The Synthesis of Potential Insecticides: Haloalkoxy Phenyl Diacyldrazines and 1,3,4-Oxadiazoles

Fall 1983

Kathleen S. Gibbs-Rein

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THE SYNTHESIS OF POTENTIAL INSECTICIDES:
HALOALKOXY PHENYL DIACYLHYDRAZINES
AND 1,3,4-OXADIAZOLES

BY
KATHLEEN S. GIBBS-REIN
B.S., University of Central Florida, 1981

RESEARCH REPORT
Submitted in partial fulfillment of the requirements
for the Master of Science degree in Industrial Chemistry
in the Graduate Studies Program of the College of Arts and Sciences
University of Central Florida
Orlando, Florida

Fall Term
1983
ABSTRACT

The syntheses of two classes of compounds, diacylhydrazines and 2,5-disubstituted 1,3,4-oxadiazoles, intended for subsequent investigation of pesticidal activity are discussed. The experimental conditions and procedures necessary for the preparation of these potential insecticides are also revealed. Finally, spectral data are interpreted and explained, and recommendations for further research are given.
ACKNOWLEDGEMENTS

I am greatly indebted to Dr. John P. Idoux and Dr. John T. Gupton for their patience, encouragement and guidance throughout my graduate research, and for the experience I gained through their expertise in synthetic organic research.

I would also like to thank my parents for their continued encouragement and moral support throughout my college years. Finally, I wish to thank my husband for his undying patience, devotion and sacrifice.
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3. Proposed mechanism for nucleophilic addition to fluoroolefins. 6
LIST OF ABBREVIATIONS

bp ......................... boiling point
°C ........................... degrees centigrade
 cm⁻¹ ......................... wave numbers
DMF .......................... dimethylformamide
DMSO ......................... dimethylsulfoxide
g  ............................ grams
hr  ............................ hours
Hz  ............................ hertz (cycles per second, NMR spectrum)
IR  ............................ infrared
J  .............................. coupling constant (NMR spectrum)
min  ............................ minutes
ml  ............................ milliliters
mm  ............................ millimeters
mol  ............................. mole
mp  ............................. melting point
NMR  ............................ Nuclear Magnetic Resonance
TFA  ............................ trifluoroacetic acid
THF  ............................ tetrahydrofuran
INTRODUCTION

Certain oxadiazoles have been found to be active in the destruction of manure breeding insects such as houseflies, faceflies, and hornflies. These compounds, which were disclosed in a 1980 patent\(^1\) are of general structure I.

\[
\begin{array}{c}
\text{Cl} & \text{Cl} \\
\text{C} & \text{C} \\
\text{N} & \text{N} \\
\text{O} & \text{Ar} \\
\end{array}
\]

(I)

These compounds may be sprayed directly on the manure or administered orally to warm-blooded animals.

It is the intent of this research to increase the lipophilicity and activity of oxadiazole system I through the synthesis and investigation of a series of haloalkoxy phenyl substituted similogs of general structure II.

\[
\begin{array}{c}
\text{Cl} & \text{Cl} \\
\text{C} & \text{C} \\
\text{N} & \text{N} \\
\text{O} & \text{G}_1 \\
\end{array}
\]

(II)
where $G =$

4 - OCF$_2$CF$_2$H  
4 - OCF$_2$CFClH  
4 - OCF$_2$CCl$_2$H  
3 - OCF$_2$CF$_2$H  
3 - OCF$_2$CFClH  
3 - OCF$_2$CCl$_2$H

These compounds and their precursor diacylhydrazines will be prepared, tested for biological activity by the UCF biochemistry group, and forwarded to the Dow Chemical Company for extensive biological screening.

In addition, three other diacylhydrazines of general structure III will be prepared.

\[
\text{Cl}\begin{array}{c}
\text{NHNH} \\
\text{Cl}
\end{array}\text{G}_1\text{G}_2
\]

(III)

where $G_1 = G_2 =$

3,5 - OCF$_2$CF$_2$H  
3,5 - OCF$_2$CFClH  
3,5 - OCF$_2$CCl$_2$H

The synthetic route to these compounds, proposed by Lizzi,$^2$ is shown in Figure 1.
Figure 1. Proposed synthetic route for the preparation of diacylhydrazines and 2,5 - disubstituted - 1,3, 4 - oxadiazoles.
In addition, it has been proposed that symmetric haloalkoxy phenyl oxadiazoles would possess enhanced lipophilicity and larvacidal activity. Thus a series of compounds of general structure IV will be prepared for biological screening.

![Diagram of compound IV](image)

(IV)

<table>
<thead>
<tr>
<th>$G_1$</th>
<th>$G_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>3 - OCF$_2$CF$_2$H</td>
</tr>
<tr>
<td>H</td>
<td>3 - OCF$_2$CFClH</td>
</tr>
<tr>
<td>H</td>
<td>3 - OCF$_2$CCl$_2$H</td>
</tr>
<tr>
<td>5 - OCF$_2$CF$_2$H</td>
<td>3 - OCF$_2$CCl$_2$H</td>
</tr>
<tr>
<td>5 - OCF$_2$CFClH</td>
<td>3 - OCF$_2$CFClH</td>
</tr>
<tr>
<td>H</td>
<td>4 - OCF$_2$CFClH</td>
</tr>
</tbody>
</table>

The proposed route to these symmetric oxadiazoles is shown in Figure 2.
Figure 2. Proposed synthetic scheme for the preparation of symmetric diacylhydrazines and 2,5-disubstituted 1,3,4-oxadiazoles.
The methyl benzoates are prepared by the acid catalyzed esterification of the carboxylic acids in methanol.

Nucleophillic additions to fluoroolefins are first reported in a patent published by Hanford and Rigby, in 1946. The addition of alcohols to tetafluoroethylene with the corresponding alkoxide catalyst were described. Since that time, many examples of the addition of alcohols and phenols to fluoroolefins have been cited in the literature. The products of addition of hydroxy compounds to fluoroethylenes are polyfluoroothers. Addition to unsymmetrical haloethylenes occurs to give products in which the nucleophile attacks at the difluoromethylene group. The mechanism proposed by Miller, Fager and Griswald indicates that it is the resonance electron-donating ability of fluorine in the difluoromethylene group which determines the orientation of addition. This shown in Figure 3.

Figure 3. Proposed mechanism for nucleophilic addition to fluoroolefins.
The addition of phenols is less facile than that of alcohols due to the lower nucleophilic strength of the aryloxide ion. The effect of substituent groups on reactivity is great. Electron withdrawing groups in the ortho and para positions decrease reactivity significantly. Phenol, for example will add to tetrafluoroethylene in acetone at 40° C while methyl-4-hydroxy benzoate will not react. Higher boiling solvents such as dioxane and dimethylformamide have been employed with considerable effect.10

One of the most widely used methods of preparing unsubstituted hydrazides is the reaction of esters with hydrazine or its hydrate.12-14 The mechanism is a nucleophilic substitution at an acyl carbon, with alkoxide as the leaving group. Esters seldom produce significant amounts of diacylhydrazine. Diacylhydrazines are prepared by the reaction of a monohydrazide with an acid chloride.15 The preparation of symmetric diacylhydrazines is accomplished by the reaction of acid chlorides with hydrazine or its hydrate. The high reactivity of acid chlorides affects diacylation. While the unsymmetrical diacylhydrazines are often preferred, this is prevented here by steric effects.16

The treatment of diacylhydrazines with phosphorusoxychloride affects cyclodehydration to 1,3,4-oxadiazoles.

All compounds prepared shall be characterized by infrared and NMR spectroscopy.
EXPERIMENTAL

The chemicals used in the various reactions and their sources are indicated in Table I.

1. Preparation of Substituted Methyl Benzoates

The following procedure is typical of the experimental conditions used in the conversion of substituted benzoic acids to substituted methyl benzoates (Table II).

