PREPARATION OF VARIOUS AMINO ALCOHOL DERIVATIVES

OF p-CHLOROPHENOXYACETIC ACID AND PHENYL-
ACETIC ACID

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CHAPTER I
INTRODUCTION

It has been known for a number of years that the presence of an excess of histamine in the body produces hay fever, asthma, and many allergies. \(^1\) This excess may arise from the ingestion of certain proteins or by their introduction through the respiratory system.

Various compounds have been used for the treatment of hay fever, asthma, and certain allergies. At the present time Adrenaline\(^2\) and Benadryl\(^3\) are widely used, but they are not completely satisfactory.

![Adrenaline and Benadryl structures]

Mayer, Huttner, and Scholtz\(^4\) prepared eleven compounds of the general formula \(R_1R_2NCH_{2}N(R_3)\), and tested them for their anti-histamine properties. The most active substance

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is the compound where $R_1$ is pyridyl, $R_2$ is benzyl, and $R_3$ is methyl.

Loew, Kaiser, and Moore\textsuperscript{5} reported compounds with the structure $\text{Ph}_2\text{CHOR}$ as having anti-histamine properties. Compounds of this type with greatest activity are those where $R$ is 2-dimethylaminooethyl, 2-piperidinoethyl, 2-morpholinoethyl, or 2-diethylaminooethyl.

Bovet, Horclois, and Walthert\textsuperscript{6} reported that 2- (p-methoxybenzyl)(2-dimethylaminooethyl) amino pyridine when injected subcutaneously into guinea pigs counteracted the effect of thirty to sixty times its weight of histamine hydrochloride.

In the rabbit, injection of histamine hydrochloride causes a marked drop in blood pressure. Ramanamanjory\textsuperscript{7} reports that this drop is completely prevented by previous subcutaneous injection of N-phenyl-N-ethylenediamine. This compound prevents the production of bronchoconstriction by histamine in guinea pigs.

Lehmann and Young\textsuperscript{8} reported that when diethylaminooethyl

\textsuperscript{5} Earl R. Loew, Margaret E. Kaiser, and Vernon Moore, J. Pharmacol., \textbf{83}, 102-9 (1945).


\textsuperscript{8} Gerhard Lehmann and James W. Young, Chem. Abst., \textbf{39}, 2334 (1945).
dihydroanthracene-carboxylate is injected subcutaneously thirty minutes before administration of shock injection, one hundred per cent protection is provided against a minimum lethal dose of histamine; diethylaminoethyl xanthine-carboxylate gives seventy per cent protection; diethylaminoethyl fluorescein-carboxylate gives thirty-seven per cent protection; and aminophylline gives thirty-seven per cent protection. Diethylaminoethyl dihydroanthracene-carboxylate intensifies intradermal skin reaction to histamine but is more potent than Adrenaline in its bronchodilator effect.

Herbert, Flis, and McGavack\textsuperscript{9} tested the influence of dimethylaminoethyl benzhydryl ether hydrochloride upon histamine flare reactions. In ten subjects, without known disturbances of the autonomic nervous system, dimethylaminoethyl benzhydryl ether hydrochloride caused a reduction in the cutaneous responses to histamine when given by mouth in divided doses. Maximum effects with the complete disappearance of the triple skin reaction were obtained. No tolerance to the drug was observed even after eighteen weeks of investigation. After discontinuance for a brief period, the responses to histamine were increased.

The action of two new synthetic histamine antagonists, 2-dimethylaminoethyl benzhydryl ether and pyridil-N-benzyl-N-dimethyl-ethylenediamine (Pyribenzamine), in preventing

histamine and anaphylactic shock in guinea pigs was reported by Friedlaender and co-workers. Five times the lethal dose of histamine was required to kill animals previously treated with 2-dimethylaminoethyl benzhydryl ether hydrochloride, while thirty-five times the lethal dose was required to produce one hundred per cent mortality in animals receiving Pyribenzamine. No apparent difference was observed between the two drugs in preventing anaphylaxis in sensitized guinea pigs. One milligram per kilogram of animal weight of either compound gave significant protection against a shocking dose of antigen, while three milligrams per kilogram prevented fatal anaphylaxis in all animals tested.

Lee, Dinwiddie, and Chen have reported that N-(2-pyridyl)-N-(2-phenyl)-N', N'-dimethylendiamine hydrochloride has been prepared and tested; it shows strong anti-histamine properties. When injected subcutaneously thirty minutes before anaphylactic shock, aminophylline provides thirty-seven per cent protection to sensitized guinea pigs against a minimum fatal dose of antigen. The increase in the resistance of the pulmonary circulation of the isolated perfused guinea pig

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12 Gerhard Lehmann and James W. Young, J. Pharmacol., 83, 90-5 (1946).
lung caused by Adrenaline, is reduced by aminophilic. Dimethylaminoethyl dihydroanthracencarboxylate \(^{13}\) has been found to give one hundred per cent protection to sensitized guinea pig against a minimum fatal dose of antigen.

