-H) 9.7 (b, 3H, NH)	320
IVb	1610, 1640	3295	1.8 (s, 3H, CH_3), 7.0–7.8 (m, 8H, Ar-H) 9.9 (b, 3H, NH)	354, 356
IVc	1615, 1635	3290	1.9 (s, 3H, CH_3), 7.1–7.9 (m, 8H, Ar-H) 9.8 (b, 3H, NH)	354, 356
IVd	1615, 1635	3285	1.7 (s, 3H, CH_3), 7.1–7.8 (m, 7H, Ar-H), 10.1 (b, 3H, NH)	388, 390, 392
IVe	1610, 1630	3270	2.0 (s, 3H, CH_3), 2.9 (s, 6H, 2 × CH_3) 7.0–7.7 (m, 8H, Ar-H), 10.0 (b, 3H, NH)	363
IVf	1610, 1635	3280	1.8 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 7.0–7.8 (m, 8H, Ar-H), 9.8 (b, 3H, NH)	334
IVg	1615, 1635	3285	1.9 (s, 3H, CH_3), 3.9 (s, 3H, OCH_3), 7.1–7.7 (m, 8H, Ar-H), 9.6 (b, 3H, NH)	350

with water, and recrystallized from aqueous ethanol. The compounds thus prepared and their analytical data are recorded in Table 1.

3-Aryl-4-methylpyrazolo[3,4-*b*][1,5]benzodiazepines (IIIa–g). A mixture of appropriate 3-arylmethylene-4-methyl-1,5-benzodiazepin-2-one (0.01 M) and hydrazine hydrate (0.012 M) in methanol was refluxed for 3 h, then cooled and poured into ice–water. The title compounds were filtered, washed, and recrystallized from aqueous ethanol. The compounds thus prepared and their analytical data are recorded in Tables 1 and 2.

4-Aryl-2-imino-5-methyl-1,3-thiazino[4,5-*b*][1,5]benzodiazepines (IVa–g). A mixture of appropriate 3-(arylmethylene)-4-methyl-1,5-benzodiazepin-2-one (0.01 M), thiourea (0.011 M), and KOH (0.012 M) in ethanol was refluxed for 4–5 h, then cooled, poured into water, and acidified with HCl. The precipitated title compounds were filtered, washed, and recrystallized from aqueous ethanol. The compounds thus prepared and their analytical data are recorded in Tables 1 and 2.

Biological Activity. *Insecticidal Activity.* The insecticidal activity of the test compounds was examined against two insects (i.e., *Spodoptera litura* and *Tetranychus utricae*) by the leaf dipping method at 500 ppm and is recorded in Table 3. The results were also compared with the insecticidal activity of the standard insecticide Propoxure, which was tested under similar conditions.

The leaf dipped method for lepidopterous insect *S. litura* consisted of applying the test compounds to detached cabbage leaves (5 × 5 cm) by dipping them in 500 ppm aqueous suspensions for 30 s. After air drying, the detached leaves were held in a polyethylene dish (9 cm diameter and 2.5 cm depth). Then, 10 second-instar larvae were placed on the leaves. The dish was kept at 25 ± 1 °C, 50–60% R.H., and 16L–8 D cycle. Two replicates were used, and mortality was assessed after 48 h.

The leaf dipped method for twospotted spider mites (*Tetranychus urticae*) consisted of infested the first two leaves of dwarf kidney bean (*Phaseolus vulgaris*) grown in a porous pot with 20 adult female spider mites. The leaves were cut into squares (3 × 3 cm) and dipped into a 500 ppm emulsion of each test compound. The test solution was prepared by diluting an emulsifiable mixture containing 30% of each compound (prepared by mixing a test compound, xylene, isopropyl alcohol, and polyoxyethylene alkylphenol at a ratio of 30:30:30:10, w/w) to the 500 ppm emulsion with water. Mite mortality on the cut leaves raised in a greenhouse at 25 °C was assessed after 48 h.

Fungistatic Activity. The fungistatic activity of the test compounds was examined against three test fungi (i.e., *Pyricularia oryzae*, *Pseudoperonospora cubensis*, and *Phytophthora infestans*) at 500 ppm on rice, cucumber, and tomato, respectively, and is recorded in Table 3. Plant seedlings were grown in plastic pots filled with soil containing some fertilizers (N, P, K). Each test chemical was dissolved in a small amount of acetone and diluted with water to obtain the desired concentration. To prepare the spore suspension, the standard potato-dextrose agar medium was used as a culture medium

Table 3. Biological Activity of III and IV

compd	insecticidal activity[a] at 500 ppm in		fungistatic activity[b] at 500 ppm in		
	S. litura	*T. urticae*	*P. oryzae*	*P. curbensis*	*P. infestans*
IIIa	−	+	1	2	2
IIIb	−	−	1	1	1
IIIc	+	++	3	2	5
IIId	+	+	2	1	2
IIIe	++	++	2	2	1
IIIf	−	−	1	1	2
IIIg	−	+	2	3	3
IVa	−	+	1	3	3
IVb	−	+	1	1	2
IVc	++	++	4	4	5
IVd	+	+	3	1	3
IVe	+	+	2	4	2
IVf	−	−	1	1	3
IVg	+	+	4	3	4
Propoxure	Δ	Δ			
Maneb	−	−	5	5	5

[a] Mortality (%) is indicated by the following symbols: (−) = 0−10%, (+) = 11−40%, (++) = 41.70%, (+++) = 71−90%, Δ = 9%. [b] Efficacy score: 1 = 0−29, 2 = 30−59, 3 = 60−79, 4 = 80−94, and 5 = 95−100% of control.

and the spores were harvested from a separately cultured fungus. The density of the spore suspension was determined with a hemocytometer, and the final concentration was adjusted to 1×10^5 per milliliter. Ten milliliters of the test mixture was sprayed onto the seedlings and, after 2 days, the seedlings were inoculated with spore suspension (10^5/mL) and kept in a greenhouse at 20−24 °C. A blank experiment was also performed with 10 mL of solution under similar conditions. Maneb was used as a standard fungicide for comparison.

The resultant efficacy of each test compound was estimated 7 days after inoculation. The inhibitory effect of fungicides was expressed by

$$\text{protective value (\%)} = 1 - \frac{A}{B} \times 100$$

where A represents the percentage of disease on the treated plants and B represents that on untreated plants.

RESULTS AND DISCUSSION

The insecticidal data of the tested compounds showed the effect of substitution on the phenyl group. With regard to the introduction of a halogen atom to the phenyl group, 4-position substitution developed higher insecticidal activity in **III** and **IV** than 2-position substitution, whereas 4-OCH_3 or 4-$N(CH_3)_2$ substitution reduced insecticidal activity. This result means that the activity is greatly influenced by the position and the kind of substituents.

The fungistatic data of the tested compounds showed that the thiazinobenzodiazepines are more effective than pyrazolinobenzodiazepines. The presence of polar groups (Cl or OCH_3) at the para position imparts more fungistatic activity than at the ortho position. However, their fungistatic activities are inferior to the standard fungicide Maneb tested under similar conditions.

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