J. Pesticide Sci. **14**, 241–243 (1989)

Note

Synthesis of Esters and Amides of 2, 3-Dimethyl-5-(substituted phenylaminocarbonyl)-6-Pyrazinecarboxylic Acid and Their Phytotoxicity

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(Received October 3, 1988)

INTRODUCTION

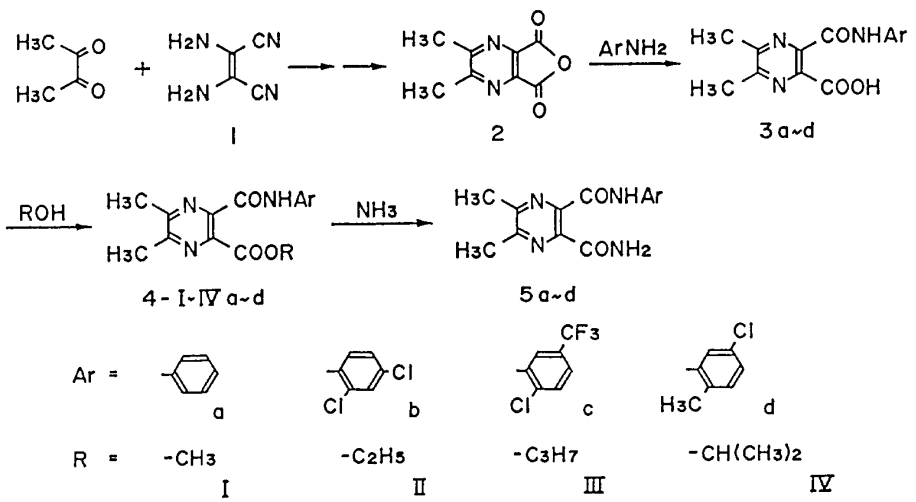
Since diaminomaleonitrile (DAMN) (**1**) was found, many useful heterocyclic compounds have been synthesized by using it. In our efforts to prepare valuable chemical compounds, we have synthesized about two hundred new pyrazine compounds starting from **1**,[1,2] among which some showed bacteriocidal and fungicidal activities,[1,2] but very few had herbicidal activity.

In the previous investigation,[2] we synthesized eighty-four 3-[(substituted phenylamino)carbonyl]-2-pyrazinecarboxylic acids and the same number of *N*-(substituted phenyl)pyrazine-2,3-dicarboximides, and examined their pesticidal activity. Some compounds in the latter chemical series showed bacteriocidal and fungicidal activities against rice bacterial leaf blight and rice blast, but the former series proved to be almost ineffective. In our more recent bioassay, 5-(4-chlorobenzyloxyphenylaminocarbonyl) - 6 - pyrazinecarboxylic acid[3] and 2-methyl-5-(4-chlorobenzyloxyphenylaminocarbonyl)- 6 -pyrazinecarboxylic acid[4] completely inhibited the germination of American millet seeds at 100 ppm. 2, 3-Dimethyl-5-(2-chloro-5-trifluoromethylphenylaminocarbonyl)-6-pyrazinecarboxylic acid (**3**-c)[5] and 2, 3-dimethyl-5-(2-methyl-5-chlorophenylaminocarbonyl)-6-pyrazinecarboxylic acid (**3**-d)[6] did not inhibit the germination itself, but killed the germ of Cos lettus and American millet at 100 ppm a few days after seeding. In the present investigation, we synthesized sixteen esters (methyl, ethyl, *n*-propyl and *i*-propyl) (**4**-I–IV-a–d) and four amides (**5**-a–d) of **3**-c, **3**-d and additional **3**-a and **3**-b with phenylaminocarbonyl and 2,4-dichloroaminocarbonyl moieties respectively, as shown in Scheme 1. The germination tests were aimed to examine the phytotoxic action of these compounds. The results are shown in Table 1.

