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REPELLENCY AND TOXICITY OF 2-ACETYLPYRIDINETHIO-SEMICARBAZONES AND RELATED CHEMICALS TO WILD BIRDS

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ABSTRACT

Twenty-five chemicals active as, or related to, 2-acetylpyridine thiosemicarbazones were investigated for their repellency and toxicity to red-winged blackbirds (Agelaius phoeniceus) and toxicity to starlings (Sturnus vulgaris). Two chemicals (1-azetidinecarbothioic acid (1-(2-pyridinyl)ethylidene)hydrazide and 1-pyrrolidinecarbothioic acid (1-(2-pyridinyl)ethylidene)hydrazide) were about twice as repellent to redwings and from 1/2 to 1/3 as toxic as methiocarb, the most effective bird repellent currently registered in the United States. The repellency of a third chemical, methyl (1-(2-pyridinyl)ethylidene)hydrazinecarbodithioate, was similar to that of methiocarb but it was almost 100 times less toxic to redwings than methiocarb and was 20 to 50 times less toxic than related thiosemicarbazones. Twenty-two other chemicals were not effective repellents or toxicants for redwings or toxicants for starlings.

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INTRODUCTION

In 1979, the U.S. Department of Agriculture (USDA) and the U.S. Department of Interior began a cooperative program to evaluate the repellent and toxic effects of various natural plant products or extracts on wild birds[1]. Recently, this program was extended to include various biologically active, synthetically produced chemicals, including 2-acetylpyridine thiosemicarbazones. Certain of these 2-acetylpyridine thiosemicarbazones are insect molt inhibitors[2,3] and antimalarial agents[4,5]. We conducted avian repellency and toxicity tests with a series of these and related chemicals and described some of their structure-activity relationships.

METHODS AND MATERIALS

Samples of 15 2-acetylpyridine thiosemicarbazones (Table 1) and 10 related chemicals (Table 2) were prepared at the USDA Laboratory in Beltsville, Maryland. All chemicals were more than 98% pure. Chemical Abstract Service Registry Numbers (CASRN) and 9th Collective Index (9CI) names were obtained from, or assigned by, the Chemical Abstracts Service. Test methods were identical to those previously described[1] and included the testing of red-winged blackbirds (*Agelaius phoeniceus*) for acute oral repellency and toxicity and of starlings (*Sturnus vulgaris*) for acute toxicity. The repellency test involved the calculation of a R_{50}, which is analogous to the LD_{50}, under no-choice conditions using one to six groups with five birds in each group[6,7]. The toxicity test involved the calculation of an LD_{50} with one to eight groups of two birds using propylene glycol intubation[8,9]. We used Thompson's[10] moving point interpolation method to

TABLE 1

Identification, toxicity, and repellency of 15 2-acetylpyridine thiosemicarbazones to wild birds

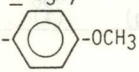
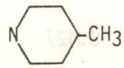
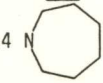
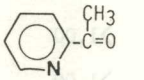
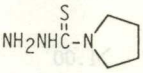
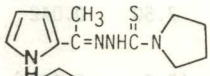
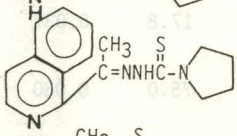
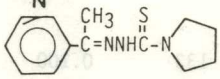
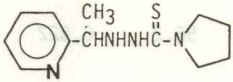
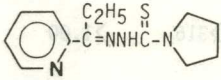
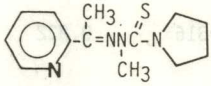
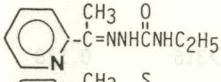
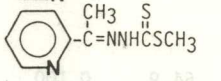
Compound	CAS registry number	Chemical structure R =	Red-winged blackbird LD50 (mg/kg)	Red-winged blackbird R50 (%)	Red-winged blackbird Percent Food Consumed*	Starling LD50 (mg/kg)
1	32646256	NH-i-C_3H_7	42.2	>1.00	69.6	>100
2	70618314	NH-  -OCH_3	>100	>1.00	100	>100
3	71555141	$N(CH_3)_2$	75.0	>1.00	65.6	>100
4	71555152	N(n-C_3H_7)$_2$	56.2	>1.00	53.6	>316
5	71555210	CH_3 NCH_2-	>100	>1.00	76.8	>100
6	71555254		7.50	0.042	45.2	>316
7	71555265		17.8	0.037	22.4	56.2
8	71555287		75.0	0.080	56.0	>316
9	71555607	CH_3	133	0.100	35.2	>316
10	71555618	 -CH_3	56.2	0.822	32.0	>316
11	71555323	C_2H_5	>316	>1.00	93.6	>316
12	71555301	CH_3 CH_3	>316	0.822	40.8	>316
13	71555312	CH_3 CH_3	>316	0.178	44.0	>316
14	71555390		64.9	0.100	20.8	>316
15	71555414		>316	>1.00	52.8	>316

TABLE 2

Identification, toxicity, and repellency of 10 chemicals related to 2-acetylpyridine thiosemicarbazones to wild birds

Compound	CAS registry number	Chemical structure	Red-winged blackbird LD_{50} (mg/kg)	Red-winged blackbird R_{50} (%)	Red-winged blackbird Percent food consumed*	Starling LD_{50} (mg/kg)
16	1122629		1000	>1.00	100	>1000
17	6499145		56.2	>1.00	73.6	56.2
18	85748556		>100	0.825	35.2	>100
19	85748578		>100	>1.00	87.2	>100
20	85748523		42.2	>1.00	59.2	>100
21	83476782		17.8	0.427	41.6	>100
22	85748396		75.0	>1.00	55.2	>100
23	85748454		>100	>1.00	87.2	>100
24	85748465		>100	>1.00	85.6	>100
25	26151768		>316	0.126	12.8	>316

statistically analyze our data. $R_{50's}$ of 0.100% or less and $LD_{50's}$ of 10.0 mg/kg or less were considered highly repellent and toxic, respectively.

