THE SYNTHESIS OF CERTAIN

ALKYL ALPHA-(2-DIALKYLAMINOALKOXY)PHENYLACETATES

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THESIS

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CHAPTER I

INTRODUCTION

For centuries men of science and medicine have been faced with the never-ending problem of healing the various physical disorders that assail mankind. In the quest for the most desirable remedies, it is necessary to determine not only the effect of a particular ill, but also the cause. Among the most prominent questions, long unanswered, is the one concerning the source and the treatment of allergies which manifest themselves in the form of asthma, hay fever, bronchial constrictions, or skin irritations.

Early investigations by Dale and Laidlaw[1] suggested that the symptoms of anaphylactic shock which had been previously regarded as identical with those produced by intravenous injections of peptone were identical with those produced by histamine (β-imidazolethylamine), which was prepared chemically by the decarboxylation of histidine (α-amino-β-imidiazolpropionic acid). Even today it is true that some of the manifestations of anaphylaxis cannot be explained by the histamine effect, but it was argued that this effect was at least the major mechanism. Substantiating

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[1] H. H. Dale and P. P. Laidlaw, J. Physiol., 41, 318-44 (1911); C. A., 5, 1622 (1911).

this idea was the work of Heubner[2] who proved that histamine was both a nerve and capillary poison. Experiments by Chambers and Thompson[3] gave evidence also that histamine shock was identical to that in anaphylaxis.

The histamine concept was gradually accepted, and it was believed that the histamine effects in man were identical with those of allergy. By the injection of histamine or a histamine complex, investigators hoped that the tolerance of histamine could be raised. After experimenting with both animals and man, they decided, due to the preponderance of evidence, that a tolerance of histamine could not be acquired by this method.[4] This condition, therefore, necessitated the identification of a synthetic antihistamine substance. Consequently extensive research was initiated and many compounds were prepared having various properties and various antihistamine characteristics.

Experiments by Staub[5] concerning the protective action of various compounds were carried out, after injecting intravenously five milligrams of the substance. The

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[2] W. H. Heubner, Arch. exptl. path. pharm., 107, 129-54 (1925); C. A., 19, 3325 (1925).

[3] E. K. Chambers and K. W. Thompson, J. Infectious Diseases, 37, 229-31 (1925).

[4] S. M. Feinberg, Chem. Eng. News, 25, 2134-36 (1947).

[5] A. M. Staub, Ann. Inst. Pasteur, 63, 400-36 (1939); C. A., 34, 5165 (1940).

β-phenoxytriethylamine, its o-, m-, and p-methyl; p-methoxy; p-allyl; m- and p-phenyl derivatives showed no protective action, whereas its 2,5-dimethyl and o-phenyl derivatives had slight protective action and its 2-methyl-5-isopropyl and 5-methyl-2-isopropyl derivatives had powerful protective action. Similarly, p-anilinotriethylamine and its o-methyl and isopropyl derivatives had no activity, but its 2,5-dimethyl derivative had slight activity, and its 2-methyl-5-isopropyl showed powerful activity. β-Ethylanilinotriethylamine showed powerful protective action, which was greatly diminished by introducing a methyl group in the o- or 2- and 5- positions and was abolished by introducing methyl and isopropyl groups in positions 2- and 5- respectively. In testing these compounds Staub noted that they counteracted the action of histamine on smooth muscle, isolated intestine, uterus and bronchi of the guinea pig.

Rosenthal and his co-workers[6] investigated thymoxyethyldiethylamine as an antagonist of histamine and anaphylactic reactions. They discovered that its action prevented anaphylaxis of guinea pigs which had been sensitized to crystaline ovalbumin. Although the shock was prevented, the pigs showed signs of malaise and prostration. This same

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[6] S. R. Rosenthal and M. L. Brown, J. Immunol., 38, 529-66 (1940); C. A., 38, 6701 (1940).

compound and N-ethyl-N-diethylaminoethylamine had been tested previously by Vandelli[7] and were found to abolish the action of histamine on intestine.

Among the many compounds which proved unsatisfactory was imidazole, which was tested by Morris and Dragdstedt.[8] It was learned that strong concentrations of the compound blocked the effect of histamine on guinea pig intestine, but the large amounts required were so great as to offer no promise of clinical or laboratory usefulness.