Many of the above compounds show high anti-histamine properties but are toxic or are difficult to adminster to the patient; those which are relatively non-toxic or are easily administered show mild anti-histamine properties.

Most of the above mentioned compounds which have been found to possess anti-histamine properties have one thing in common, namely, all possess a dialkyaminealkoxy grouping. This grouping may be present either as the alcohol portion of an ester or as an ether linkage. In light of this observation, it was decided that the preparation of substances containing dialkyaminealkoxy groups would yield compounds likely to be active as anti-histamines.

This thesis deals with the preparation of dialkyaminealkoxy derivatives of \(p\)-chlorophenoxyacetic acid and phenylacetic acid. The following formulae serve to illustrate the general types of compounds proposed for this investigation.

\(^{13}\) Lehmann and Young, op. cit., 2334.
$R = \text{alkyl}, \ n = 2 \text{ or } 3$

Dialkylaminoalkyl p-chlorophenoxyacetate

$R = \text{alkyl}, \ n = 2 \text{ or } 3$

Dialkylaminoalkyl α-(dialkylaminoalkoxy) phenylacetate
CHAPTER II
EXPERIMENTAL PROCEDURE

\( p\)-Chlorophenoxyacetyle Chloride

\[ \begin{array}{c}
\text{Cl} \\
\text{O} \\
\text{O} \\
\text{CH}_2
\end{array} \]

A solution of 180 g. (1.0 mole) of \( p\)-chlorophenoxyacetic acid dissolved in 400 ml. of benzene was charged to 1000 ml., three-neck flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel. To this stirred solution were added dropwise 117 g. (1.5 mole) of thionyl chloride. This solution was heated at reflux temperature for three hours after the thionyl chloride had been added. The resulting solution was transferred to a distilling flask and the benzene and excess thionyl chloride were distilled under a water pump vacuum. The residual liquid was distilled in vacuo and 185 g. (90 per cent yield) of \( p\)-chlorophenoxyacetyle chloride were obtained, b. p. 132° C. (9 mm.), \( n^\circ_D \) 1.587, \( d^\circ_4 \) 1.36.

Analysis: Calculated for \( \text{C}_8\text{H}_6\text{Cl}_2 \): Cl, 37.53 per cent.
Found: Cl, 37.16 per cent.

---

2-Dimethylaminoethyl p-Chlorophenoxyacetate

$$\text{Cl} - \text{O} - \text{CH}_2 - \text{C} - \text{O} - \text{CH}_2 - \text{CH}_2 - \text{N} - \text{CH}_3$$

To a 1000-ml., three-neck flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel was charged a solution of 30 g. (0.37 mole) of 2-dimethylaminoethanol dissolved in 200 ml. of toluene. To this stirred solution were added 4.6 g. (0.2 mole) of sodium. After the reaction had subsided 45 g. (0.2 mole) of p-chlorophenoxyacetyl chloride dissolved in 300 ml. of toluene were added dropwise while stirring and heating. This mixture was heated at reflux temperature with stirring for six hours after the addition of p-chlorophenoxyacetyl chloride solution. The toluene solution was washed with water, the washings discarded, and the toluene distilled under a water-pump vacuum. The liquid residue was distilled in vacuo and 40 g. (70 per cent yield) of 2-dimethylaminoethyl p-chlorophenoxyacetate were obtained, b. p. 176° C. (3 mm.) $d_4^{20}$ 1.17.

Analysis: Calculated for $C_{12}H_{16}ClNO_3$: Cl, 13.63 per cent.

Found: Cl, 14.00 per cent.
2-Diethylaminoethyl p-Chlorophenoxyacetate

\[
\begin{align*}
\text{Cl} & \quad \text{O} \\
\text{C}_6\text{H}_4\text{C} & \quad \text{O} \\
\text{C}_2\text{H}_5 & \quad \text{N} \\
\text{C}_2\text{H}_5 & \quad \text{C}_3
\end{align*}
\]

To a 500-ml., three-neck flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel was charged a solution of 25.74 g. (0.22 mole) of 2-diethylaminoethanol dissolved in 152 ml. of toluene. To this stirred solution were added 2.3 g. (0.1 mole) of sodium. After the reaction had subsided 20.0 g. (0.1 mole) of p-chlorophenoxyacetyl chloride dissolved in 125 ml. of toluene were added dropwise while stirring and heating. This mixture was heated at reflux temperature with continued stirring for six hours after the addition of p-chlorophenoxyacetyl chloride solution. The toluene solution was washed with water, the washings discarded, and the toluene distilled under a water pump vacuum. The liquid residue was distilled in vacuo and 19 g. (69 per cent yield) of 2-diethylaminoethyl p-chlorophenoxyacetate were obtained, b. p. 136° C. (5 mm.), \( \rho^2_0 \) 1.5115.