EXPERIMENTAL

1. Chemicals

Methyl ester of 2,3-dimethyl-5-(2-methyl-5-chlorophenylaminocarbonyl) - 6 -pyrazinecarboxylic acid (**4**-I-d)[7]: To anhydrous methanol (100 ml)



Scheme 1 Synthesis of esters (**4**) and amides (**5**) of 2,3-dimethyl-5-(substituted phenylaminocarbonyl)-6-pyrazinecarboxylic acids.

Table 1 Inhibitory values (%) of esters and amides of 2,3-dimethyl-5-(substituted phenylaminocarbonyl)-6-pyrazinecarboxylic acids against Cos lettuce and American millet.

Compd. No.	Cos lettus				American millet			
	300	100	50	10	300	100	50	10
			(ppm)				(ppm)	
3-a	− 8	− 8			−10	− 8		
b	15	− 3			− 7	− 7		
c	51	35			31	25		
d	51	42			33	30		
4-I-a	25	17			6	0		
b	36	25			17	8		
c	8	0			3	0		
d	25	17			47	22		
4-II-a	14	11			19	17		
b	40	36			11	8		
c	28	6			6	0		
d	69	47	50	17	50	31	35	12
4-III-a	22	19			25	25		
b	14	6			31	33		
c	17	6			11	0		
d	42	36	30	8	39	31	17	17
4-IV-a	17	3			28	28		
b	42	11			25	11		
c	36	17			8	0		
d	69	48	35	25	36	33	18	17
5-a	8	3			0	− 3		
b	17	11			6	0		
c	25	25			11	14		
d	58	56	50	27	47	44	28	8

saturated with dry hydrogen chloride, 2,3-dimethyl-5-(2-methyl-5-chlorophenylaminocarbonyl)-6-pyrazinecarboxylic acid[2] (**3**-d, 3.0 g) was added and the mixture was stirred with passing of hydrogen chloride for 30 min under reflux. The reaction mixture was concentrated *in vacuo* and the residue was chilled overnight in a refrigerator and filtered off. Recrystallization of the product from methanol gave white needles (3.0 g, yield 95%). mp 227°C, MS *m/z*: 333 (M^+). Compounds **4**-I-a–c were prepared in a similar manner [mp°C, yield % and MS *m/z* (M^+) given]: **4**-I-a, 191–192, 84, 285; b, 277–278, 91, 387; c, 208–209, 95, 353.

Ethyl ester of 2,3-dimethyl-5-(2-methyl-5-chlorophenylaminocarbonyl)-6-pyrazinecarboxylic acid (**4**-II-d)[8,9] *and other esters*: 2,3-Dimethyl-5-(2-methyl-5-chlorophenylaminocarbonyl)-6-pyrazinecarboxylic acid (**3**-d) (2.0 g) was added to a solution of anhydrous ethanol (5 ml), toluene (2 ml) and conc. sulfuric acid (5 drops). The mixture was refluxed for about 2 hr with stirring to remove water by azeotropic distillation. After cooling the white precipitate was collected through filtration and purified by recrystallization from ethanol to give **4**-II-d (2.1 g, yield 96%). mp 181–183°C, MS *m/z*: 347 (M^+). Ethyl esters **4**-II-a–c, *n*-propyl esters **4**-III-a–d and isopropyl esters **4**-IV-a–d were prepared in a similar manner [mp°C, yield % and MS *m/z* (M^+) given]: **4**-II-a, 199–200, 95, 299; b, 192–193, 78, 401; c, 192–193, 88, 367. **4**-III-a, 161–162, 82, 313; b, 177–180, 75, 415; c, 179–180, 84, 381; d, 178–181, 76, 361; **4**-IV-a, 171–172, 23, 313; b, 169–172, 74, 415; c, 187–188, 71, 381; d, 182–183, 84, 361.