When injected subcutaneously thirty minutes before shock injection, diethylaminoethyl dihydroanthracenecarboxylate provided one-hundred per cent protection to sensitized guinea pigs against a minimum fatal dose of antigen but only partial protection against larger doses. This work was done by Lehmann and Young.[9]

Further research was done by D'Agostino[10] in which intradermal skin tests were made with histamine on nineteen patients who had been injected previously with two to five

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[7] I. Vandelli, Boll. soc. ital. biol. sper., 18, 74-5 (1943); C. A., 41, 805 (1947).

[8] H. G. Morris and C. A. Dragdstedt, Proc. Soc. Exptl. Bio. Med., 59, 311 (1945); C. A., 39, 4151 (1945).

[9] G. Lehmann and J. W. Young, J. Pharmacol., 83, 905 (1945); C. A., 39, 2334 (1945).

[10] L. D'Agostino, Boll. soc. ital. biol. sper., 22, 644-5 (1946); C. A., 41, 2167 (1947).

cubic centimeters of twenty-five per cent sodium cinchophen solution. In fifteen instances the cinchophen reduced the histamine reaction and in four it had no effect.

Rather extensive investigations have been carried out using Antergan (N'-phenyl-N'-benzyl-N-dimethylethylenediamine) as a possible histamine antagonist. Leya[11] reported that parenteral administration of ten milligram per kilogram of animal weight of Antergan completely prevented anaphylactic shock in rabbits, but this protective action lasted less than twenty-four hours. The testings of Decourt[12] included not only Antergan but also Neoantergan (N, p-methoxybenzyl-N-dimethylaminoethyl-a-aminopyridine). In using two one-hundredths gram intravenous injections of these two compounds, he discovered that almost all effects of physiological doses of histamine were suppressed in human patients, with the Neoantergan being the more active. A similar report was made by Bovet, Harcleis, and Furnel[13] who used one one-tenth to one milligram per kilogram of animal weight injections of Neoantergan in dogs and found that the effect of small and moderate doses of histamine were either diminished or abolished.

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[11] A. Leya, Compt. rend. soc. biol., 140, 1931-3 (1946); C. A., 41, 905 (1947).

[12] J. Decourt, A. Kinieri, and P. Sonnet, Compt. rend. soc. biol., 139, 470-1 (1945); C. A., 40, 4797 (1946).

[13] D. Bovet, R. Harcleis and J. Furnel, Compt. rend. soc. biol., 138, 165-6 (1944); C. A., 39, 3583 (1945).

When Radot, Mauric, and Halpern[14] gave human patients appropriate doses of N-dimethylaminoethyl-N-benzylaniline or N, p-methoxybenzyl-N-dimethylaminoethyl-a-aminopyridine both orally and intramuscularly, the intradermal injection of histamine produced no reaction. Halpern[15] had previously reported the study of the antagonism to the action of histamine by (dimethylaminoethyl)ethylaniline and (dimethylaminoethyl)-benzylaniline and some twenty other related compounds. These relaxed the isolated guinea pig intestine contracted by histamine and also antagonized histamine bronchiospasm. By the use of previous injections of these compounds guinea pigs were protected against many times the lethal dose of histamine and also from anaphylactic shock.

In a rat or guinea pig twenty-five one-hundredths milligram of histamine injected intraperitoneally increased the peripheral sensory and motor-nerve chronaxia and cortical chronaxia (depression of the central nervous system). Chauchard and Chauchard[16] found that twelve and five-tenths

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[14] P. V. Radot, G. Mauric and B. N. Halpern, Compt. rend. soc. biol., 140, 400-3 (1946); C. A., 41, 807 (1947).

[15] B. N. Halpern, Arch. intern. pharmacodynamie, 68, 339-48 (1942); C. A., 38, 5957 (1944).

[16] B. Chauchard and P. Chauchard, Compt. rend. soc. biol., 137, 708-9 (1943); C. A., 39, 3587 (1945).

milligrams of N-dimethylaminoethyl-N-benzylaniline produced exactly the opposite effects.

An important series of experiments were carried out by Mayer, Huttner, and Scholtz,[17] who tested eleven compounds of the general formula $R_1R_2\text{-}NCH_2CH_2N(R_3)_2$ on isolated guinea pig intestine. The substances were also tested on guinea pigs actively synthesized to horse serum, and the pigs were protected from anaphylactic shock in doses of one-tenth milligram per kilogram of animal weight. The most active substance was with R_1 as pyridyl, R_2 as benzyl, and R_3 as methyl. This compound is commonly known as Pyribenzamine. A close relationship was found to exist between the antihistamine activity *in vitro* and the anaphylactic property *in vivo*.

