

# Improved Synthesis and Spectral Characterization of D5281, an Oxadiazine Miticide/Insecticide

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An improved synthesis of the novel dihydrooxadiazine pesticide D5281 was obtained, resulting in a yield increase from 19 to 60%. The structure of D5281 was characterized by carbon-13 and high-field proton NMR spectroscopy and mass spectrometry. The evidence is consistent with and therefore supports the proposed structure.

**Keywords:** Oxadiazine synthesis and characterization

## INTRODUCTION

The 1,3,4-oxadiazine class of compounds has shown useful biological activities; certain 4-*H* and 4-methyl dihydrooxadiazines are anticonvulsants (Trepanier *et al.*, 1966) and insecticides (Dekeyser *et al.*, 1993a,b), and oxadiazinones are also insecticides (Dekeyser *et al.*, 1988, 1991; Dekeyser and Moore, 1991).

In our earlier study, new 4-fluoroethyl dihydrooxadiazines were synthesized to determine the effect of this type of substitution on miticidal and insecticidal activity (Dekeyser *et al.*, 1993c). The compounds were active against the twospotted spider mite, *Tetranychus urticae*, and the tobacco budworm, *Heliothis virescens*, which are two serious pests of agricultural crops. The most active of these was the 4-bromophenyl compound, D5281 (Figure 1). Subsequently, it was shown that D5281 interacted with the octopamine-sensitive adenylate cyclase complex of the twospotted spider mite (Ismail *et al.*, 1993).

We now report an improved synthesis of this potent miticide/insecticide and characterization of its dihydrooxadiazine structure.

**Chemistry.** Synthesis of the title compound was achieved according to the method outlined in Scheme 1. The fluoroethyl oxadiazine, D5281, was prepared from the appropriate substituted benzhydrazide by reaction with 3 molar equiv of potassium hydroxide followed by 3 molar equiv of bromofluoroethane. The 4-fluoroethyl dihydrooxadiazine was purified by column chromatography and then converted to its hydrochloride salt.

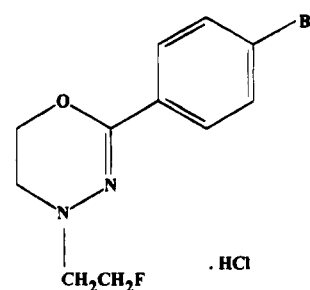
**Spectral Characterization.** D5281 was characterized using high-field NMR techniques, as outlined in Table 1 and Figures 2 and 3, and mass spectrometry, as indicated below.

## EXPERIMENTAL PROCEDURES

NMR spectra were obtained using a Bruker AM500 NMR spectrometer (500.138 MHz for proton and 125.760 MHz for carbon). All samples were prepared in deuteriochloroform with tetramethylsilane as internal standard. All chemical shifts are reported in parts per million downfield from TMS.

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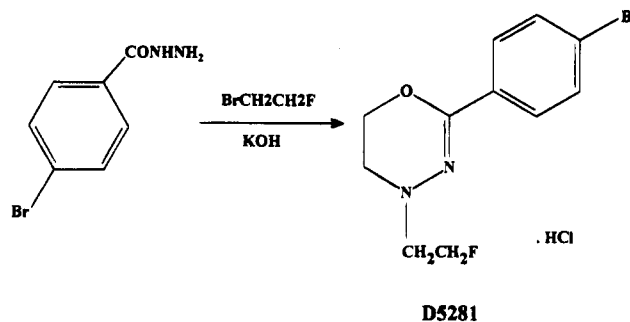
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D5281

Figure 1. Chemical structure of D5281.

Scheme 1. Synthesis of D5281



D5281

Mass spectra were recorded using a VG Analytical ZAB-E mass spectrometer.

**2-(4-Bromophenyl)-4-(2-fluoroethyl)-5,6-dihydro-4H-1,3,4-oxadiazine Hydrochloride (D5281).** A solution of 4-bromobenzhydrazide (0.01 mol) in ethanol (100 mL) was treated with potassium hydroxide (0.03 mol) and stirred until no further solid was seen. Next, 1-bromo-2-fluoroethane (0.03 mol) was added dropwise. The reaction mixture was stirred for 2 h and then refluxed for 6 h on an oil bath; the solution thus obtained was allowed to cool, filtered, and then evaporated. The crude material remaining after evaporation was poured into water (100 mL) and extracted with diethyl ether (300 mL). The ether extract was dried over sodium sulfate and then evaporated, leaving an oil. The oil was purified by column chromatography on silica gel by eluting with dichloromethane. The purified oil was dissolved in diethyl ether (100 mL) and treated with hydrogen chloride gas until no further precipitate formed. The precipitated solid was collected, washed with diethyl ether, and air-dried to furnish D5281: mp 160–162 °C; yield 60%; *m/z* 288 ( $M^+$ ,  $C_{11}H_{12}N_2OF^{81}Br$ ), 286 ( $M^+$ ,  $C_{11}H_{12}N_2OF^{79}Br$ ), 255 ( $C_{11}H_{12}N_2OF^{81}Br - CH_2F$ ), 253

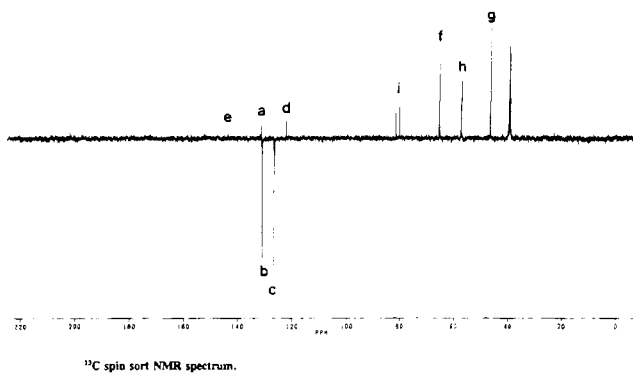
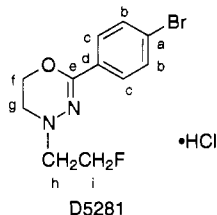


Figure 2.  $^{13}\text{C}$  spin sort NMR spectrum.