Methyl 3-hydroxy benzoate. A 250-ml round-bottomed flask was equipped with a stirring bar and condenser. The flask was charged with 36 g (0.263 mol) of 3-hydroxy benzoic acid, 0.5 ml (3-5 g per mole of benzoic acid) of conc. H₂SO₄, and 150 ml of methanol. The solution was allowed to reflux for five days. Upon cooling to room temperature, the pH was made neutral with sodium bicarbonate. The resulting precipitate (sodium sulfate) was filtered and the methanol removed on a rotary evaporator. The remaining solid was filtered, washed with water and dried on a Kugelrhor apparatus, yielding 38.7 g (97% yield) of a white solid; NMR (d⁶-DMSO) 83.90 (s, 3H), 7.0-7.6 (m, 4H); IR (nujol mull) 3395 (O-H stretch), 1690 (C=O ester stretch), 1610, 1440 (aromatic C=C), 760, 870, 795, 690 cm⁻¹ (m-substitution); mp 69-71° C.
Table I
Chemicals Used and Their Sources

3-Chloro-4-hydroxy benzoic acid hemihydrate; Aldrich Chemical Company, Inc.

2,4-Dichloro benzoylchloride; Aldrich Chemical Company, Inc.

1,1-Dichloro -2,2 -difluoroethylene; PCR Research Chemicals, Inc.

3,5-Dichloro -4-hydroxy benzoic acid; Aldrich Chemical Company, Inc.

3,5-Dihydroxy benzoic acid; Aldrich Chemical Company, Inc.

Hydrazine monohydrate; Kodak

m-Hydroxy benzoic acid; Aldrich Chemical Company, Inc.

p-Hydroxy benzoic acid hydrazide; Aldrich Chemical Company, Inc.

Phosphorousoxychloride; Aldrich Chemical Company, Inc.

Polyphosphoric acid; Aldrich Chemical Company, Inc.

Tetrafluoroethylene; PCR Research Chemical, Inc.

Thionyl Chloride; Aldrich Chemical Company, Inc.

Trifluorochloroethylene; PCR Research Chemicals, Inc.
Table II
Experimental Data for the Preparation of Substituted Methy Benzoates

![Chemical diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>G₁</th>
<th>G₂</th>
<th>G₃</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>3-OH</td>
<td>97% a</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>3-OH</td>
<td>5-OH</td>
<td>98% b</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>3-Cl</td>
<td>4-OH</td>
<td>84% c</td>
</tr>
<tr>
<td>4</td>
<td>3-Cl</td>
<td>5-Cl</td>
<td>4-OH</td>
<td>98% d</td>
</tr>
</tbody>
</table>

a. NMR (d⁶-DMSO) δ3.90 (s, 3H), 7.70-7.76 (m, 4H); IR (nujol mull) 3395, 1690, 1610, 1440, 760 cm⁻¹; mp, 69-71° C.

b. NMR (d⁶-DMSO) δ3.90 (s, 3H), 6.94 (d, J=2Hz, 2H), 6.55 (t, J=2Hz, 1H); IR (nujol mull) 3260, 1695, 1610, 1490, 1450, 760, 870, 670 cm⁻¹; mp, 297-299° C.

c. NMR (d⁶-acetone) δ3.90 (s, 3H), 7.21 (d, J=9Hz, 1H), 7.83-8.20 (m, 2H), 8.51 (broad s, 1H); IR (nujol mull) 3350, 1690, 1605, 1420, 765, 880, 710 cm⁻¹; mp, 106-109° C.

d. NMR (d⁶-DMSO) δ3.88 (s, 3H), 7.90 (s, 2H); IR (nujol mull) 3450, 1710, 1595, 1440, 910, 770 cm⁻¹; mp, 297-299° C.
2. Preparation of Haloalkoxy Substituted Methyl Benzoates

The following procedure is typical of the experimental conditions used in the conversion of substituted methyl benzoates to haloalkoxy substituted methylbenzoates (Table III).

**Methyl-4-(2-chloro-1,1,2-trifluoroethoxy) benzoate.** A 250-ml, three neck, round-bottomed flask was equipped with a Claisen adaptor, condenser, mechanical stirrer, thermometer, and a 125-ml addition funnel. The flask was charged with 200 ml of dimethylformamide (DMF) and 38.05g (0.25 mol) of methyl p-hydroxy benzoate. A solution of methanol (50 ml) and sodium methoxide (0.125 mol) was then added dropwise at room temperature. The reaction mixture was stirred for 20 minutes, followed by removal of the methanol on a rotary evaporator. The resulting solution was heated to 95° C, 19.5g (0.168 mol) of trifluorochloroethylene were added through a gas dispersion tube and the solution was stirred at 95° C overnight. Upon cooling, the DMF was removed, using a Kugelrhor apparatus, water (100 ml) was added and the resulting solution extracted with ether 3 x 100 ml), dried over anhydrous sodium sulfate and the solvent flashed off on a rotary evaporator leaving 26.818g of a yellow oil (80% yield); NMR (CDCl₃) δ3.98 (s,3H), 7.33 (d, J=8Hz, 2H), 8.13 (d, J=8Hz, 2H), 6.30 (dt, J(geminal) = 3Hz, J(vicinal)=48Hz, 1H); IR (neat) 3000 (aromatic C-H stretch), 2950, 2830 (aliphatic C-H stretch), 1720 (C=O ester stretch), 2950, 2830 (aliphatic C-H stretch), 1720 (C=O ester stretch), 1600, 1500, 1435 (C=C stretch), 1270, 1170, 1100 (C-F stretch), 1020 (aryl-alkyl ether stretch), 710 (C-H bend), 1680 (C=C out of plane bend), 860 cm⁻¹ (p-substitution).
Table III
Experimental Data for the Preparation of Haloalkoxy Substituted Methyl Benzoates

![Chemical Structures]

<table>
<thead>
<tr>
<th>Entry</th>
<th>G₁</th>
<th>G₂</th>
<th>X₁</th>
<th>X₂</th>
<th>G₃</th>
<th>G₄</th>
<th>G₅</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>4-OH</td>
<td>F</td>
<td>F</td>
<td>F</td>
<td>4- HCF₂CF₂O-</td>
<td>H</td>
<td>80% a</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>4-OH</td>
<td>Cl</td>
<td>F</td>
<td>H</td>
<td>4- HCClCF₂O-</td>
<td>H</td>
<td>80% b</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>4-OH</td>
<td>Cl</td>
<td>Cl</td>
<td>H</td>
<td>4- HCCl₂CF₂O-</td>
<td>H</td>
<td>37% c</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>3-OH</td>
<td>F</td>
<td>F</td>
<td>H</td>
<td>3- HCF₂CF₂O-</td>
<td>H</td>
<td>69% d</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>3-OH</td>
<td>Cl</td>
<td>F</td>
<td>H</td>
<td>3- HCFC₁CF₂O-</td>
<td>H</td>
<td>91% e</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>3-OH</td>
<td>Cl</td>
<td>Cl</td>
<td>H</td>
<td>3- HCCl₂CF₂O-</td>
<td>H</td>
<td>88% f</td>
</tr>
<tr>
<td>7</td>
<td>3-OH</td>
<td>5-OH</td>
<td>F</td>
<td>F</td>
<td>3- HCF₂CF₂O-</td>
<td>5- HCF₂CF₂O-</td>
<td>Na⁺O⁻</td>
<td>87% g</td>
</tr>
<tr>
<td>8</td>
<td>3-OH</td>
<td>5-OH</td>
<td>Cl</td>
<td>F</td>
<td>3- HCFC₁CF₂O-</td>
<td>5- HCFC₁CF₂O-</td>
<td>Na⁺O⁻</td>
<td>92% h</td>
</tr>
<tr>
<td>9</td>
<td>3-OH</td>
<td>5-OH</td>
<td>Cl</td>
<td>Cl</td>
<td>3- HCCl₂CF₂O-</td>
<td>5- HCCl₂CF₂O-</td>
<td>Na⁺O⁻</td>
<td>65% i</td>
</tr>
<tr>
<td>10</td>
<td>3-Cl</td>
<td>4-OH</td>
<td>F</td>
<td>F</td>
<td>Cl</td>
<td>4- HCF₂CF₂O-</td>
<td>H</td>
<td>No Reaction</td>
</tr>
</tbody>
</table>