Perhaps the most common antihistamine drug in America today is Benadryl (dimethylaminoethylbenhydryl ether hydrochloride). Before its effectiveness as a histamine antagonist was accepted, extensive investigations were executed. Loew and Kaiser[18] reported that Benadryl and benzohydryl-B-morpholinoethyl ether showed marked effectiveness in allevating anaphylactic shock in guinea pigs. The potency of the Benadryl was thought to exceed that of N-phenyl-N-ethyl-N-diethylethylenediamine, previously one of the most effective histamine antagonists known.

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[17] R. L. Mayer, C. P. Huttner, and C. F. Scholtz, Science, 102, 93-4 (1945).

[18] E. R. Loew and M. E. Kaiser, Proc. Soc. Exptl. Bio. Med., 58, 235-7 (1945); C. A., 39, 2912 (1945).

The effects of Benadryl in human patients on the reduction of the histamine skin reaction was determined by McGavack, Elias, and Boyd.[19] They reported that the degree of reduction was proportional to the daily dose of drug administered and when the doses were discontinued for brief periods, response to histamine increased. Definite therapeutic effects were obtained from the drug in certain gastro-intestinal neuroses, asthma, and dermal allergy. However, Benadryl produced, in a mild degree and on infrequent occurrences, dizziness, blurring of vision, weakness, and somnolence. Each disappeared promptly upon discontinuing the drug or decreasing the dose. Friesen and his fellow workers[20] discovered that one hundred milligrams of Benadryl in a beeswax mixture injected intramuscularly failed to protect dogs against histamine provoked-ulcer.

Loew and Kaiser[21] did extensive research not only with Benadryl but with some seventeen compounds of the general formula Ph_2CHOR. The activity of the various compounds was estimated, using aminophylline as an activity

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[19] T. H. McGavack, H. Elias, and L. J. Boyd, J. Lab. Clin. Med., 31, 560-74 (1946); C. A., 40, 6666 (1946).

[20] S. R. Friesen, I. D. Baronofsky, and O. H. Wangensteen, Proc. Soc. Exptl. Biol., 63, 23-5 (1946); C. A., 41, 524 (1947).

[21] E. R. Loew and M. E. Kaiser, J. Pharmacol., 83, 120-9 (1945); C. A., 39, 2570 (1945).

index of unity and that of papaverine as two. The relative potencies were estimated for the following values of R:

B-Dimethylaminoethyl	33
B-Piperidinoethyl	33
B-Morpholinoethyl	16
B-Methylaminoethyl	8
Diethylaminopropyl	8
Diethylaminoethyl	4
ϒ-Morpholinopropyl	4
B-Aminoethyl	2
B-(B-Morpholinoethylamine) ethyl	2

In compounds of the type Ph_2 CHNHR where R was B-morpholinoethyl, B-diethylaminoethyl, ϒ-diethylaminopropyl, B-amino-ethyl, very weak activity was exhibited.

Many of the compounds identified as antihistamine drugs resemble histamine in structure and therefore seem to inhibit the histamine action by displacing it from the cell. As yet there has been no ideal histamine antagonist synthesized, as some are too mild in their therapeutic value and others are too toxic. Since it was believed that Benadryl was the most satisfactory antihistamine drug thus prepared, compounds resembling the structure of Benadryl were prepared in this study in the hope that at least one might prove to be of value in the fight against allergy.

CHAPTER II

EXPERIMENTAL PROCEDURE

α-Bromophenylacetyl Chloride[1]

$$C_6H_5-\underset{\displaystyle Br}{\underset{|}{CH}}-COCl$$

In a three-neck, one-liter flask, fitted with a West condenser, mercury-seal stirrer, and dropping funnel, were placed 136 g. (1.0 mole) of powdered phenylacetic acid.[2] After the acid was melted by means of a water bath, 130 g. (80 cc., 1.1 moles) of thionyl chloride were added dropwise over a period of two hours, with constant stirring. Heating was continued for eighteen hours. Care was taken to trap the evolved gases, hydrogen chloride and sulfur dioxide, in a concentrated sodium hydroxide solution.

To the cool, amber, homogenous liquid contained in the above flask were added dropwise 176 g. (60 cc., 1.1 moles) of bromine (d/2.93). This addition, with constant stirring,

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[1] F. K. Beilstein, Handbuch Der Organischen Chemie, edited by B. Prager, 9, 452-453.

