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Synthesis of Potential Anti-Tumor Agents Related to Ethanolamine. I. Phenoxyacetic Acid Derivatives

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SYNTHESIS OF POTENTIAL ANTI-TUMOR AGENTS RELATED TO ETHANOLAMINE. I. PHENOXYACETIC ACID DERIVATIVES

by

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INTRODUCTION

Derivatives of phenoxyacetic acid (PAA), because of their activity as synthetic auxins, have long been of interest in the botanical sciences. PAA itself was noted (29) to have some auxin activity. However, real interest in PAA derivatives awaited the establishment of 2,4-dichlorophenoxyacetic acid (2,4-D) as a powerful, selective herbicide (12). An enormous number of PAA analogs and homologs have been investigated for their potential in the herbicide industry, and the statistical evidence from these investigations has been used as the basis for several interesting and sometimes conflicting theories of auxin mechanisms (17, 26, 23, 27).

Physiological effects of PAA derivatives on animals have been observed, but, as in the case with plants, the exact nature of these effects and the chemical reactions causing them are not known. Various PAA derivatives uncouple oxidative phosphorylation (4, 28), lower serum protein bound iodine (9), reduce the permeability of peritoneal blood vessels (19), inhibit lactic dehydrogenase (20) and produce local anesthetic effects (15). Whether any PAA derivatives have value as anti-tumor agents has yet to be proved. Indeed, Bucher (5) has found, in experiments with several types of animals, that 2,4-D neither causes tumors nor has any effect on tumor growth rates.

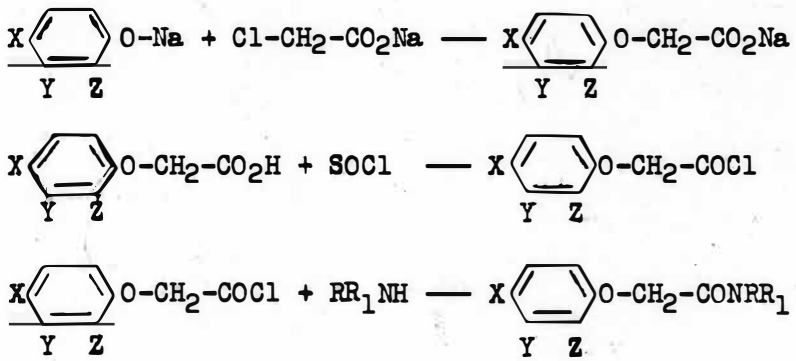
However, Baker (2), because of the function of inhibition of lactic dehydrogenase, has further investigated the potential of some PAA

analogs as anti-tumor agents. This study was made to evaluate the effect of PAA analogs in the inhibition of lactic dehydrogenase (LDH). It is this enzyme system which furnishes nicotinamide adenine dinucleotide (NAD) to the oxygen-deficient neoplastic cells with reduction of pyruvate. Since this function of LDH is possibly unnecessary in normal tissue cells, inhibition of the enzyme system would probably only inhibit the tumor that is dependent on this reaction for regeneration of NAD. Although Baker's work did not provide evidence that PAA derivatives were effective anti-tumor agents, it did show that further investigation of PAA analogs with various ring substitutions and functional group changes on the alkyl moiety was warranted.

The purpose of the work presented in this thesis was the syntheses of three amides of each of five phenoxyacetic acid analogs. The fifteen amides were to be tested for anti-tumoral activity in the hope that they would offer some clues in the quest for effective chemotherapeutic agents.

Amides can be synthesized from carboxylic acids by several methods. Among these, a standard method is the continuous removal of water from an ammonium or amine salt of the carboxylic acid by gentle distillation (7). Another is the classical method of Aschan (1) for reacting the acid chloride of the carboxylic acid with aqueous ammonia or the desired amine and subsequent purification of the amide by crystallization or distillation. The latter method was used for syntheses of the ring substituted phenoxyacetamide homologs required for this study.

The general outline of the method of preparation of the compounds synthesized in the work for this thesis is as follows:



where: X is either Br or Cl,

Y is H or $-CH_3$,

Z is Cl, Br, $-CH_3$ or $-CH(CH_3)_2$ and

R and R_1 are either H or $-CH_2-CH_3$

EXPERIMENTAL

All temperatures reported are uncorrected and expressed in degrees centigrade.