Explanation:
- **G₁, G₂**: The starting materials.
- **X₁, X₂**: Substituents on the starting materials.
- **G₃**: The product of the reaction.
- **G₄, G₅**: Additional products.
- **Yield**: The yield of the reaction, expressed as a percentage.
Table III (continued)

a. NMR (CDCl₃) δ3.94 (s, 3H), 7.24 (d, J=8Hz, 2H), 8.03 (d, J=8Hz, 2H), 6.22 (tt, J(geminal)=2Hz, J(vicinal)=54Hz, 1H); IR (thin film) 2970, 2830, 3020, 1730, 1610, 1510, 1440, 1280, 1200, 1120, 1020, 860 cm⁻¹.

b. NMR (CDCl₃) δ3.98 (s, 3H), 7.33 (d, J=8Hz, 2H), 8.13 (d, J=8Hz, 2H), 6.30 (dt, J(geminal)=3Hz, J(vicinal)=48Hz, 1H); IR (thin film) 3000, 2950, 2830, 1720, 1600, 1500, 1435, 1270, 1170, 1100, 1020, 860 cm⁻¹.

c. This refers to distilled yield. (bp 134, 5 mm); NMR (CDCl₃) δ3.91 (s, 3H), 7.24 (d, J=8Hz, 2H), 8.09 (d, J=8Hz, 2H), 6.10 (t, J=4Hz, 1H); IR (thin film) 3010, 2960, 2825, 1730, 1610, 1510, 1440, 1240, 1170, 1120, 1020, 830 cm⁻¹.

d. NMR (CDCl₃) δ3.99 (s, 3H), 7.53 (m, 2H), 8.00 (m, 2H), 6.15 (tt, J(geminal)=3Hz, J(vicinal)=54Hz); IR (thin film) 3310, 2980, 2830, 1730, 1590, 1490, 1450, 1300, 1200, 1130, 1010, 740 cm⁻¹.

e. Upon removal of the DMF, 100 ml of chloroform was added to the residue and the mixture was filtered. The chloroform was flashed off on a rotary evaporator leaving an orange oil. NMR (CDCl₃) δ3.90 (s, 3H) 7.41-7.98 (m, 4H), 6.47 (dt, J(geminal)=4Hz, J(vicinal)=48Hz, 1H); IR (thin film) 3310, 2980, 2830, 1730, 1590, 1490, 1450, 1300, 1200, 1100, 1010, 870 cm⁻¹.

f. This reaction was run at 110° C. NMR (CDCl₃) δ3.93 (s, 3H), 7.45-8.00 (m, 4H), 6.18 (t, J=4Hz, 1H); IR (thin film) 3310, 2970, 1730, 1590, 1490, 1450, 1290, 1005, 830 cm⁻¹.

g. NMR (CDCl₃) δ4.00 (s, 3H), 7.33 (s, 1H) 7.90 (d, J=2Hz, 2H), 6.00 (tt, J(geminal)=2Hz, J(vicinal)=48Hz, 2H); IR (thin film) 2980, 1740, 1600, 1450, 1310, 1180, 1130, 1000, 850 cm⁻¹.

h. NMR (CDCl₃) δ4.00 (s, 3H), 7.36 (s, 1H), 7.94 (d, J=2Hz, 2H), 7.78 (dt, J(geminal)=4Hz, J(vicinal)=48Hz, 2H); IR (thin film) 3010, 2990, 1735, 1605, 1455, 1375, 1320, 1180, 1100, 1010, 870 cm⁻¹.

i. NMR (CDCl₃) δ4.09 (s, 3H), 7.50 (s, 1H), 7.98 (d, J=2Hz, 2H), 6.02 (t, J=4Hz, 2H); IR (thin film) 3000, 2980, 2920, 1730, 1600, 1440, 1270, 1125, 1000, 820 cm⁻¹.
3. Preparation of Substituted Benzhydrazides

The following procedure is typical of the experimental conditions used in conversion of substituted methyl benzoates to substituted benzhydrazides (Table IV).

4-(2-chloro 1,1,2-trifluoroethoxy) benzhydrazide.

Methyl 4-(2-chloro-1,1,2-trifluoroethoxy) benzoate, (5.0g, 0.0186mol), hydrazine monohydrate (5.587g, 0.112mol) and 50 ml of methanol were added to a 100-ml round-bottomed flask equipped with a stirring bar and condenser and the solution refluxed for 18 hrs. Upon cooling, the methanol was removed using a rotary evaporator and 4.637g of a yellow solid (83% yield) was obtained (some analogs require cooling in an ice bath or addition of ice to induce crystalization). The solid was filtered and dried on a Kugelrhor apparatus at reduced pressure. NMR (d6-DMSO, CDCl3) δ7.27 (d, J=8Hz, 2H), 8.20 (d, J=8Hz, 2H), 7.04 (dt, J(geminal)= 4Hz, J(vicinal)= 46 Hz, 1H), 4.69 (s, broad, 2H); IR (nujol mull) 3320 (1° amine stretch), 3210, (2° amide stretch), 1630 (C=O amide stretch), 1610 (N-H 1° amide bend) 1590, 1470 (C=C aromatic), 1160 (C-F bend), 1020, cm -1, (aryl-alkyl ether stretch); mp, 99-102° C. The solid was found to be soluble in 5% hydrochloric acid solution.
### Table IV
Experimental Data for the Preparation of Substituted Benzhydrazides

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>G₁</th>
<th>G₂</th>
<th>G₃</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>4 - HCF₂CF₂-O-</td>
<td>83% a</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>H</td>
<td>4 - HCClFCF₂-O-</td>
<td>83% b</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>H</td>
<td>4 - HCCl₂CF₂-O-</td>
<td>58% c</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>3 - HCF₂CF₂-O-</td>
<td>91% d</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>H</td>
<td>3 - HCClFCF₂-O-</td>
<td>84% e</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>H</td>
<td>3 - HCCl₂CF₂-O-</td>
<td>58% f</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>3 - HCF₂CF₂-O-</td>
<td>5 - HCF₂CF₂-O-</td>
<td>72% g</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>3 - HCClFCF₂-O-</td>
<td>5 - HCClFCF₂-O-</td>
<td>92% h</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>3 - HCCl₂CF₂-O-</td>
<td>5 - HCCl₂CF₂-O-</td>
<td>65% i</td>
</tr>
<tr>
<td>10</td>
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<td>3 - Cl</td>
<td>4 - OH</td>
<td>70%  j</td>
</tr>
<tr>
<td>11</td>
<td>3 - Cl</td>
<td>5 - Cl</td>
<td>4 - OH</td>
<td>70%  k</td>
</tr>
</tbody>
</table>

a. NMR (d⁶-DMSO, CDCl₃) δ7.40 (d, J=8Hz, 2H), 8.10 (d, J=8Hz, 2H), 6.45 (tt, J(geminal)=4Hz, J(vicinal)=43Hz, 1H), 5.00 (s, broad, 2H); IR (nujol mull) 3310, 3220, 1630, 1620, 1590, 1470, 1130, 1020, 860 cm⁻¹; mp, 110-112° C; Soluble in 5% hydrochloric acid solution.
b. NMR (d$_6$-DMSO, CDCl$_3$) $\delta$7.27 (d, $J=8$Hz, 2H), 8.00 (d, $J=8$Hz, 2H), 7.04 (dt, $J$(geminal)=$4$Hz, $J=$(vicinal)=$46$Hz, 1H), 4.69 (s, broad, 1H); IR (nujol mull) 3300, 3200, 1630, 1590, 1460, 1180, 1080, 1020 cm$^{-1}$; mp, 99-102° C; Soluble in 5% HCl.