[2] Eastman Kodak, White Label, m. p. 76-77° C.

required six hours. Care was taken to control the rate of bromine added, because the rate of the reaction was very fast; consequently pressure built up rapidly. Again, the evolved gases, mainly hydrogen bromide, were trapped in an alkaline solution. The mixture was heated for twelve hours on a water bath.

Since the α-bromophenylacetyl chloride was only an intermediate compound in the preparation of the methyl α-bromophenylacetate, the author did not consider it worthwhile to isolate and purify the acid chloride before bromination.

Methyl α-Bromophenylacetate[3]

$$C_6H_5\text{-}\underset{\displaystyle Br}{\underset{|}{CH}}\text{-}CO\text{-}OCH_3$$

The flask containing the α-bromophenylacetyl chloride was equipped with a Hopkins condenser, which replaced the dropping funnel. To the neck of a 500-cc. distilling flask, containing 192 g. (240 cc., 6 moles) of absolute methanol, was attached a West condenser, and 6 g. (approximately three per cent by weight) of finely divided sodium metal were added. During this addition an ice bath was used to cool the alcohol mixture. The West condenser was then replaced by a thermometer, and distillation commenced. After the first 50 cc. of distillate were discarded, the distilling flask was connected to the Hopkins condenser. Approximately three moles of methanol were distilled into the reaction flask. Again, an ice bath was used to cool the reactants until distillation was completed. The ice bath was removed, distillation apparatus dismantled, and the contents of the flask heated to reflux for eighteen hours.

The liquid was poured into 200 cc. of water and extracted with ether. The etheral solution was washed several

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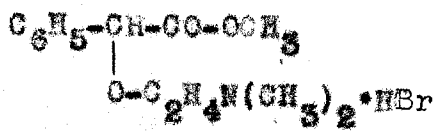
[3] Beilstein, op. cit.

times with portions of ten per cent sodium bicarbonate solution. Any solid impurities present were filtered, and the filtrate, after 100 g. of anhydrous sodium sulfate were added, was allowed to stand fourteen hours.

The above mixture was filtered into a 500-cc., round-bottom flask, equipped with a modified Claisen head, and the excess ether removed by means of an aspirator. The residue was distilled under 12 mm. pressure, yielding four fractions: (1) 125-38° C, (2) 138° C, (3) 141° C, (4) 150° C. Fraction (4) was discarded and the remaining fractions combined for redistillation as several possible products were indicated by the temperature range.

Upon refractionation, using a spinning-vane column 33 mm. in diameter and 81 cm. in length, one hundred and twenty-four grams of yellow liquid (144° C/12 mm., 113° C/3 mm.) were obtained, representing fifty-five per cent of the theoretical yield. The index of refraction was determined for the product: $n_d^{20^\circ}$, 1.5493.

Methyl α-(2-Dimethylaminoethoxy)phenylacetate Hydrobromide



Into a 125-cc., round-bottom flask was introduced 9.16 g. (0.04 mole) of methyl α-bromophenylacetate, 3.56 g. (0.04 mole) of 2-dimethylaminoethanol, and 70 cc. of toluene. The mixture was heated to reflux for twenty-four hours, during which time a white solid had separated.

The contents of the flask were filtered and the solid dissolved in a minimum of hot absolute methanol. Anhydrous ether was added until precipitation was complete. Again the solid was recovered by filtration and recrystallized from n-butyl alcohol. The crystals were filtered, washed several times with anhydrous ether and dried under vacuum.

The process gave five grams of methyl α-(2-dimethylaminoethoxy)phenylacetate hydrobromide, representing thirty-nine per cent of the theoretical yield, which melted at 201.5° C.

Analysis: Calculated for $C_{13}H_{20}BrNO_3$: N, 4.58;
Found: 4.94.

Methyl α-(2-Diethylaminoethoxy)phenylacetate

$$C_6H_5-CH(O-C_2H_4N(C_2H_5)_2)-CO-OCH_3$$

Into a three-neck, 500-cc. flask, fitted with a mercury-seal stirrer, West condenser and dropping funnel, were placed 11.7 g. (0.1 mole) of 2-diethylaminoethanol and 150 cc. of toluene. The alcoholate was prepared by adding 2.07 g. (0.9 mole) of finely divided sodium metal. After the reaction had subsided 16.25 g. (0.7 mole) of methyl α-bromophenylacetate dissolved in 50 cc. of toluene were added dropwise, with constant stirring. The mixture was heated to reflux for eighteen hours, during which time a solid separated out.