Special chemicals used in these preparations were obtained from the following sources and used directly. The 2,4-dibromophenol and 4-chloro-2-isopropylphenol starting materials were received through the courtesy and generosity of The Dow Chemical Company, Midland, Michigan. Chemicals purchased from Eastman Organic Chemicals included 4-chloro-2-methylphenol (#6471), 4-chloro-3-methylphenol (#930), 4-chloro-2-methylphenoxyacetic acid (#P6815), 2,4-dichlorophenoxyacetic acid (#5532) and the necessary amines.

Preparation of ring substituted phenoxyacetic acids

The following general preparative method was applied to the

formation of all the desired substituted phenoxyacetic acids. According to the method of Palmer and Kester (21), suitable ring substituted phenol was dissolved in sodium hydroxide solution and mixed well with chloroacetic acid previously converted to chloroacetate by dissolving in sodium hydroxide solution. Alternatively, the phenol was dissolved in sodium hydroxide solution and reagent grade sodium chloroacetate added. A mole ratio of 1:10:15 for phenol:chloroacetic acid:sodium hydroxide produced the best yields. About two liters of water was used for a solution containing one mole of phenol and appropriate quantities of chloroacetic acid and sodium hydroxide. The solution was refluxed overnight, cooled, and any precipitated phenoxyacetate separated by filtration. The filtrate was poured into excess hydrochloric acid in ice water, and the resulting phenoxyacetic acid filtered. The sodium phenoxyacetate and phenoxyacetic acid obtained in the two filtrations were thoroughly stirred into dilute hydrochloric acid solution to convert all to the acid and this was then separated by filtration. After washing several times with water, the phenoxyacetic acid was recrystallized twice from methanol/water solution and dried over sulfuric acid in a desiccator.

Although filtering the precipitated sodium phenoxyacetate prior to acidification of the reaction mixture appears to be superfluous, subsequent filtration was greatly simplified by this procedure. Acidifying the reaction mixture containing solid phenoxyacetate caused the precipitated phenoxyacetic acid to be gelatinous and difficult to filter. Once the precipitated salts were removed, the soluble salts could be acidified to the phenoxyacetic acid and filtered without difficulty. Table I contains essential data on 2,4-dibromophenoxyacetic acid, 4-chloro-2-

TABLE I

RING SUBSTITUTED PHENOXYACETIC ACIDS

Product	Phenol Weight g.	Phenol Moles	Yield Weight g.	Yield %	m.p. Exptl.	m.p. Lit.
2,4-dibromophenoxy-acetic acid	252	1.0	105	34	150-1.5°	151.8-3.5° (18)
4-chloro-2-methylphenoxy-acetic acid	7.2	0.05	8.1	80	114-7°	119-20° (24)
4-chloro-3-methylphenoxy-acetic acid	9.3	0.065	10.5	80	177-8.5°	177-8° (24)
4-chloro-2-isopropylphenoxy-acetic acid	17.1	0.1	16.7	73	167-8.5°	———

methylphenoxyacetic acid, 4-chloro-3-methylphenoxyacetic acid, 4-chloro-2-isopropylphenoxyacetic acid and their syntheses.

Preparation of ring substituted phenoxyacetyl chlorides

All phenoxyacetyl chlorides were prepared according to the method of Helferich and Schaefer (14). The ring substituted phenoxyacetic acid and thionyl chloride, in mole ratio of 1:1.6, were mixed well and refluxed with suitable trapping of the effluent gases over sodium hydroxide solution. The completion of the reaction was discerned by intermittently placing a beaker of sodium carbonate solution under the funnel of the vapor trap until the absence of carbon dioxide bubbles in the beaker indicated that no more sulfur dioxide and hydrogen chloride gases were being evolved in the reaction flask. Upon completion of the reaction the excess thionyl chloride was separated from the acid chloride by distillation at atmospheric pressure. The 2,4-dibromo- and 2,4-dichlorophenoxyacetyl chlorides were low melting crystalline compounds and were purified by recrystallization from petroleum ether. The 4-chloro-2-methyl-, 4-chloro-3-methyl- and 4-chloro-2-isopropylphenoxyacetyl chlorides were clear, water-white liquids and were purified by distillation under reduced pressure. Table II lists data on the phenoxyacetyl chlorides and their syntheses.