c. NMR (d$_6$-DMSO, CDCl$_3$) $\delta$7.41 (d, $J=8$Hz, 2H), 8.08 (d, $J=8$Hz, 2H), 7.26 (t, $J$(geminal)=$6$Hz, 1H), 4.67 (s, broad, 2H); IR (nujol mull) 3310, 3190, 1640, 1590, 1530, 1490, 1120, 1005, 810 cm$^{-1}$; mp, 186-192° C; Soluble in 5% HCl.

d. NMR (d$_6$-DMSO, CDCl$_3$) $\delta$7.38 (m, 2H), 7.74 (m, 2H), 6.99 (tt, $J$(geminal)=$4$Hz, $J$(vicinal)=$54$Hz, 1H), 5.10 (s, broad, 2H); IR (nujol mull) 3310, 3190, 1640, 1590, 1530, 1490, 1120, 1005, 810 cm$^{-1}$; mp, 80-82° C; Soluble in 5% HCl.

e. NMR (d$_6$-DMSO, CDCl$_3$) $\delta$7.48 (m, 2H), 7.88 (m, 2H), 7.15 (dt, $J$(geminal)=$4$Hz, $J$(vicinal)=$44$Hz, 1H), 4.44 (s, broad, 2H), 10.00 (s, broad, 1H); IR (nujol mull) 3310, 3220, 1610, 1580, 1530, 1490, 1090, 1000, 850 cm$^{-1}$; mp, 83-84° C; Soluble in 5% HCl.

f. NMR (CDCl$_3$) $\delta$7.41 (m, 2H), 7.70 (m, 2H), 5.98 (t, $J=4$Hz, 1H), 4.71 (s, broad, 2H); IR (neat) 3300, 1595, 1440, 1175, 1090, 1030, 1000, 860 cm$^{-1}$; This product was a viscous oil thus no melting point data was obtained.

g. NMR (d$_6$-DMSO, CDCl$_3$) $\delta$7.41 (t, $J=2$Hz, 1H), 7.90 (d, $J=2$Hz, 2H), 6.78 (tt, $J$(geminal)=$4$Hz, $J$(vicinal)=$50$Hz, 2H), 4.42 (s, broad, 2H); IR (nujol mull) 3310, 3220, 1610, 1540, 1470, 1130, 1020, 870 cm$^{-1}$; mp, 79-80° C; Soluble in 5% HCl.

h. NMR (d$_6$-DMSO, CDCl$_3$) $\delta$7.37 (s, 1H), 7.97 (s, 2H), 7.17 (dt, $J$(geminal)=$4$Hz, $J$(vicinal)=$46$Hz, 2H), 4.60 (s, broad, 2H); IR (neat) 3300, 1595, 1440, 1175, 1090, 1030, 1000, 860 cm$^{-1}$; Soluble in 5% HCl. This product was a viscous oil thus no melting point data was obtained.

i. NMR (d$_6$-DMSO, CDCl$_3$) $\delta$7.28 (s, broad 1H), 7.80 (s, 2H), 7.02 (t, $J=4$Hz, 2H), 5.30 (s, broad, 2H); IR (neat) 3310, 1620, 1590, 1160, 1080, 1000, 830 cm$^{-1}$; Soluble in 5% HCl. This product was a viscous oil thus no melting point data was obtained.

j. NMR (TFA) $\delta$7.22 (d, $J=8$Hz, 1H), 7.80 (m, 2H); IR (nujol mull) 3320, 3000, 1620, 1610, 1580, 1470 cm$^{-1}$; mp, 252-256° C; Soluble in 5% HCl.

k. NMR (d$_6$-DMSO, d$_6$-acetone) $\delta$7.95 (s, 2H) 6.69 (s, broad, 2H); IR (nujol mull) 3310, 3160, 3000, (broad), 1640, 1580, 1560, 1480, 810 cm$^{-1}$; mp, 297-299° C. Soluble in 5% HCl.
4. Preparation of Substituted Diacylhydrazides

The following is typical of the experimental conditions used in the conversion of substituted benzhydrazides to substituted diacylhydrazides (Table V).

\[N-(4\text{-hydroxybenzoyl})-N'-(2,4\text{-dichlorobenzoyl})\text{ hydrazine.}\]

A 250-ml three neck, round-bottomed flask was equipped with a condenser, thermometer, 125-ml addition funnel and a Teflon stirring bar. The flask was charged with 7.636g (0.0502mol) of 4-hydroxy benzoic acid hydrazide, 4.287g (0.0510mol) of sodium bicarbonate, 60 ml of tetrahydrofuran (THF) and 60 ml of water. After dropwise addition of 2,4-dichlorobenzoyl chloride, the reaction mixture was stirred for one hour at room temperature. Removal of the THF (rotary evaporator) gave 14.732g (91% yield) of a white solid which was filtered, washed with water and dried on a Kugelrhor apparatus at reduced pressure. NMR (d6-DMSO, CD3OD) \( \delta 6.96 \) (d, J=8Hz, 2H), 7.46 -7.67 (m, 3H), 7.90 (d, J=8Hz, 2H); IR (nujol mull) 3300 (N-H, 2° amide stretch), 3200 (broad OH stretch), 1630 (C=O amide stretch), 1450. (aromatic C=C), 865 (2,4 disubstituted), 810 cm\(^{-1}\) (p-substituted); mp 234-240° C.
Table V
Experimental Data for the Preparation of Substituted Diacylhydrazines

\[
\begin{array}{ccccc}
\text{Entry} & G_1 & G_2 & G_3 & \text{Yield} \\
1 & H & H & 4 - \text{HCF}_2\text{CF}_2-\text{O}- & 92\% a \\
2 & H & H & 4 - \text{HCCl}\text{FCF}_2-\text{O}- & 78\% b \\
3 & H & H & 4 - \text{HCCl}_2\text{CF}_2-\text{O}- & 84\% c \\
4 & H & H & 3 - \text{HCF}_2\text{CF}_2-\text{O}- & 94\% d \\
5 & H & H & 3 - \text{HCFC}\text{ClCF}_2-\text{O}- & 96\% e \\
6 & H & H & 3 - \text{HCCl}_2\text{CF}_2-\text{O}- & 74\% f \\
7 & H & 3 - \text{HCF}_2\text{CF}_2-\text{O}- & 5 - \text{HCF}_2\text{CF}_2-\text{O}- & 93\% g \\
8 & H & 3 - \text{HCFC}\text{ClCF}_2-\text{O}- & 5 - \text{HCCl}\text{FCF}_2-\text{O}- & 93\% h \\
9 & H & 3 - \text{HCCl}_2\text{CF}_1-\text{O}- & 5 - \text{HCCl}_2\text{CF}_2-\text{O}- & 97\% i \\
10 & H & H & 4 - \text{OH} & 91\% j \\
11 & H & 3 - \text{Cl} & 4 - \text{OH} & 92\% k \\
12 & 3 - \text{Cl} & 5 - \text{Cl} & 4 - \text{OH} & 92\% l \\
\end{array}
\]
Table V (Continued)