**Analysis:** Calculated for \( \text{C}_{14}\text{H}_{20}\text{ClNO}_3 \); Cl, 12.27 per cent; N, 4.91 per cent.

Found: Cl, 12.15 per cent; N, 5.31 per cent.
3-Diethylaminopropyl p-Chlorophenoxyacetate

\[
\begin{align*}
\text{O} & \quad \text{H}_2 \quad \text{H}_2 \quad \text{CH}_2 \quad \text{N} \\
\text{Cl} & \quad \text{H}_2 \quad \text{H}_3
\end{align*}
\]

To a 500-ml, three-neck flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel were charged 28.82 g. (0.22 mole) of 3-diethylaminopropanol dissolved in 125 ml. of toluene. To this stirred solution were added 2.3 g. (0.1 mole) of sodium. After the reaction had subsided 20.0 g. (0.1 mole) of p-chlorophenoxyacetyl chloride dissolved in 125 ml. of toluene were added dropwise while stirring and heating. This mixture was heated at reflux temperature with continued stirring for six hours after the addition of p-chlorophenoxyacetyl-chloride-toluene solution. The toluene solution was washed with water, the washings discarded, and the toluene distilled under a water-pump vacuum. The residual liquid was distilled in vacuo and 22.7 g. (78 per cent yield) of 3-diethylaminopropyl p-chlorophenoxyacetate were obtained, b. p. 193° C. (2 mm.), \( b_\text{D} = 1.5061 \).

**Analysis**: Calculated for \( \text{C}_{15}\text{H}_{22}\text{ClNO}_3 \): N, 4.67 per cent.

**Found**: N, 4.52 per cent.
2-Di-n-Butylaminoethyl p-Chlorophenoxyacetate

To a 500-ml., three-neck flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel was charged a solution of 17.3 g. (0.1 mole) of 2-di-n-butylaminoethanol dissolved in 125 ml. of toluene. To this stirred solution were added 2.3 g. (0.1 mole) of sodium. After the reaction had subsided, 20.0 g. (0.1 mole) p-chlorophenoxyacetyl chloride dissolved in 125 ml. of toluene were added dropwise while stirring and heating. The reaction mixture was heated at reflux temperature with continued stirring for six hours after the addition of p-chlorophenoxyacetyl chloride solution. The toluene solution was washed with water, the washings discarded, and the toluene was distilled under a water-pump vacuum. The liquid residue was distilled in vacuo and 10 g. (29.4 per cent yield) of 2-di-n-butylaminoethyl p-chlorophenoxyacetate were obtained b. p. 215°C (8 mm.), \( \rho_D^{20} \) 1.5095.

Analysis: Calculated for \( C_{18}H_{28}ClNO_2 \): N, 4.17 per cent; Cl, 10.40 per cent.

Found: N, 4.12 per cent; Cl, 10.98 per cent.
2-Morpholinoethyl p-Chlorophenoxyacetate

\[
\begin{align*}
&\text{O} \\
\text{Cl} &\quad \text{O} \\
\text{C} &\quad \text{O} \\
\text{C} &\quad \text{N} \\
\text{CH}_2 &\quad \text{CH}_2 \\
\text{CH}_2 &\quad \text{CH}_2
\end{align*}
\]

To a 500-ml., three-neck flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel was charged a solution of 26.2 g. (0.2 mole) of 2-morpholinoethanol dissolved in 125 ml. of toluene. To this stirred solution were added 2.3 g. (0.1 mole) of sodium. After the reaction had subsided 20.0 g. (0.1 mole) of p-chlorophenoxyacetyl chloride dissolved in 125 ml. of toluene were added dropwise while stirring and heating. This mixture was heated at reflux temperature with continued stirring for six hours after the addition of the p-chlorophenoxyacetyl chloride solution. The toluene solution was washed with water, the washings discarded, and toluene distilled under a water-pump vacuum. The liquid residue was distilled in vacuo and 36.0 g. (60 per cent yield) of 2-morpholinoethylaminooethyl p-chlorophenoxyacetate were obtained, b. p. 240° C. (15 mm.), \( n_D^{20} = 1.5386 \).