This was filtered and proved to be water soluble as was expected; the solid being sodium bromide. The filtrate was washed with several portions of water to insure complete removal of all solid material. The toluene solution was then added to 50 cc. of five per cent hydrochloric acid solution and washed with several portions of ether. After the acid solution was made basic with ten per cent sodium hydroxide, an amber liquid separated out, which was extracted with ether. The etheral solution was dried over anhydrous sodium sulfate and filtered.

Upon distillation (160-65° C/4 mm.) only a very small amount of methyl α-(2-diethylaminoethoxy)phenylacetate was obtained; this being sufficient for analysis purposes only.

Analysis: Calculated for $C_{15}H_{23}NO_3$: N, 5.27;
Found: 5.40.

Methyl α-(2-Morphilinoethoxy)phenylacetate

$$C_6H_5-CH(O-C_2H_4NC_4H_8O)-CO-OCH_3$$

Into a three-neck, 500-cc. flask, fitted with a mercury-seal stirrer, heat condenser, and dropping funnel, were placed 20.96 g. (0.16 mole) of 2-morphilinoethanol and 150 cc. of toluene. The alcoholate was prepared by adding 3.45 (0.15 mole) of finely divided sodium metal. After the reaction had subsided, 27.48 g. (0.12 mole) of methyl α-bromophenylacetate dissolved in 50 cc. of toluene were added dropwise, with constant stirring. The mixture was heated to reflux for eighteen hours, during which time a solid separated out.

This was filtered and proved to be water soluble. It was necessary to use several washings of water to remove all of the sodium bromide from the filtrate, which was then dissolved in 100 cc. of five per cent hydrochloric acid and washed with 50 cc. of ether. The acid solution was then made basic by ten per cent sodium hydroxide solution. An amber liquid separated and was extracted with ether. The etheral solution was dried over anhydrous sodium sulfate, filtered, then distilled, and only a very small amount of methyl α-(2-morphilinoethoxy)phenylacetate (168-70° C/4 mm.) was obtained; this being sufficient for analysis purposes only.

It is believed that the unusually low yields obtained in the syntheses of the ethyl and morpholino derivatives of methyl α-bromophenylacetate are a peculiarity exhibited by this particular method. Substantiating this is the fact that no product was obtained in the case of the condensation of the methyl ester with 2-piperidinoethanol.

Analysis: Calculated for $C_{15}H_{21}NO_4$: N, 5.03;
Found: 5.25.

Ethyl α-Bromophenylacetate[4]

$$C_6H_5-\underset{\underset{Br}{|}}{CH}-CO-OC_2H_5$$

A three-neck, one-liter flask, fitted with a mercury-seal stirrer, West condenser, and dropping funnel, was charged with 155 g. (1.0 mole) of phenylacetyl chloride which was prepared as previously described.[5] The acid chloride was distilled and purified for this preparation. Over a period of six hours, 176 g. (60 cc., 1.1 moles) of bromine (d/2.93) were added dropwise, with constant stirring. The reaction mixture was then heated on a water bath for fourteen hours. Due to the evolution of hydrogen bromide, this synthesis was carried out under a hood.

To the neck of a 500-cc. distilling flask, containing 266 g. (331 cc., 6 moles) of absolute ethanol, was attached a West condenser and 8 g. (approximately three per cent by weight) of finely divided sodium metal were added. During this addition an ice bath was used to cool the alcohol mixture. The West condenser was replaced by a thermometer, and distillation commenced. After the first 50 cc. of distillate were discarded, approximately three moles of absolute ethanol were distilled through a Hopkins condenser, which had replaced the dropping funnel attached

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[4] Ibid.

[5] Supra, p. 10.

to the reaction flask. Again, an ice bath was used to cool the reactants, until distillation was complete. It was then removed, distillation apparatus dismantled, and the contents of the flask heated to reflux for eighteen hours.

The mixture was then filtered into a 500-cc., round-bottom flask, equipped with a modified Claisen head, and all low boiling components removed by asperation. The remaining liquid was distilled under 4 mm. pressure, yielding three fractions: (1) 100-125° C, (2) 125-30° C, (3) 130-35° C. As three possible products were indicated by the wide temperature range, all the fractions were combined for redistillation.