Preparation of ring substituted phenoxyacetamides

Ring substituted phenoxyacetamides were prepared by Aschan's classical method (1) as described by Sidgwick (22). Ten times the required mole ratio of ammonium hydroxide (28%) was placed in a flask and cooled in an

TABLE II

RING SUBSTITUTED PHENOXYACETYL CHLORIDES

Product	Phenoxy-acetic acid g.	Phenoxy-acetic acid moles	Yield Weight g.	Yield %	m.p./b.p. Exptl.	m.p./b.p. Lit.	n_D^{25}
2,4-dibromophenoxy-acetyl chloride	150	0.49	122	76	46-7°	———	———
2,4-dichlorophenoxy-acetyl chloride	221	1.0	218	91	52-3°	52.5-3.5° (6)	———
4-chloro-2-methyl-phenoxyacetyl chloride	82.5	0.39	60	69	152-3° 13mm	138-9° 6mm (10)	1.5416
4-chloro-3-methyl-phenoxyacetyl chloride	201	1.0	176	80	149-56° 15mm	———	1.5450
4-chloro-2-isopropyl-phenoxyacetyl chloride	230	1.0	94	38	164-6° 15mm	———	1.5321

ice bath. Substituted phenoxyacetyl chloride was then added dropwise to the flask with much swirling and constant cooling to control the quite violent and exothermic reaction. After all the acid chloride had been added, the mixture was diluted with water and filtered. The phenoxyacetamide was recrystallized once from methanol/water solution and, after drying, once from petroleum ether. All the ring substituted phenoxyacetamides were white crystalline compounds. Table III lists essential data on the phenoxyacetamide analogs and their syntheses.

Preparation of ring substituted N-ethylphenoxyacetamides

A group of N-ethylphenoxyacetamide analogs was prepared in a manner similar to that described for the syntheses of ring substituted phenoxyacetamides. In mole ratio of 1:10, acid chloride was added dropwise to ice cold ethylamine (70%), with agitation of the mixture. After dilution with water, the resulting N-ethylphenoxyacetamide analog was appropriately separated from the excess aqueous ethylamine and ethylammonium chloride.

The crystalline 2,4-dibromo-, 2,4-dichloro-, 4-chloro-2-methyl- and 4-chloro-3-methyl- analogs of N-ethylphenoxyacetamide were removed from the reaction mixture by filtration, recrystallized once from methanol/water solution and, after drying, once from petroleum ether. The N-ethyl(4-chloro-2-isopropylphenoxy)acetamide was liquid and this was washed twice with dilute hydrochloric acid, then extracted from the aqueous reaction mixture with 1,1,1-trichloroethane and dried over anhydrous magnesium perchlorate. After filtration, the solvent was

TABLE III

RING SUBSTITUTED PHENOXYACETAMIDES

Product	Phenoxy-acetyl chloride g.	Phenoxy-acetyl chloride moles	Yield g.	Yield %	m.p. Exptl.	m.p. Lit.
2,4-dibromophenoxy-acetamide	33	0.1	22	71	174-6°	———
2,4-dichlorophenoxy-acetamide	24	0.1	18	82	154-5°	155° (16)
4-chloro-2-methyl-phenoxyacetamide	28.5	0.14	19	66	148-9.5°	149-50° (10)
4-chloro-3-methyl-phenoxyacetamide	11	0.05	6	60	145-5.5°	146-7° (8)
4-chloro-2-isopropyl-phenoxyacetamide	32.5	0.13	23	76	105-7°	———

removed by evaporation and the amide was purified by distillation under reduced pressure. Table IV lists data on the N-ethylphenoxyacetamide analogs and their syntheses.

Preparation of ring substituted N,N-diethylphenoxyacetamides

In a manner similar to that described for syntheses of ring substituted phenoxyacetamides, a group of N,N-diethylphenoxyacetamides was prepared by the reaction of diethylamine with suitable ring substituted phenoxyacetyl chlorides. Diethylamine and acid chloride were reacted in the same mole ratio as used in the above syntheses. After dilution with water and washing twice with dilute hydrochloric acid, the liquid amide was separated from the aqueous solution by extraction with 1,1,1-trichloroethane. The extract was dried over anhydrous magnesium perchlorate and filtered. The solvent was removed by evaporation and, except for the solid 2,4-dibromo- analog, which was recrystallized, the amides were purified by distillation at reduced pressure.