Table 1. Characterization of D5281 by NMR



site	carbon resonance	proton resonance	proton/proton correlation
a	131.453		
b	131.152	7.50–7.65 (dd)	
c	126.715	7.50–7.65 (dd)	
d	122.376		
e	143.898		
f	65.505	4.476 (t)	f/g
g	46.638	3.113 (t)	f/g
h	57.409 <sup>a</sup>	3.15–3.30 (dt) <sup>b</sup>	h/i
i	80.851 <sup>a</sup>	4.60–4.80 (dt) <sup>b</sup>	h/i

<sup>a</sup> Due to the carbon–fluorine coupling, these carbon resonances appear as doublets. <sup>b</sup> Due to the hydrogen–fluorine coupling, these triplets are further split into a doublet of triplets.

( $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}\text{F}^{79}\text{Br} - \text{CH}_2\text{F}$ ), 185 ( $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}\text{F}^{81}\text{Br} - \text{C}_4\text{H}_8\text{N}_2\text{O}$ ), 183 ( $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}\text{F}^{79}\text{Br} - \text{C}_4\text{H}_8\text{N}_2\text{O}$ ).

## RESULTS AND DISCUSSION

The synthesis of D5281 was modified from our earlier procedure (Dekeyser *et al.*, 1993c) by using excess potassium hydroxide in place of sodium hydroxide in a two-stage process using a slightly longer reaction time. A yield increase from 19 to 60% was obtained.

The spin sort carbon-13 NMR spectrum of D5281 is shown in Figure 2 and detailed in Table 1. The spectrum shown in Figure 2 clearly indicates 11 distinct carbon atoms. The five low-field resonances correspond to the quaternary carbons (a, d, e) and the aromatic methine carbons (b, c). Of the four methylene groups (f, g, h, i), the fluoroethyl carbons (h, i) are easily assigned due to the prominent carbon–fluorine couplings. The carbon spectrum, therefore, is indicative of the structure proposed for D5281.

The proton NMR resonances of D5281 are shown in Figure 3 and detailed in Table 1. The spectrum shown in Figure 3 indicates 12 protons in total, as expected from the proposed structure: four protons appear in the aromatic region, and the remaining eight protons are located between 3 and 5 ppm. From the  $^1\text{H}$ – $^1\text{H}$  COSY spectrum shown in Figure 3, the fluoroethyl protons are easily assigned due to the large H–F couplings resulting in doublets of the methylene triplets [h, 3.15–3.30 ppm (dt),  $J_{\text{H-F}} = 27.8$  Hz; i, 4.60–4.80 ppm (dt),  $J_{\text{H-F}} = 47.7$

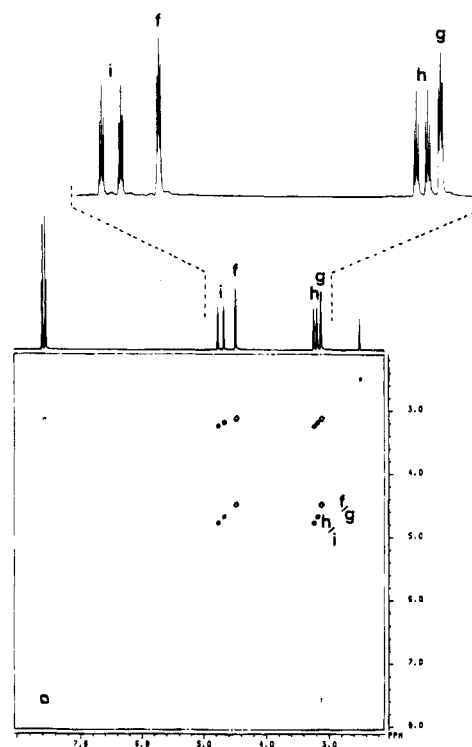


Figure 3.  $^1\text{H}$ – $^1\text{H}$  COSY NMR spectrum.

Hz]. These methylene groups show strong off-diagonal correlations to each other. The fluoroethyl proton chemical shift assignments are consistent with those reported for other fluoroethyl heterocycles (Baklouti and Hedhli, 1989). The methylene groups of the oxadiazine ring, as expected, appear as triplets and also show correlations. The dihydrooxadiazine proton chemical shift assignments are similar to those of the related dihydrooxadiazinecarboxylates (Milcent and Barbier, 1992), which showed a  $\text{NCH}_2$  triplet at 3.85 ppm and an  $\text{OCH}_2$  triplet at 4.45 ppm, and the dihydrooxadiazinecarboxamides of Kristinsson *et al.* (1986), which similarly showed an  $\text{NCH}_2$  multiplet at 3.8 ppm and  $\text{OCH}_2$  multiplet at 4.5 ppm. The discrepancy between the chemical shift of the  $\text{NCH}_2$  protons reported by these workers and that found in the current series is likely due to the deshielding influence of the carboxylic ester and carboxamide groups on the  $\text{NCH}_2$  chemical shift of their compounds, whereas the  $\text{NCH}_2$  chemical shift of the current series of compounds is not influenced by the hydrogen, methyl, and fluoroethyl groups.

In conclusion, this evidence, along with previous data (Dekeyser *et al.*, 1993c), clearly supports the proposed structure of this novel type of pesticide.

## ACKNOWLEDGMENT

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