Upon refractionation, with the use of a spinning-vane column, one hundred and ninety-two grams of yellow liquid (131-2°C/5 mm., 127°C/3 mm.) were obtained, representing seventy-nine per cent of the theoretical yield.

Ethyl a-(2-Dimethylaminoethoxy)phenylacetate

$$\begin{array}{l} C_6H_5\text{-}CH\text{-}CO\text{-}OC_2H_5 \\ \qquad\quad | \\ \qquad\quad O\text{-}C_2H_4N(CH_3)_2 \end{array}$$

Into a three-neck, 500-cc. flask, fitted with a West condenser, mercury-seal stirrer, and dropping funnel were placed 10.68 g. (0.12 mole) of 2-dimethylaminoethanol and 150 cc. of toluene. The alcoholate was prepared by adding 2.53 g. (0.11 mole) of finely divided sodium metal. After the reaction had subsided, 24.3 g. (0.10 mole) of ethyl a-bromophenylacetate dissolved in 50 cc. of toluene were added dropwise, with constant stirring. The mixture was heated to reflux for eighteen hours, during which time a solid separated out.

This was filtered and proved to be water soluble as was expected; the solid being sodium bromide. The filtrate was then distilled under 3 mm. pressure and three fractions were obtained: (1) 155° C, (2) 155-60° C, (3) 160-65° C. Since it was thought that fraction (3) contained most of the desired product, this was redistilled (155-60° C/2 mm.) and the distillate, upon analysis, contained 7.71 per cent nitrogen as compared to 5.58 for ethyl a-(2-dimethylamino-ethoxy)phenylacetate.

Fractions (1) and (2) were then combined, dissolved in 50 cc. of five per cent hydrochloric acid, and washed

with 50 cc. of ether. The acid solution was then made basic using ten per cent sodium hydroxide solution. An amber liquid separated and was extracted with ether. The etheral solution, after being over anhydrous sodium sulfate, was distilled and four games of ethyl a-(2-dimethylamino-ethoxy)phenylacetate (145-50° C/3 mm.) were obtained, representing only seventeen per cent of the theoretical yield.

Analysis: Calculated for $C_{14}H_{21}NO_3$: N, 5.68.
Found: 5.55.

Ethyl α-(2-Diethylaminoethoxy)phenylacetate

$$C_6H_5\text{-}CH(O\text{-}C_2H_4N(C_2H_5)_2)\text{-}CO\text{-}OC_2H_5$$

Into a three-neck, 500-cc. flask, fitted with a West condenser, mercury-seal stirrer, and dropping funnel were placed 14.04 g. (0.12 mole) of 2-diethylaminoethanol and 150 cc. of toluene. The alcoholate was prepared by adding 2.53 g. (0.11 mole) of finely divided sodium metal. After the reaction had subsided, 24.3 g. (0.10 mole) of ethyl α-bromophenylacetate dissolved in 50 cc. of toluene were added dropwise, with constant stirring. The mixture was heated to reflux for eighteen hours, during which time a solid separated out.

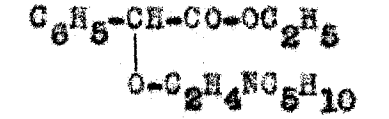
This was filtered and proved to be water soluble as before. It was necessary to use several washings of water to remove all of the solid material from the filtrate, which then was distilled under 4 mm. pressure. Four fractions, (1) 162-168° C, (2) 168-185° C, (3) 185-190° C, were obtained.

Following the preceding procedure, fraction (2) was dissolved in 50 cc. of five per cent hydrochloric acid, and washed with 50 cc. of ether. The acid solution was then made basic by ten per cent sodium hydroxide solution. An amber liquid separated and was extracted with ether.

The ethereal solution was dried over anhydrous sodium sulfate; then distilled, and five grams of ethyl α-(2-diethylaminoethoxy)phenylacetate (148-54° C/3 mm.) were obtained, representing only eighteen per cent of the theoretical yield.

Analysis: Calculated for $C_{16}H_{25}NO_3$: N, 5.02.
Found: 5.27.

Ethyl α-(2-piperidinoethoxy)phenylacetate



Into a three-neck, 500-cc. flask, fitted with a West condenser, mercury-seal stirrer, and dropping funnel were placed 15.48 g. (0.12 mole) of 2-piperidinoethanol and 150 cc. of toluene. The alcoholate was prepared by adding 2.53 g. of finely divided sodium metal. After the reaction had subsided, 24.3 g. (0.10 mole) of ethyl α-bromophenylacetate dissolved in 50 cc. of toluene were added dropwise, with constant stirring. The mixture was heated to reflux for eighteen hours, during which time a solid separated out.