Analysis: Calculated for C<sub>14</sub>H<sub>18</sub>ClN<sub>4</sub>O: N, 4.74 per cent; Cl, 11.85 per cent.
Found: N, 4.65 per cent; Cl, 12.20 per cent.
Phenylacetyl Chloride

\[
\begin{array}{c}
\text{O} \\
\text{-CH}_2\text{-C-Cl}
\end{array}
\]

A solution of 372.0 g. (2.7 moles) of phenylacetic acid dissolved in 1000 ml. of benzene was charged to a 2000-ml., three-neck flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel. To this stirred solution were added dropwise 355.2 g. (3 moles) of thionyl chloride. The solution was heated at reflux temperature for three hours after the thionyl chloride had been added. The resulting solution was transferred to a distilling flask and the benzene and excess thionyl chloride distilled under a water-pump vacuum. The liquid residue was distilled in vacuo and 100 g. (74.5 per cent yield) of phenylacetyl chloride were obtained, b. p. 140° C. (20 mm.).

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a-Bromophenylacetyl Chloride

\[ \text{To a 500-ml., three-neck flask equipped with a reflux condenser, mechanical stirrer, and dropping funnel were charged 174.0 g. (1.2 moles) of phenylacetyl chloride. The flask and its contents were placed in a ice bath and 170.0 g. (1.0 mole) of bromine were added dropwise while stirring. After the addition of bromine was completed the reaction mixture was heated over a water bath for twelve hours. The a-bromophenylacetyl chloride was used without other purification.} \]

Beilstein, System Number 891-1050, Vol. IX 452-3.
2-Dimethylaminoethyl a-(2-Dimethylaminoethoxy)phenylacetate

To a 500-ml., three-neck flask equipped with a mechanical stirrer, reflux condenser, and dropping funnel was charged a solution of 56.0 g. (0.75 mole) of 2-dimethylaminoethanol dissolved in 125 ml. of toluene. To this stirred solution were added 11.5 g. (0.25 mole) of sodium. After the reaction had subsided, 58.25 g. (0.25 mole) of a-bromophenylacetyl chloride dissolved in 125 ml. of toluene were added drop-wise while stirring and heating. The reaction mixture was heated at reflux temperature with continued stirring for six hours after the addition of a-bromophenylacetyl chloride solution. The reaction mixture was filtered, the precipitate discarded, and the toluene distilled under a water-pump vacuum. The liquid residue was distilled in vacuo and 15 g. (20.6 per cent yield) of 2-dimethylaminoethyl a-(2-dimethylaminoethoxy)phenylacetate were obtained, b. p. 215° C. (20 mm.), $n_D^{20} 1.5011$.

Analysis: Calculated for C H N O : N, 9.49 per cent.

Found: N, 9.06 per cent.
2-Diethylaminoethyl a-(2-Diethylaminoethoxy)phenylacetate

\[
\begin{array}{c}
\text{O} \\
\text{CH}_2 \text{O} - \text{CH}_2 \text{CH}_3 \\
\text{O} - \text{CH}_2 \text{CH}_3 \\
\end{array}
\]

To a 500-ml., three-neck flask equipped with a reflux condenser, mechanical stirrer, and dropping funnel was charged a solution of 25.75 g. (0.25 mole) of 2-diethylaminoethanol dissolved in 100 ml. of toluene. To this stirred solution were added 4.6 g. (0.2 mole) of sodium. After the reaction had subsided, 23.3 g. (0.1 mole) of a-bromophenylacetyl chloride dissolved in 100 ml. of toluene were added dropwise while stirring and heating. The reaction mixture was heated at reflux temperature with continued stirring for six hours after the addition of a-bromophenylacetyl chloride solution was complete. This reaction mixture was filtered, the precipitate discarded, and the toluene distilled under a water-pump vacuum. The liquid residue was distilled in vacuo and 12.0 g. (34.4 per cent yield) of 2-diethylaminoethyl a-(2-diethylaminoethoxy)phenylacetate were obtained, b. p. 200°C. (2mm.), \( n_D \) 1.4943.