<table>
<thead>
<tr>
<th></th>
<th>NMR (d\textsubscript{6}-DMSO, CDCl\textsubscript{3}) δ6.35 (tt, J(geminal) = 4Hz, J(vicinal) = 56Hz, 1H), 7.16 -7.65 (m, 5H), 8.14 (d, J=10Hz, 2H); IR (nujol mull) 3220, 1640, 1460, 1220, 1110, 870 cm\textsuperscript{-1}; mp 198-200° C.</th>
</tr>
</thead>
<tbody>
<tr>
<td>b.</td>
<td>NMR (d\textsubscript{6}-DMSO, CDCl\textsubscript{3}) δ7.10 (tt, J(geminal) = 4Hz, J(vicinal) = 48Hz, 1H), 7.33 -7.65 (m, 5H), 8.20 (d, J=8Hz, 2H); IR (nujol mull) 3220, 1640, 1180, 1090, 1020, 850 cm\textsuperscript{-1}; mp 198-200° C.</td>
</tr>
<tr>
<td>c.</td>
<td>NMR (d\textsubscript{6}-DMSO) δ7.47 -8.00 (m, 6H), 8.40 (d, J=8Hz, 2H); IR (nujol mull) 3220, 1645, 1250, 1170, 1020, 890 cm\textsuperscript{-1}; mp 210 -212° C.</td>
</tr>
<tr>
<td>d.</td>
<td>NMR (d\textsubscript{6}-DMSO, CDCl\textsubscript{3}) δ6.48 (tt, J(geminal) = 4Hz, J(vicinal) = 52Hz, 1H), 7.58 (d, J=2Hz, 3H), 7.63 (s, 2H), 8.00 (d, J=2Hz, 2H); IR (nujol mull) 3220, 1650, 1470, 1300, 1200, 1130, 1005, 870 cm\textsuperscript{-1}; mp 165 -168° C.</td>
</tr>
<tr>
<td>e.</td>
<td>NMR (d\textsubscript{6}-DMSO, CDCl\textsubscript{3}) δ6.66 (tt, J(geminal) = 4Hz, J(vicinal) = 50Hz), 7.45 (d, J=2Hz, 3H), 7.59 (s, 2H), 7.98 (t, J=2Hz, 2H); IR (nujol mull) 3240, 1645, 1470, 1300, 1200, 1090, 1005, 880 cm\textsuperscript{-1}; mp 169-171° C.</td>
</tr>
<tr>
<td>f.</td>
<td>NMR (d\textsubscript{6}-DMSO, CDCl\textsubscript{3}) δ6.36 (t, J=4Hz, 1H), 7.33 (d, J=2Hz, 3H), 7.68 (s, 2H), 7.93 (d, J=2Hz, 2H); IR (nujol mull) 3300, 1640, 1590, 1275, 1120, 1000, 830 cm\textsuperscript{-1}; mp 171-172° C.</td>
</tr>
<tr>
<td>g.</td>
<td>NMR (d\textsubscript{6}-DMSO, CDCl\textsubscript{3}) δ6.90 (tt, J(geminal) = 4Hz, J(vicinal) = 52Hz, 2H), 7.48 (t, J=2Hz, 1H), 7.69 (s, 2H), 7.78 (s, 1H), 8.00 (d, J=2Hz, 2H); IR (nujol mull) 3210, 1600, 1470, 1200, 1130, 1010, 880 cm\textsuperscript{-1}; mp 157-163° C.</td>
</tr>
<tr>
<td>h.</td>
<td>NMR (d\textsubscript{6}-DMSO, CDCl\textsubscript{3}) δ7.20 (dt, J(geminal) = 4Hz, J(vicinal) = 44Hz, 2H), 7.28 (s, 1H), 7.60 (m, 3H), 7.90 (s, 2H); IR (nujol mull) 3200, 1600, 1470, 1170, 1100, 1005, 870 cm\textsuperscript{-1}; mp 110-114° C.</td>
</tr>
<tr>
<td>i.</td>
<td>NMR (d\textsubscript{6}-DMSO, CDCl\textsubscript{3}) δ7.15 (t, J=4Hz, 2H), 7.45 (t, J=2Hz, 1H), 7.65 (s, 3H), 7.93 (d, J=2Hz, 2H); IR (nujol mull) 3200, 1600, 1470, 1160, 1100, 1000, 830 cm\textsuperscript{-1}; mp 110-114° C.</td>
</tr>
<tr>
<td>j.</td>
<td>NMR (d\textsubscript{6}-DMSO, CD\textsubscript{3}OD) δ6.96 (d, J=8Hz, 2H), 6.92 (d, J=8Hz, 2H), 7.60 (s, 1H), 7.68 (s, 2H), 7.90 (d, J=8Hz, 2H); IR (nujol mull) 3300, 3200, 1630, 1450, 865 cm\textsuperscript{-1}; mp 234-238° C.</td>
</tr>
<tr>
<td>k.</td>
<td>NMR (unisol) δ7.04 (d, J=8Hz, 1H), 7.43 (s, 3H), 7.62 (d, J=8Hz, 1H), 8.00 (s, 1H); IR (nujol mull) 3315, 3200, 1620, 1450, 830 cm\textsuperscript{-1}; mp 244-247° C.</td>
</tr>
<tr>
<td>l.</td>
<td>NMR (d\textsubscript{6}-DMSO) δ7.70 (s, 2H), 7.85 (s, 1H), 7.14 (s, 2H); IR (nujol mull) 3315, 3190, 1620, 870 cm\textsuperscript{-1}; mp 238-242° C.</td>
</tr>
</tbody>
</table>
5. Preparation of Haloalkoxy Substituted Benzoic Acids.

The following procedure is typical of the experimental conditions used in the conversion of haloalkoxy substituted methyl benzoates to haloalkoxy substituted benzoic acids (Table VI).

3-(1,1,2,2-tetrafluoroethoxy) benzoic acid. Methyl 3-(1,1,2,2-tetrafluoroethoxy) benzoate (4.0g, 0.0159 mol) and 50 ml of 5% sodium hydroxide were stirred in a 125-ml Erlenmeyer flask at room temperature for 24 hrs. The solution was made slightly acid with 10% hydrochloric acid and the resulting precipitate filtered, taken up in 50 ml of ether and washed with 3 x 50 ml of saturated sodium bicarbonate. The aqueous extracts were combined and the pH made acid. The resulting precipitate was filtered, washed with 100 ml of water and dried overnight in a vacuum dessicator yielding 3.67g (97% yield) of a white solid. NMR (CDCl3, d6-DMSO) δ6.40 (tt, J(geminal)= 3Hz, J(vicinal) = 54Hz, 1H), 7.48 (m, 2H), 7.90 (m, 2H); IR (nujol mull) 2850, (OH stretch), 1690 (C=O, carboxylic acid stretch), 1595, 1490 (C=C, aromatic), 1320, 1120 (C-F stretch) 1005 cm⁻¹ (aryl-alkyl ether); mp 123-126° C.
Table VI
Experimental Data for the Preparation of Haloalkoxy Substituted Benzoic Acids

<table>
<thead>
<tr>
<th>Entry</th>
<th>G₁</th>
<th>G₂</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>3 - HCF₂CF₂-0-</td>
<td>97% a</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>3 - HCFC₁CF₂-0-</td>
<td>96% b</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>3 - HCCl₂CF₂-0-</td>
<td>97% c</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>3 - HCF₂CF₂-0-</td>
<td>95% d</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>3 - HCFC₁CF₂-0-</td>
<td>92% e</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
<td>3 - HCCl₂CF₂-0-</td>
<td>94% f</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>4 - HCFC₁CF₂-0-</td>
<td>96% g</td>
</tr>
</tbody>
</table>

a. NMR (CDCl₃, d₆-DMSO) δ6.40 (tt, J(geminal) = 3Hz, J(vicinal)=54Hz, 1H), 7.48 (m, 2H), 7.90 (m, 2H); IR (nujol mull) 2850, 1690, 1595, 1490, 1320, 1120, 1005 cm⁻¹; mp 123-126° C.

b. NMR (CDCl₃, d₆-DMSO) δ6.73 (dt, J(geminal)=4Hz, J(vicinal)=48Hz, 1H), 7.44-7.52 (m, 2H), 7.86-7.94 (m, 2H); IR (nujol mull) 2900, 1700, 1590, 1310, 1090, 1005, 870 cm⁻¹; mp, 84-87° C.