This was filtered and proved to be water soluble as before. It was necessary to use several washings of water to remove all of the sodium bromide from the filtrate, which was then distilled under 5 mm. pressure. Three fractions, (1) 150° C, (2) 150-65° C, (3) 165-70° C, were obtained.

Following the same procedure as before, the fractions were combined, dissolved in 50 cc. of five per cent hydrochloric acid, and washed with 50 cc. of ether. The acid solution was then made basic using ten per cent sodium hydroxide solution. The amber liquid which separated was extracted with ether. The ethereal solution was then dried

over anhydrous sodium sulfate and upon distillation four and two-tenths grams of ethyl α-(2-piperidinoethoxy)-phenylacetate (178-82° C/4 mm.) were obtained. This represented only eleven per cent of the theoretical yield.

Analysis: Calculated for $C_{17}H_{25}NO_3$: N, 4.82;
Found: 5.10.

Ethyl α-(2-Morpholinoethoxy)phenylacetate

$$C_6H_5\text{-}CH(O\text{-}C_2H_4NC_4H_8O)\text{-}CO\text{-}OC_2H_5$$

Into a three-neck, 500-cc. flask, fitted with a West condenser, mercury-seal stirrer, and dropping funnel, were placed 23.58 g. (0.18 mole) of 2-morpholinoethanol and 150 cc. of toluene. As before, the alcoholate was prepared by adding 3.68 g. (0.16 mole) of finely divided sodium metal. After the reaction had subsided, 36.45 g. (0.15 mole) of ethyl α-bromophenylacetate dissolved in 50 cc. of toluene were added dropwise, with constant stirring. The mixture was heated to reflux for eighteen hours, during which time a solid separated out.

This was filtered and proved water soluble, as in the preceding preparations. To remove all of this from the toluene solution, several washings with water were necessary.

The toluene solution was then poured into 50 cc. of five per cent hydrochloric acid and washed with 50 cc. of ether. The acid solution was then made basic using ten per cent sodium hydroxide and extracted with ether. The etheral solution was then dried over anhydrous sodium sulfate.

Upon distillation of this solution under 3 mm. pressure, three fractions, (1) 160-65° C, (2) 175-80° C, (3) 180-90° C,

were obtained. Fractions (1) and (2) were combined and upon redistillation only two and one-tenth grams of ethyl α-(2-morpholinoethoxy)phenylacetate (177-79° C/3 mm.) were obtained. This represents only four and eight-tenths per cent of the theoretical yield.

Analysis: Calculated for $C_{16}H_{23}NO_4$: N, 4.78;
Found: 4.83.

Isopropyl a-Bromophenylacetate

$$C_6H_5-\underset{\underset{Br}{|}}{CH}-CO-OC_3H_7$$

A three-neck, one-liter flask, fitted with a mercury-seal stirrer, West condenser, and dropping funnel, was charged with 155 g. (1.0 mole) of phenylacetyl chloride which was prepared as previously described.[6] The acid chloride was distilled and purified for this preparation. Over a period of six hours, 176 g. (60 cc., 1.1 moles) of bromine (d/2.93) were added dropwise, with constant stirring. The reaction mixture was then heated on a water bath for fourteen hours. Due to the evolution of hydrogen bromide, this preparation was carried out under a hood.

Next was added 180 g. (230 cc., 6 moles) of isopropyl alcohol dropwise, over a period of two hours. The contents of the flask were heated to reflux for a period of fourteen hours, after which time the excess alcohol was removed by asperation.

Upon distillation, only one very distinct fraction (124° C/2 mm.) of two-hundred and thirty-five grams of isopropyl a-bromophenylacetate was obtained. It was not necessary to refractionate the product as in the preparations

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[6] Supra, p. 10.

of the other two a-bromo esters. Ninety-one per cent of the theoretical yield was obtained.

Analysis: Calculated for $C_{11}H_{13}O_2Br$: Br: 31.12

Found: 30.82.

CHAPTER III

DISCUSSION OF RESULTS

In the preceding chapter, only the detailed procedures followed in the preparation of the derivatives of certain alkyl phenylacetates and the necessary intermediate compounds were described. No discussion of the techniques used nor of the difficulties encountered has been presented. In addition to an explanation of these, various attempted procedures, plausible explanations for these apparent failures and recommendations concerning future research in the synthesis of similar compounds will be discussed in this chapter.