RESULTS

The majority of closely related 2-acetylpyridine thiosemicarbazone derivatives that we tested possessed cyclic amino groups attached to the thiocarbonyl moiety (No. 6-15, Table 1) while the other derivatives (No. 1-5) possessed acyclic amine groups. In redwings, thiosemicarbazones No. 1, 3, and 4 evoked similar, but minimal, levels of acute repellency (based on similar food reduction values at 1.00%) and moderate levels of toxicity (42.2-75.0 mg/kg). They were not toxic to starlings at the tested levels. R_{50} values could not be calculated for these chemicals due to insufficient activity at the 1.00% treatment level. Chemical No. 5, a dialkylamino-substituted thiosemicarbazone, was less repellent and toxic than chemicals No. 1, 3, and 4. Chemical No. 2, a benzenamine derivative, was inactive. In general, thiosemicarbazones possessing acyclic amino groups were poor repellents for redwings and displayed only a moderate degree of toxicity.

In the cyclic amine series (No. 6-15), the most active thiosemicarbazones were those with unsubstituted 4- or 5-membered rings, i.e., azetidine (No. 6, 1-azetidinecarbothioic acid (1-(2-pyridinyl)ethylidene)hyrazide) and pyrrolidine (No. 7, 1-pyrrolidinecarbothioic acid (1-(2-pyridinyl)ethylidene)hydrazide). These chemicals were highly repellent ($R_{50's}$ of 0.037-0.042%) and toxic ($LD_{50's}$ of 7.50-17.8 mg/kg) to redwings (Table 1) and No. 7 was also moderately toxic to starlings. Chemicals with larger,

unsubstituted rings, such as piperidine (No. 8), morpholine (No. 14) and azepine (No. 15), were less repellent and toxic. Five alkyl-substituted piperidine analogs were also tested (No. 9-13) but were generally less repellent and toxic than the unsubstituted piperidine analog (No. 8). Thus, the addition of alkyl substituents to the piperidine ring (regardless of size, number, or location) generally decreased repellent and toxic activity. Substituent size also influenced activity; the ethyl-substituted analog (No. 11) was one-tenth as repellent as its corresponding methyl analog (No. 9). Of the alkyl-substituted piperidine analogs, the monomethyl derivative (No. 9) was the most repellent to redwings while its positional isomer (No. 10) was the most toxic. Interestingly, the positional activity of these analogs is similar to the repellency and toxicity patterns observed for two bird damage control agents widely used in the U.S.: 3,5-dimethyl-4-(methylthio)phenyl methylcarbamate (methiocarb), a repellent[11]; and 4-aminopyridine (Avitrol), a frightening agent/toxicant[11].

Thiosemicarbazones can hydrolyze under certain conditions. Two potential hydrolysis products of thiosemicarbazone No. 7 are 2-acetylpyridine (No. 16, Table 2) and 1-pyrrolidinecarbothioic acid hydrazide (No. 17). Except for moderate toxicity caused by No. 17 in redwings and starlings, the general lack of repellency associated with these potential hydrolysis products indicates that most biological activity stems from the intact thiosemicarbazone.

Chemicals related to 1-pyrrolidinecarbothioic acid (1-(2-pyridinyl)ethylidene)hydrazide (No. 7), but containing different aromatic rings (i.e., pyrrole, No. 18; isoquinoline, No. 19; and benzene, No. 20), were less repellent and toxic than No. 7 (Table 2). Apparently the pyridine ring of No. 7 is essential for the high repellency and toxicity of this chemical. If the ethylidene moiety of compound No. 7 is

modified by elimination of the double bond (i.e., reduction) or by alteration of attached or neighboring substituents, the results are chemicals No. 21-23. Of these analogs, the reduction product (1-pyrrolidinecarbothioic acid 2-(1-(2-pyridinyl)ethyl)hydrazide, No. 21) was the most active on redwings and the closest of the chemicals tested to the activity levels of chemicals No. 6 and 7. Semicarbazone No. 24 was the only oxygen analog of the thiosemicarbazones tested and was only marginally active. Chemical No. 25 (methyl (1-(2-pyridinyl)ethylidene)hydrazinecarbodithioate), a synthetic precursor to many of the thiosemicarbazones tested in Table 1, was highly repellent to redwings (Table 2). Methiocarb, the most active bird repellent currently registered in the U.S. (R_{50} of 0.089%)[7] also contains the methylthio group, but methiocarb (LD_{50} of 4.6 mg/kg[9]) is about 100 times more toxic than No. 25 to redwings.

DISCUSSION

Of the 25 chemicals tested, two thiosemicarbazone derivatives (1-azetidinecarbothioic acid (1-(2-pyridinyl)ethylidene)hydrazide and 1-pyrrolidinecarbothioic acid (1-(2-pyridinyl)ethylidene)hydrazide) were excellent redwing repellents. The two thiosemicarbazones were approximately twice as repellent to redwings as methiocarb and about 1/2 to 1/3 as toxic. These materials have potential for commerical development if their chemical, physical, and toxicological properties can meet Federal registration requirements.

In summary, we identified two thiosemicarbazone-derived bird repellents worthy of further investigation and described important structure-activity relationships that could guide future synthetic probes in this novel class of avian

repellents. The unexpected discovery of the high bird repellent activity associated with the minimal toxicity of methyl (1-(2-pyridinyl)ethylidene)hydrazinecarbodithioate also points out a new direction to pursue in the development of bird repellents derived from hydrazine adducts of 2-acetylpyridine.

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