Amide of 2,3-dimethyl-5-(2-methyl-5-chlorophenylaminocarbonyl)-6-pyrazinecarboxylic acid (**5**-d)[7]: Methyl ester (**4**-I-d, 2 g) was dissolved in 100 ml of hot anhydrous methanol and refluxed for 30 min while gaseous ammonia was passing through. The mixture was kept in a refrigerator overnight and concentrated *in vacuo*. The white amorphous amide was filtered and recrystallized

from methanol to give **5**-d (1.0 g, yield 52%). mp 231–232°C, MS *m/z*: 318 (M^+). Amides **5**-a–c were prepared in a similar manner [mp °C, yield % and MS *m/z* (M^+) given]: **5**-a, 187–188, 59, 270; b, 220–223, 57, 372; c, 250–251, 83, 338.

2. Germination Tests

Four milligrams of a test chemical was weighed precisely and dissolved in acetone (10 ml). One milliliter of the acetone solution was poured into a Petri dish 9 cm in diameter, in which two sheets of filter papers had been placed at the bottom. After acetone had been evaporated, 30 seeds of Cos lettus (*Lactuea sativa* L. *longifolia Lams*) and 30 seeds of American millet (*Eleusine indica* Gaertner var. *coracana*) were seeded on the filter sheets and 4 ml of 100 ppm Tween-80 aqueous solution was poured into a Petri dish to afford a 100 ppm chemical solution. Two dishes were used for a test. Into another Petri dish prepared, 3 ml of the above-mentioned acetone solution was poured and worked up in a similar manner as above to afford a 300 ppm chemical solution. These Petri dishes were placed in a biotron at 25°C and 80% humidity under illumination for 12 hr a day. Five days after seeding, the plants were harvested and their fresh weights were measured. Inhibitory values (%) of test chemicals were evaluated according to the following equation.

$$\text{Inhibitory value (\%)} = \left(1 - \frac{\text{Fresh weight of treated plants}}{\text{Fresh weight of controlled plants}}\right) \times 100$$

To confirm the results at 100 and 300 ppm, the test was repeated at low concentrations of 50 ppm and 10 ppm for **4**-II-d, **4**-III-d, **4**-IV-d and **5**-d. The results are shown in Table 1.

RESULTS AND DISCUSSION

Ethyl ester (**4**-II-d) and amide (**5**-d) of 2,3-dimethyl-5-(2-methyl-5-chlorophenylaminocarbonyl)-6-pyrazinecarboxylic acid showed a considerable phytotoxic action against Cos lettus and American millet, as shown in Table 1. Both compounds at 100 ppm turned Cos lettus leaves from green to brown and stems to semitransparent, and the whole plants died three days after seeding. Four days after seeding, American millet completely stopped growing and died. The results were the same with **3**-d. Each compound at 50 ppm inhibited the growth of Cos lettus (50%), but the colors of the leaves and stems remained unchanged, while the germ of American millet grew unaffected at the same concentration. Other esters and amides of the pyrazinecarboxylic acid (**3**-d), however, failed to increase bioactivity.

The previous and present experimental data indicated that our attempts to obtain more effective herbicidal compounds simply by modifying substituent groups at phenyl and pyrazine skeltons were far from satisfactory. In succeeding investigations, therefore, our efforts are to be directed to design new-type compounds by introducing some other chemical groups, such as carbamate, diphenyl ether, dithiophosphate, urea, phenoxyfatty acid and triazine to the pyrazine moiety.

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3) See Ref. 2), Compound **3**-a-19.
4) See Ref. 2), Compound **3**-b-19.
5) See Ref. 2), Compound **3**-c-21.
6) See Ref. 2), Compound **3**-c-13.
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要　　約

2,3-ジメチル-5-(置換フェニルアミノカルボニル)-6-ピラジンカルボン酸のエステルおよびアミド類の合成と植物毒性

津田忠敬，保井宏之，上田博夫

ジアミノマレオニトリルを出発原料にして，2,3-ジメチル-5-(置換フェニルアミノカルボニル)-6-ピラジンカルボン酸を合成し，これを数種のエステルおよびアミドに変換し，植物毒性を調べた．その結果，発芽テストにおいて，2,3-ジメチル-5-(2-メチル-5-クロロフェニルアミノカルボニル)-6-ピラジンカルボン酸のエチルエステルおよびアミドが 50 ppm の濃度でコスレタスの成長を阻害した．