The 2,4-dibromo- and 2,4-dichloro- analogs of N,N-diethylphenoxyacetamide were white, crystalline compounds. Crystallization of the 2,4-dibromo- analog occurred as soon as all of the 1,1,1-trichloroethane had evaporated. The 2,4-dichloro- analog, however, crystallized with much difficulty. After purification by distillation under reduced pressure, crystallization of the N,N-diethyl(2,4-dichlorophenoxy)acetamide was attempted by the usual methods without success, and only when a small amount of the liquid was placed onto the sodium chloride prism used for infrared analyses did crystals of the amide form. These were used to seed the remaining mass of liquid amide. Subsequent recrystallizations

TABLE IV

RING SUBSTITUTED N-ETHYLPHENOXYACETAMIDES

Product	Phenoxy-acetyl chloride g.	Phenoxy-acetyl chloride moles	Yield g.	Yield %	m.p./b.p. Exptl.	m.p./b.p. Lit.	n_D^{25}
N-ethyl(2,4-dibromo-phenoxy)acetamide	33	0.1	22	65	117-9°	———	———
N-ethyl(2,4-dichloro-phenoxy)acetamide	25	0.1	21	84	107-9°	108-8.5° (16)	———
N-ethyl(4-chloro-2-methylphenoxy)acetamide	16.5	0.075	12.5	73	98.5-100°	———	———
N-ethyl(4-chloro-3-methylphenoxy)acetamide	22	0.1	22	96	78-9°	———	———
N-ethyl(4-chloro-2-isopropylphenoxy)-acetamide	24.8	0.1	15.4	58	197-9° 4mm	———	1.5305

from petroleum ether were carried out with comparative ease. Each of the solid amides was recrystallized twice from petroleum ether.

The 4-chloro-2-methyl-, 4-chloro-3-methyl- and 4-chloro-2-isopropyl- analogs of N,N-diethylphenoxyacetamide were clear, water-white, high boiling liquids. Attempts to crystallize these compounds were unsuccessful.

Table V lists data on the N,N-diethylphenoxyacetamide analogs and their syntheses.

Micro-analyses

All of the fifteen amides synthesized were analyzed for carbon and hydrogen content by Galbraith Laboratories, Knoxville, Tennessee. The solid amides were dried over phosphorous pentoxide at reduced pressure, while the liquid amides were analyzed after distillation without additional drying. Analytical results, listed in Table VI, were all well within allowable percentage limits.

Infrared analyses

Infrared spectra of all the amides synthesized were obtained with a Beckman IR-8 Spectrophotometer and sodium chloride cells. Liquid amides were placed on the sodium chloride plates in the pure state while the solid amides were suspended in mineral oil for spectral analyses.

Bands of interest for these amides were those which have been attributed to the NH stretching modes, Amide I (CO absorption), Amide II (primary and secondary amides only), the ether C-O- stretching vibration, the aromatic CH out-of-plane deformations and the CH in-plane deformation modes characteristic of 1,2,4- ring substitution. Band assignments were according to Bellamy (3).

TABLE V

RING SUBSTITUTED N,N-DIETHYLPHENOXYACETAMIDES

Product	Phenoxy-acetyl chloride g.	Phenoxy-acetyl chloride moles	Yield g.	Yield %	m.p./b.p. Exptl.	m.p./b.p. Lit.	n_D^{25}
N,N-diethyl(2,4-dibromo-phenoxy)acetamide	33	0.1	8	21	66-8°	———	———
N,N-diethyl(2,4-dichloro-phenoxy)acetamide	25	0.1	15.5	52	55.5-57° 199-202° 6mm	———	1.5472
N,N-diethyl(4-chloro-2-methylphenoxy)-acetamide	22	0.1	24	84	199.5-202° 2mm	———	1.5309
N,N-diethyl(4-chloro-3-methylphenoxy)-acetamide	22	0.1	22	77	195-6° 10mm	———	1.5339
N,N-diethyl(4-chloro-2-isopropylphenoxy)-acetamide	25	0.1	19	61	210-212° 4mm	———	1.5259