No unusual difficulty was encountered in the preparation of the alkyl a-bromophenylacetates. The bromination of the acid chloride progressed satisfactorily. It was necessary in the condensation of both methanol and ethanol with the a-bromophenylacetyl chloride to insure the absence of water by the distillation of the alcohol over sodium into the reaction flask. This was done to prevent possible hydrolysis of the a-bromophenylacetyl chloride into a-bromophenylacetic acid and possibly into mandelic acid. In the case of the isopropyl alcohol, the drying procedure was omitted due to its low water content.

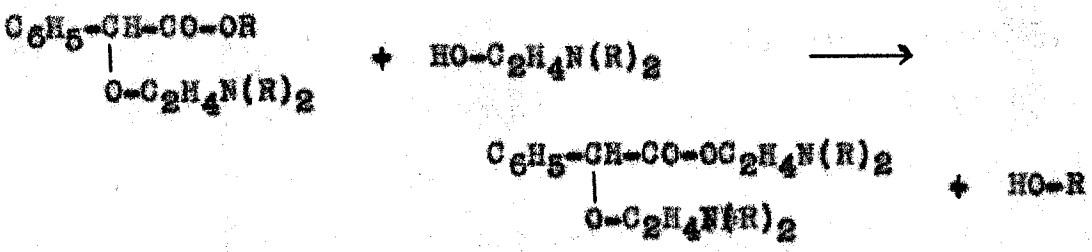
The primary procedure followed was outlined in the synthesis of methyl α-(2-dimethylaminoethoxy)phenylacetate hydrobromide. However, when this procedure was applied in the case of the diethyl, dibutyl, piperidino, and morpholino derivatives, solids were obtained that could not be purified by ordinary means. Recrystallization was attempted from absolute methanol, absolute ethanol, propyl alcohol, isopropyl alcohol, n-butyl alcohol, amyl alcohol, isoamyl alcohol, hexyl alcohol, cetyl alcohol, ethyl acetate, and acetic acid. When a trace of water was added, the solids dissolved, but recovery proved impossible. Had this procedure been satisfactory in all cases, it would have been most desirable as the hydrobromides would have been formed, thereby rendering the various phenylacetates soluble in water and in a readily usable form.

It was necessary to modify the procedure by preparing the sodium salts of the amino alcohols before condensation with the α-bromo esters. Benzene was used originally as a solvent, but toluene proved more satisfactory due to its higher boiling point.

The removal of the sodium bromide formed in the condensation was effected by filtration and subsequent washings with water. It is believed that the low percentage yields obtained were due to the moderate water-solubility of the various products which were partially removed unknowingly by the initial washings.

Distillation of the final product in each synthesis proved difficult due to the high boiling point and high viscosity of each liquid. Even with the use of low pressure and small Claisen flasks, extreme bumping was encountered.

Analysis of the higher boiling fractions obtained indicated that a possible ester exchange had taken place.



The formation of such a dibasic compound would aid in explaining the high per cent of nitrogen found. Insufficient pure material was obtained to prove definitely the foregoing postulation. However, the boiling points of these high fractions were of the same magnitude as those obtained by Richardson[1] for such dibasic compounds. It is believed that to prevent such an exchange, a higher boiling solvent and a shorter time of refluxing should be used.

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[1] E. E. Richardson, "Preparation of Various Amino Alcohol Derivatives of p-Chlorophenoxyacetic Acid and Phenylacetic Acid", Unpublished Master's thesis, Department of Chemistry, North Texas State Teachers College, 1947, pp. 7-20.

Compounds which were obtained in sufficient quantity to warrant clinical analysis were sent to Parke-Davis Company, Detroit, Michigan. As yet, no results concerning the therapeutic activity of the various compounds have been received.

The condensation of the isopropyl ester with various amino alcohols has been initiated, but this study has not been completed. The formation of other α-bromophenylacetates using long chain alkyl alcohols and cyclic alcohols would lead to additional interesting research. Also an increase in the number of amino alcohols used would introduce the possibility of more compounds having antihistamine properties. It is suggested that the general procedure previously described be modified and the synthesis of similar compounds be attempted by condensing the sodium salts of various mandelic esters with certain dialkylaminoalkyl halides.

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