c. NMR (CDCl₃, d₆-DMSO) δ6.31 (t, J=4Hz, 1H), 7.58-7.68 (m, 2H), 7.98-8.18 (m, 2H); IR (nujol mull) 2900, 1690, 1590, 1160, 1070, 1000, 820 cm⁻¹; mp, 80-81° C.

d. NMR (CDCl₃, d₆-DMSO) δ6.33 (tt, J(geminal)=3Hz, J(vicinal)=54Hz, 2H), 7.35 (t, J=2Hz, 1H), 8.01 (d, J=2Hz, 2H); IR (nujol mull) 2850, 1710, 1610, 1125, 1010, 850 cm⁻¹; mp, 99-105° C.
Table VI (Continued)

e. NMR (CDCl₃) δ6.37 (dt, J(geminal)=4Hz, J(vicinal)=50Hz, 2H), 7.48 (t, J=2Hz, 1H), 8.00 (d, J=2Hz, 2H); IR (nujol mull) 2900, 1700, 1600, 1290, 1170, 1110, 1000, 870 cm⁻¹; mp, 206-213° C.

f. NMR (CDCl₃) δ5.74 (t, J=4Hz, 2H), 7.40 (t, J=2Hz, 1H), 7.92 (d, J=2Hz, 2H); IR (nujol mull) 2900, 1700, 1600, 1300, 1270, 1150, 990, 850 cm⁻¹; mp 206-213° C.

g. NMR (d⁶-DMSO, CDCl₃) δ6.90 (dt, J(geminal)=4Hz, J(vicinal)=48Hz, 1H), 7.37 (d, J=8Hz, 2H), 8.15 (d, J=8Hz, 2H); IR (nujol mull) 2900, 1690, 1600, 1290, 1160, 1090, 1010, 870 cm⁻¹; mp 139-145° C.
6. Preparation of Substituted Symmetric Diacylhydrazines

The following procedure is typical of the experimental conditions used in the conversion of substituted benzoic acids to substituted symmetric diacylhydrazines (Table VII).

*N,N'-di-4-(1,1,2-trifluoro - 2 - chloroethoxy) benzoylhydrazine.*

4-(1,1,2-trifluoro-2-chloroethoxy) benzoic acid (4.138g, 0.0163 mol) and 75 ml of toluene were added to a 250-ml three neck round-bottomed flask equipped with a condenser and a 125-ml addition funnel. Thionyl chloride (5.82g, 0.0498 mol) was added dropwise and the solution was then refluxed for 72 hr. After cooling to room temperature, the toluene was removed (flash evaporator) and the residue checked for OH absorption (IR). Some compounds required a longer reaction time or additional thionyl chloride. The acid chloride was added to 50 ml of THF followed by dropwise addition of aqueous NaHCO₃ (1.361g, 0.0161 mol) and hydrazine (2.279g, 0.008 mol). The solution was stirred at room temperature for one hour whereupon the THF was removed (flash evaporator). The resulting precipitate was filtered and dried yielding 3.995g (98% yield) of a yellow solid. NMR (d6-DMSO, CDCl₃) δ6.90 (dt, J(geminal)=4Hz, J(vicinal)=46Hz, 2H), 7.35 (d, J=8Hz, 4H), 8.18 (d, J=8hz, 4H); IR (mujol mull) 3240 (N-H, 2° amide stretch), 1650 (C=O amide stretch), 1270, 1170, 1080 (C-F, stretch), 1010 (C-O-C, aryl-alkyl ether), 810 cm⁻¹ (p-substitution); mp, 139 -145°C.
Table VII
Experimental Data for the Preparation of Substituted Symmetric Diacylhydrazines

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Entry</th>
<th>$G_1$</th>
<th>$G_2$</th>
<th>Yield</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>3-0-CF$_2$CF$_2$H</td>
<td>85% a</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>3-0-CF$_2$CFClH</td>
<td>82% b</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>3-CF$_2$CCl$_2$H</td>
<td>80% c</td>
</tr>
<tr>
<td>4</td>
<td>3-0-CF$_2$CF$_2$H</td>
<td>5-0-CF$_2$CF$_2$H</td>
<td>86% d</td>
</tr>
<tr>
<td>5</td>
<td>3-0-CF$_2$CClFH</td>
<td>5-0-CF$_2$CClFH</td>
<td>90% e</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>4-0-CF$_2$CClH</td>
<td>98% f</td>
</tr>
</tbody>
</table>

a. NMR (d$_6$-DMSO, CDC$_1$$_3$) ~6.34 (tt, J(geminal)=4Hz, J(vicinal)=54Hz, 2H), 7.32-7.58 (m, 4H), 7.74-8.08 (m, 4H); IR (nujol mull) 3220, 1610, 1580, 1210, 1110, 1000, 810 cm$^{-1}$; mp, 154-159° C.

b. NMR (d$_6$-DMSO, CDC$_1$$_3$) ~7.08 (dt, J(geminal)=4Hz, J(vicinal) = 48Hz, 2H), 7.40-7.63 (m, 4H), 7.90-8.10 (m, 4H); IR (nujol mull) 3210, 1610, 1580, 1200, 1090, 1000, 810; mp, 116-121° C.

c. NMR (d$_6$-DMSO, CDC$_1$$_3$) ~6.48 (t, J=4Hz, 2H), 7.65 (s, 4H), 8.16 (s, 4H); IR (nujol mull) 3300, 1640, 1580, 1310, 1170, 1070, 1000, 820 cm$^{-1}$; mp, 94-100° C.
Table VII (Continued)

d. NMR (d$_6$-DMSO, CDC$_1$$_3$) $\delta$ 6.64 (tt, $J_{(geminal)}$=4Hz, $J_{(vicinal)}$= 54Hz, 4H), 7.48 (s, 2H), 8.09 (s, 4H); IR (nujol mull) 3210, 1630, 1580, 1300, 1200, 1130, 1000, 870 cm$^{-1}$; mp, 140-146$^\circ$ C.

e. NMR (d$_6$-DMSO, CDC$_1$$_3$) $\delta$ 6.66 (dt, $J_{(geminal)}$=4Hz, $J_{(vicinal)}$= 48Hz, 4H), 7.50 (s, 2H), 8.18 (s, 4H); IR (nujol mull) 3210, 1630, 1590, 1270, 1170, 1100, 1000, 870 cm$^{-1}$; mp, 209-213$^\circ$ C.

f. NMR (d$_6$-DMSO, CDC$_1$$_3$) $\delta$ 6.90 (dt, $J_{(geminal)}$=4Hz, $J_{(vicinal)}$ =46Hz, 2H), 7.35 (d, $J$=8Hz, 4H), 8.18 (d, $J$=8Hz, 4H); IR (nujol mull) 3240, 1650, 1600, 1270, 1170, 1080, 1010, 810 cm$^{-1}$; mp, 155-159$^\circ$ C.
7. **Preparation of 2,5 Disubstituted 1,3,4-Oxadiazoles**

The following procedure is typical of the experimental conditions used in the conversion of substituted diacylhydrazides to substituted 1,3,4-oxadiazoles (Table VIII).