TABLE VI

MICRO-ANALYTICAL DATA

Compound	Formula	Calc'd	Found
2,4-dibromophenoxy-acetamide	$C_8H_7Br_2NO_2$	C, 31.10 H, 2.28	C, 30.94 H, 2.13
2,4-dichlorophenoxy-acetamide	$C_8H_7Cl_2NO_2$	C, 43.66 H, 3.21	C, 43.87 H, 3.32
4-chloro-2-methyl-phenoxyacetamide	$C_9H_{10}ClNO_2$	C, 54.14 H, 5.05	C, 54.03 H, 5.01
4-chloro-3-methyl-phenoxyacetamide	$C_9H_{10}ClNO_2$	C, 54.14 H, 5.05	C, 53.95 H, 4.91
4-chloro-2-isopropyl-phenoxyacetamide	$C_{11}H_{14}ClNO_2$	C, 58.02 H, 6.20	C, 57.84 H, 6.21
N-ethyl(2,4-dibromo-phenoxy)acetamide	$C_{10}H_{11}Br_2NO_2$	C, 35.63 H, 3.29	C, 35.56 H, 3.21
N-ethyl(2,4-dichloro-phenoxy)acetamide	$C_{10}H_{11}Cl_2NO_2$	C, 48.40 H, 4.47	C, 48.17 H, 4.33
N-ethyl(4-chloro-2-methylphenoxy)acetamide	$C_{11}H_{14}ClNO_2$	C, 58.02 H, 6.20	C, 57.95 H, 6.21
N-ethyl(4-chloro-3-methylphenoxy)acetamide	$C_{11}H_{14}ClNO_2$	C, 58.02 H, 6.20	C, 57.88 H, 6.16
N-ethyl(4-chloro-2-isopropylphenoxy)acetamide	$C_{13}H_{18}ClNO_2$	C, 61.05 H, 7.09	C, 60.82 H, 6.90
N,N-diethyl(2,4-dibromo-phenoxy)acetamide	$C_{12}H_{15}Br_2NO_2$	C, 39.48 H, 4.14	C, 39.45 H, 3.98
N,N-diethyl(2,4-dichloro-phenoxy)acetamide	$C_{12}H_{15}Cl_2NO_2$	C, 52.18 H, 5.47	C, 51.98 H, 5.63
N,N-diethyl(4-chloro-2-methylphenoxy)acetamide	$C_{13}H_{18}ClNO_2$	C, 61.05 H, 7.09	C, 60.85 H, 6.94
N,N-diethyl(4-chloro-3-methylphenoxy)acetamide	$C_{13}H_{18}ClNO_2$	C, 61.05 H, 7.09	C, 60.94 H, 7.03
N,N-diethyl(4-chloro-2-isopropylphenoxy)acetamide	$C_{15}H_{22}ClNO_2$	C, 63.48 H, 7.81	C, 63.65 H, 7.76

Spectral data for the analogs of phenoxyacetamide, N-ethylphenoxyacetamide and N,N-diethylphenoxyacetamide are shown in Tables VII, VIII and IX respectively.

TABLE VII

INFRARED SPECTRAL DATA

ANALOGS OF PHENOXYACETAMIDE

Compound	Bands cm^{-1}						
	a*	b*	c*	d*	e*	f*	g*
2,4-dibromophenoxy-acetamide	3472 3367	3279 3155	1689	1587	1248	790 896	1031 1050 1092 1117
2,4-dichlorophenoxy-acetamide	3484 3367	3279 3155	1706	1592	1244	807 865	1053 1073 1103 1245
4-chloro-2-methylphenoxy-acetamide	3472 —	3279 3145	1704	1582	1242	800 867	1033 1053 1131 1188
4-chloro-3-methylphenoxy-acetamide	— 3378	— 3155	1645	1592	1235	801 —	1038 1068 1111 1235
4-chloro-2-isopropyl-phenoxyacetamide	3484 3436	— 3165	1678	1587	1232	801 881	1057 1078 1117 1185

*Approximate Band Positions According to Bellamy (3)

a. Free NH - 3500 and 3400
b. Bonded NH - 3350 and 3180
c. Amide I - 1690
d. Amide II - 1650 to 1620
e. Ether - 1270 to 1230
f. CH out-of-plane - 900 to 860 and 860 to 800
g. CH in-plane - 1225 to 1175, 1125 to 1090 and 1070 to 1000 (2 bands)

TABLE VIII

INFRARED SPECTRAL DATA

ANALOGS OF N-ETHYLPHENOXYACETAMIDE

Compound	Bands cm^{-1}						
	a*	b*	c*	d*	e*	f*	g*
N-ethyl(2,4-dibromophen-oxy)acetamide	3279	1653	1541	1299	1235	805 866	1049 1075 1149 1235
N-ethyl(2,3-dichloro-phenoxy)acetamide	3279	1653	1550	1302	1235	805 864	— 1053 1101 1235
N-ethyl(4-chloro-2-methyl-phenoxy)acetamide	3401	1645	1515	1290	1239	791 866	1031 1058 1133 1189
N-ethyl(4-chloro-3-methyl-phenoxy)acetamide	3268	1653	1550	1300	1235	792 855	1038 1081 1149 1235
N-ethyl(4-chloro-2-iso-propylphenoxy)acetamide	3311	1658	1527	1285	1235	803 877	1049 1070 1119 1189