**Analysis:** Calculated for C \( \text{H}_2 \text{N}_2 \text{O} \); N, 8.60 per cent.  
20 32 2 3

**Found:** N, 8.60 per cent.
2-Morpholinoethyl a-(2-Morpholinoethoxy) phenylacetate

To a 500-ml., three-neck flask equipped with a reflux condenser, mechanical stirrer, and dropping funnel was charged a solution of 32.75 g. (0.25 mole) of 2-morpholinoethanol dissolved in 125 ml. of toluene. To this stirred solution were added 4.6 g. (0.2 mole) of sodium. After the reaction had subsided, 23.3 g. (0.1 mole) of a-bromophenylacetyl chloride dissolved in 100 ml. of toluene were added dropwise while stirring and heating. The reaction mixture was heated at reflux temperature with continued stirring and heating for twelve hours after the addition of a-bromophenylacetyl chloride solution. The reaction mixture was heated at reflux temperature with continued stirring and heating for twelve hours after the addition of a-bromophenylacetyl chloride solution. The reaction mixture was filtered, the precipitate discarded, and the toluene distilled in vacuo and 14.0 g. (37.8 per cent yield) of 2-morpholinoethyl a-(2-morpholinoethoxy) phenylacetate were obtained, b. p. 155° C. (3 mm.), n D 1.5170.

Analysis: Calculated for C H N O : N, 7.22 per cent.

   Found: N, 6.942 per cent.
2-diethylaminopropyl a-(2-diethylaminopropoxy)phenylacetate

To a 500-ml., three-neck flask equipped with a reflux condenser, mechanical stirrer, and dropping funnel was charged a solution of 30.0 g. (0.3 mole) of 2-diethylamino propane dissolved in 125 ml. of toluene. To this stirred solution 2.4 g. (0.2 mole) of a-bromophenylacetyl chloride dissolved in 125 ml. of toluene were added dropwise while stirring and heating. The reaction mixture was heated at reflux temperature with continued stirring for six hours after the addition of a-bromophenylacetyl chloride solution was complete. The reaction mixture was filtered, the precipitate discarded, and the toluene distilled under a water-pump vacuum. The liquid residue was distilled in vacuo and 11.0 g. (31.3 per cent yield) of 2-diethylaminopropyl a-(2-diethylaminopropoxy)phenylacetate were obtained, b. p. 145° C., 20 (3 mm.), n_D^20 1.6948.

**Analysis:** Calculated for C_{22}H_{33}N_2O: N, 7.41 per cent.

Found: N, 6.89 per cent.
CHAPTER III
DISCUSSION OF RESULTS

The preceding chapter concerned itself only with those preparations which yielded the desired products. No mention is made of the difficulties encountered in the preparation, separation, or purification of the desired compound. This chapter is restricted primarily to a discussion of these problems.

When p-chlorophenoxyacetic acid was refluxed with 2-dimethylaminoethanol dissolved in benzene a white solid was obtained. A water solution of this solid was made basic with five per cent sodium hydroxide but none of the expected free base was obtained. An attempt to prepare and purify the hydrochloride of 2-dimethylaminoethyl p-chlorophenoxyacetate proved futile due to the hygroscopicity of this hydrochloride. This was found to be true not only for the hydrochloride of 2-dimethylaminoethyl p-chlorophenoxyacetate, but for hydrochlorides of all the esters prepared. These esters were extremely viscous and as a result were difficult to distill because of the violent bumping; several redistillations were necessary before a pure compound could be obtained.

The same problems were encountered in the preparations of phenylacetic acid derivatives as were encountered in the
preparations of the p-chlorophenoxyacetic acid derivatives. Not only were the hydrochlorides of these compounds hydroscopic, but also their picrates and citrates were hydroscopic.

The preparation of esters of amino alcohols and p-chlorophenoxyacetic acid or of phenylacetic acid by the action of the acid chloride on the sodium alcoholate has proven very satisfactory, since the esters are liquids and may be purified by the fractional distillation of the solution remaining after the sodium chloride or bromide is removed by filtration. In the preparation of these esters it was necessary to reflux the reaction mixtures for six hours after the addition of the acid chloride. Shorter periods of heating did not increase the yields. All the compounds prepared became colored after being exposed to the atmosphere for periods of ten days or more.

In summary, the following new compounds have been prepared for testing by Parke, Davis and Company for anti-histamine properties:

2-Dimethylaminoethyl p-Chlorophenoxyacetate
2-Diethylaminoethyl p-Chlorophenoxyacetate
3-Diethylaminopropyl p-Chlorophenoxyacetate
2-Di-n-Butylaminoethyl p-Chlorophenoxyacetate
2-Morpholinoethyl p-Chlorophenoxyacetate
2-Dimethylaminoethyl a-(2-Dimethylaminethoxy)phenylacetate
2-Diethylaminoethyl a-(2-Diethylaminethoxy)phenylacetate
2-Morpholinoethyl a-(2-Morpholinoethoxy) phenylacetate
2-Diethylaminopropyl a-(2-Diethylaminoproxy)phenylacetate
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