2-[(4-(2,2-dichloro-1,1-difluoroethoxy)phenyl) 5-(2,4-dichlorophenyl) 1,3,4 oxadiazoles. To a 50-ml, round-bottomed flask was added 1.679g (0.00367mol) of N-[4-(2,2-dichloro-1,1-difluoroethoxyphenyl]-N'-(2,4-dichlorophenyl) hydrazide and 16 ml of phosphorousoxychloride. The solution was allowed to reflux for 20 hrs. Upon cooling to room temperature, the solution was poured slowly, while stirring, into 100 ml of an ice/water mixture. The resulting precipitate was filtered and dried extensively on a Kugelrhor apparatus yielding 1.501g (93% yield) of a yellow precipitate. NMR (TFA) δ6.15 (t, J=3Hz, 1H), 7.77 (d, J=8Hz, 2H), 7.90 (s, 2H), 8.50 (d, J=8Hz, 2H); IR (nujol mull) 1595 (C=N stretch), 1020 (C-O aryl-alkyl ether stretch), 1045, 970, (C-O stretch), 830 cm⁻¹ (aromatic C-H); mp, 91-94°C.
Table VIII

Experimental Data for the Preparation of 1, 3, 4 Oxadiazoles

\[
\text{Entry} \quad \text{G}_1 \quad \text{G}_2 \quad \text{G}_3 \quad \text{G}_4 \quad \text{G}_5 \quad \text{Yield}
\]

<table>
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<tr>
<th>Entry</th>
<th>G₁</th>
<th>G₂</th>
<th>G₃</th>
<th>G₄</th>
<th>G₅</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>4 - HCF₂CF₂-O-</td>
<td>2-Cl</td>
<td>4-Cl</td>
<td>90% a</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>H</td>
<td>4 - HCFC₁CF₂-O-</td>
<td>2-Cl</td>
<td>4-Cl</td>
<td>89% b</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>H</td>
<td>4 - HCC₁₂CF₂-O-</td>
<td>2-Cl</td>
<td>4-Cl</td>
<td>93% c</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>H</td>
<td>3 - HCF₂CF₂-O-</td>
<td>2-Cl</td>
<td>4-Cl</td>
<td>90% d</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>H</td>
<td>3 - HCF₂CF₂-O-</td>
<td>2-Cl</td>
<td>4-Cl</td>
<td>88% e</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>3-Cl</td>
<td>4-OH</td>
<td>2-Cl</td>
<td>4-Cl</td>
<td>83% f</td>
</tr>
<tr>
<td>7</td>
<td>3-Cl</td>
<td>5-Cl</td>
<td>4-OH</td>
<td>2-Cl</td>
<td>4-Cl</td>
<td>92% g</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>H</td>
<td>4-OH</td>
<td>2-Cl</td>
<td>4-Cl</td>
<td>93% h</td>
</tr>
<tr>
<td>9</td>
<td>3 - HCF₂CF₂-O-</td>
<td>H</td>
<td>H</td>
<td>3' - HCF₂CF₂-O-</td>
<td>H</td>
<td>80% i</td>
</tr>
<tr>
<td>10</td>
<td>4 - HCC₁FCF₂-O-</td>
<td>H</td>
<td>H</td>
<td>4' - HCFC₁CF₂-O-</td>
<td>H</td>
<td>83% j</td>
</tr>
<tr>
<td>11</td>
<td>3 - HCC₁₂CF₂-O-</td>
<td>H</td>
<td>H</td>
<td>3' - HCC₁₂CF₂-O-</td>
<td>H</td>
<td>76% k</td>
</tr>
<tr>
<td>12</td>
<td>3 - HCF₂CF₂-O-</td>
<td>H</td>
<td>5 - HCF₂CF₂-O-</td>
<td>3' - HCF₂CF₂-O-</td>
<td>5' - HCF₂CF₂-O-</td>
<td>83% l</td>
</tr>
<tr>
<td>13</td>
<td>3 - HCFC₁CF₂-O-</td>
<td>H</td>
<td>5 - HCFC₁CF₂-O-</td>
<td>3' - HCFC₁CF₂-O-</td>
<td>5' - HCFC₁CF₂-O-</td>
<td>89% m</td>
</tr>
</tbody>
</table>
Table VIII (Continued)

<table>
<thead>
<tr>
<th>Letters</th>
<th>NMR (unisol) or (TFA)</th>
<th>Chemical Shifts</th>
<th>Multiplicities and Couplings</th>
<th>IR (nujol mull)</th>
<th>Melting Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>a.</td>
<td>NMR (unisol) $\delta$6.34 (tt, J(geminal)=3Hz, J(vicinal)=54Hz, 1H), 7.50 (d, J=10Hz, 2H), 7.44-7.70 (m, 2H), 8.20 (d, J=8Hz, 1H), 8.29 (d, J=10Hz, 2H); IR (nujol mull) 1590, 1040, 1010, 970 cm$^{-1}$; mp, 137-144° C.</td>
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<td>b.</td>
<td>NMR (unisol) $\delta$6.69 (dt, J(geminal)=3Hz, J(vicinal)=48Hz, 1H), 7.46 (d, J= 10Hz, 2H), 7.40-7.68 (m, 2H), 8.13 (d, J=8Hz, 1H), 8.20 (d, J=8Hz, 2H); IR (nujol mull) 1590, 1040, 1020, 970, 870 cm$^{-1}$; mp, 135-141° C.</td>
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<td>c.</td>
<td>NMR (TFA) $\delta$6.15 (t, J=3Hz, 1H), 7.78 (d, J=8Hz, 2H), 7.97 (s, 2H), 8.30 (s, 1H), 8.62 (d, J=8Hz,2H); IR (nujol mull) 1595, 1045, 1020, 970, 830 cm$^{-1}$; mp, 91-94° C.</td>
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<td>d.</td>
<td>NMR (d$^6$-DMSO, CDCl$_3$) $\delta$6.44 (tt, J(geminal)=3Hz, J(vicinal)=54Hz, 1H), 7.45-7.70 (m, 4H) 7.98-8.21 (m, 3H); IR (nujol mull) 1595, 1050, 1005, 930, 840 cm$^{-1}$; mp, 69-72° C.</td>
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<td>e.</td>
<td>NMR (d$^6$-DMSO) $\delta$7.30 (dt, J(geminal)=3Hz, J(vicinal)=46Hz, 1H), 7.55-7.84 (m, 4H), 8.00-8.34 (m, 3H); IR (nujol mull) 1595, 1050, 1020, 970, 850 cm$^{-1}$; mp, 71-73° C.</td>
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<tr>
<td>f.</td>
<td>NMR (TFA) $\delta$7.45-7.90 (m, 3H), 8.21-8.58 (m, 3H); IR (nujol mull) 3100, 1600, 1040, 745 cm$^{-1}$; mp, 169-170° C.</td>
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<tr>
<td>g.</td>
<td>NMR (TFA) $\delta$7.54-7.78 (m, 2H), 8.69 (s, 1H), 8.20 (s, 2H); IR (nujol mull) 3300, 1590, 800 cm$^{-1}$; mp, 168-170°.</td>
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<tr>
<td>h.</td>
<td>NMR (d$^6$-DMSO) $\delta$7.50 (d, J=9Hz, 2H), 7.73-7.84 (m,2H), 8.15 (d, J=9Hz, 2H), 8.18 (d, J=8Hz, 2H); IR(nujol mull) 3300 (broad), 1600, 1390, 850 cm$^{-1}$; mp, 219-223° C.</td>
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</tr>
<tr>
<td>i.</td>
<td>NMR (TFA) $\delta$6.04 (tt, J(geminal)=4Hz, J(vicinal)=54Hz, 2H), 7.83 (d, J=4Hz, 4H), 8.21 (s, broad, 4H); IR (nujol mull) 1590, 1550, 1490, 1300, 1190, 1100, 1000, 870 cm$^{-1}$; mp, 148-151° C.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>j.</td>
<td>NMR (d$^6$-DMSO, CDCl$_3$) $\delta$7.15 (dt, J(geminal)=4Hz, J(vicinal)= 40Hz, 2H), 7.50 (d, J=8Hz, 4H), 8.28 (d, J=8Hz, 4H); IR (nujol mull) 1610, 1490, 1300, 1160, 1080, 1015, 850 cm$^{-1}$; mp, 90-94° C.</td>
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</tr>
<tr>
<td>k.</td>
<td>NMR (TFA) $\delta$5.43 (t, J=4Hz, 2H), 7.11 (m, 4H), 7.54 (s, broad, 4H); IR (nujol mull) 1590, 1550, 1380, 1260, 1150, 1080, 1000, 810 cm$^{-1}$; mp, 129-134° C.</td>
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</tbody>
</table>
Table VIII (Continued)