*Approximate Band Positions According to Bellamy (3)

a. Bonded NH (trans) 3320 to 3270
b. Amide I - 1680 to 1630
c. Amide II - 1570 to 1515
d. Amide III - 1290
e. Ether - 1270 to 1230
f. CH out-of-plane - 900 to 860 and 860 to 800
g. CH in-plane - 1225 to 1175, 1125 to 1090 and 1070 to 1000 (2 bands)

TABLE IX

INFRARED SPECTRAL DATA

ANALOGS OF N,N-DIETHYLPHENOXYACETAMIDE

Product	Bands cm^{-1}			
	a*	b*	c*	d*
N,N-diethyl(2,4-dibromo-phenoxy)acetamide	1667	1250	797 860	1064 1087 1136 1235
N,N-diethyl(2,4-dichloro-phenoxy)acetamide	1647	1250	800 858	1068 1096 1140 1212
N,N-diethyl(4-chloro-2-methylphenoxy)acetamide	1653	1250	800 877	1034 1067 1095 1189
N,N-diethyl(4-chloro-3-methylphenoxy)acetamide	1653	1238	806 893	1038 1076 1122 1238
N,N-diethyl(4-chloro-2-isopropylphenoxy)acetamide	1653	1232	800 877	1022 1070 1119 1189

*Approximate Band Positions According to Bellamy (3)

a. Amide I - 1670 to 1630
b. Ether - 1270 to 1230
c. CH out-of-plane 900 to 860 and 860 to 800
d. CH in-plane - 1225 to 1175, 1125 to 1090 and 1070 to 1000 (2 bands)

DISCUSSION

The preparation of amides from phenoxyacetic acid analogs was accomplished without difficulty and without novel incidents. The methods involved in these syntheses were straightforward, time-tested, and were not expected to result in any great surprises. However, a number of the compounds in the series appeared to be completely new, or at least unreported. Evaluation of anti-tumor activity of this group of compounds will be of value as an extension of previously reported interest in their analogs.

Williamson syntheses of phenoxyacetic acid analogs from the four different phenols and chloroacetic acid offered an opportunity to observe any yield variations due to steric hindrance at the ortho position. If steric effects were the only consideration, yields in this S_N2 reaction would be expected to decrease in the order: 4-chloro-3-methyl-, 4-chloro-2-methyl-, 2,4-dibromo- and 4-chloro-2-isopropyl- because of the increasing bulk (25) of the groups at the ortho positions. However, Hammond (11) found that the activity of phenols was not significantly influenced by steric hindrance due to ortho substitution and, indeed, yields of the three alkylated phenoxyacetic acids were quite similar (73%, 80% and 80%) while the yield of 2,4-dibromophenoxyacetic acid was exceptionally low (34%). These results indicate that electronic effects are probably of more importance than steric hindrance for preparation of phenoxyacetic acid analogs. Circumventing the electronic effects of ortho groups can be accomplished by halogenation of the phenyl ring after synthesis of phenoxyacetic acid. Yields of 74% for the synthesis of 2,4-dibromophenoxyacetic acid were obtained by Haskelberg (13) by this method.

Yields for the preparation of the fifteen amides were as expected except for the synthesis of N,N-diethyl(2,4-dibromophenoxy)acetamide, which was of unusually low yield.

Infrared absorption bands were in reasonable agreement with the bands prescribed by the theoretical structures of the amides. Some weak bands described by Bellamy (3), such as some of the NH stretching modes at about 3400 cm^{-1}, were not discerned on the spectra. Correlation of Bellamy's theoretical absorption band requirements with the actual spectral data was good, however, and when these correlations were combined with the micro-analytical results and, in some cases, the comparison of experimental melting and boiling point data with literature data, the amides could, with considerable certainty, be assumed to be what their names indicated.

SUMMARY

The preparation of fifteen amide analogs of phenoxyacetamide was accomplished. Melting and boiling points, refractive indices (when applicable) and infrared spectral data for the amides were recorded. The presence of a bulky electron-withdrawing bromine group ortho to the phenoxide oxygen inhibited the Williamson synthesis reaction. The chemistry involved in the preparations was straightforward and time-tested. Analytical data and infrared spectra agreed with the structural assignments in the products.

Several of the compounds synthesized are new or unreported.

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