1. NMR (d$_6$-DMSO, CDCl$_3$) $\delta$6.60 (tt, $J$(geminal)=4Hz, $J$(vicinal)=54Hz, 4H), 7.44 (t, $J$=2Hz, 2H), 8.08 (d, $J$=2Hz, 4H); IR (nujol mull) 1600, 1550, 1380, 1300, 1190, 1110, 1000, 850 cm$^{-1}$; mp, 95-98°C.

m. NMR (TFA) $\delta$6.48 (dt, $J$(geminal)=4Hz, $J$(vicinal)=48Hz, 4H), 7.61 (s, broad, 2H), 8.13 (s, broad, 4H); IR (nujol mull) 1590, 1550, 1260, 1170, 1090, 1000, 860, 810 cm$^{-1}$; mp, 95-96°C.
N,N'-di- 2,5 - (2 - chloro 1,1,2-trifluoroethoxy) phenyl 1,3,4-oxadiazole.

\[
\begin{align*}
\text{RO} & \quad \text{OH} \\ \\
\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O} & \quad \xrightarrow{\text{PPA}} \\
\text{RO} & \quad \text{OR}
\end{align*}
\]

A 100-ml round-bottomed flask was equipped with a Claisen adaptor, mechanical stirrer and condenser. The flask was charged with 3.076g (0.0118 mol) of 3 -(2-chloro-1,1,2-trifluoroethoxy) benzoic acid, 1.04g hydrazine monohydrate and 15.5g of polyphosphoric acid. The reaction mixture was stirred vigorously at 130° C for five hours. Upon cooling to 95° C, 100 ml of water was added and the reaction mixture was allowed to cool to room temperature. The resulting precipitate was filtered and dried extensively on a Kugelrhör apparatus yielding 1.747g (61% yield) of a grey solid.

NMR (d6-DMSO), 67.39 (dt, J(geminal)=4Hz, J(vicinal)=48Hz, 2H), 7.65 (s, broad, 4H), 7.99 - 8.28 (m, 4H); IR (nujol mull) 1590 (C=N stretch), 1180, 1090 (C-F stretch), 1005 (aryl-alkyl ether) 980 cm⁻¹ (C-O stretch); mp, 128-133° C.
DISCUSSION OF RESULTS

A number of potential insecticides, haloalkoxy substituted diacylhydrazines and oxadiazoles, have been prepared in good yields and have been characterized by NMR and IR spectroscopy.

The esterification of substituted benzoic acids is confirmed by the presence of a singlet integrating for three hydrogens at 3.8-4.0 ppm in the NMR, indicative of a methoxy group. In addition, there is a loss of -OH absorption at 2990 cm\(^{-1}\) and a strong carbonyl absorption at 1690 cm\(^{-1}\) in the infrared spectrum. After the addition of the haloethoxy group, a characteristic splitting pattern of the alkyl hydrogen is observed in the NMR. The absorption is shifted downfield to 6.0-6.5 ppm due to the deshielding effect of the halogens. This is split by fluorine into a triplet of triplets for tetrafluoroethoxy, a doublet of triplets for chloro-trifluoroethoxy and a triplet for dichloro-difluoro-ethoxy. The geminal coupling constant is 3-4 Hz and the vicinal coupling constant is 44-54 Hz. These findings are consistent with those of Alperman\(^{10}\) who reported NMR data for tetrafluorolthoxylated phenylethylamines. Simmons\(^{18}\) and Park\(^{19}\) state that the C-H stretch of the -CF\(_2\)H group of polyalkyl fluorides is observed at 2290-3008 cm\(^{-1}\). In addition, Simmons\(^{18}\) observed a strong, broad absorption at 1120-1280 cm\(^{-1}\) which he attributed to C-F stretching. These bands were observed in the polyhaloethoxylated
methyl benzoates. Hydrolysis of the esters to acids was confirmed by
the loss of a singlet at 3.8-4.0 ppm in the NMR, the appearance of an
-OH absorption at 2990 cm\(^{-1}\), and a decrease in carbonyl absorption
frequency of 20-40 cm\(^{-1}\) in the infrared. After conversion of the
esters to hydrazides, the carbonyl stretching frequency is decreased
by 50 cm\(^{-1}\). The characteristic frequencies seen in the infrared of
hydrazides are at 3440-3420 cm\(^{-1}\) (1° N-H amine stretch), 3324 cm\(^{-1}\)
(2° N-H amide stretch), 1670 cm\(^{-1}\) (1° N-H amine bend). Smith\(^{20}\) states
that two bands appear in the carbonyl region at 1620 cm\(^{-1}\) and
1670-1630 cm\(^{-1}\). Prevorsek\(^{21}\) cites these absorptions also. Zabicky\(^{22}\)
states that crystalline hydrazides show three absorptions; 1670-1625
cm\(^{-1}\), 1570-1530 cm\(^{-1}\) and 1305-1200 cm\(^{-1}\). He attributes the band at
1620-1610 cm\(^{-1}\) to NH\(_2\) deformation. The NMR shows a loss of the
methoxy singlet (3.8-4.0 ppm) and the appearance of a broad singlet at
3.6-4.0 ppm integrating for two hydrogens (NH\(_2\)).

The diacylhydrazines also exhibit a 2° N-H amide stretch at
3360-3340 cm\(^{-1}\). The 1° N-H amine stretch is absent as is the broad
singlet at 3.6-4.0 ppm in the NMR. The C=O absorption is shifted
to a lower frequency by 45 cm\(^{-1}\). The cyclodehydration of
N, N'-diacylhydrazines to 1,3,4-oxadiazoles is confirmed primarily
by IR data. The 2° N-H amide stretch and the C=O carbonyl stretch
are absent. Bands at 970 and 1030-1020 cm\(^{-1}\) due to C-O absorption
and 1610-1580 cm\(^{-1}\) due to C=N valence vibration are observed.
These findings are consistent with the values given by Katritsky\(^{23}\)
and others\(^{24}\) for 1,3,4-oxadiazoles.
CONCLUSIONS

Two classes of compounds, diacylyhydrazines and oxadiazoles (Figure 4) have been prepared and forwarded to the Dow Chemical Company for biological screening. These compounds may exhibit greater biological activity than the known pesticides of this type and may be prepared in good to excellent yields. The structure these compounds have been characterized by IR and NMR spectroscopy.

![Figure 4. Classes of compounds prepared for biological screening.](image)

\[
\text{Ar} - \overset{\text{O}}{\text{CH}} - \overset{\text{NH}}{\text{NH}} - \overset{\text{O}}{\text{CH}} - \text{Ar}
\]

\[
\overset{\text{N}}{\text{O}} - \overset{\text{N}}{\text{O}} - \overset{\text{N}}{\text{O}}
\]
RECOMMENDATIONS

The following are suggestions for future research.

1. When performing the haloethoxylation reaction, strict attention should be paid to reaction temperature. Optimum temperatures appear to be 95-100° C for tetrofluoroethylene and chlorotrifluoroethylene, and 110-115° C for dichloro-difluoroethylene. An exotherm is observed and the reaction temperature should be adjusted throughout the course of the reaction. Haloethoxy substituted methyl benzoates appear to be highly susceptible to basic hydrolysis, particularly the dichloro-difluoroethoxy substituted compounds. For this reason, the high concentrations of base should be avoided during the base extraction (5% NaOH).

2. The reaction conditions for the preparation of the haloethoxy substituted benzoyl chlorides should be optimized. These compounds appear to be very unreactive to this type of substitution. Perhaps a higher boiling solvent would be helpful.
REFERENCES


