SYNTHESIS OF SOME SUBSTITUTED PHENOXY ETHYL AMINES

Thesis for the Degree of M. S.

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John V. Simenian

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This is to certify that the

thesis entitled

''Synthesis of Some Substituted
Phenoxy Ethyl Amines''

presented by

John V. Simonian

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Robert M. Hecht
Major professor

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SYNTHESIS OF SOME SUBSTITUTED

PHENOXY ETHYL AMINES

By

John V. Simonian

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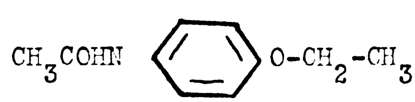
INTRODUCTION

Compounds in which the aromatic nucleus and the amino group are attached to the neighboring or adjacent carbon atoms (I) show an optimum pressor activity (production of a rise in blood pressure).

Ar-C-C-N   Ar-O-C-C-N

(I)   (II)

However, if the aromatic nucleus and the side chain of (I) are separated, as in the case of ethers (II), they become sympatholytics (1,2). Compounds of structure (II) without the nitrogen group show antipyretic and analgesic properties. Acetophenetedine (III) is a good example of such a compound.



(III)

This thesis describes the preparation of some substituted phenoxy ethyl amines which contain certain of the structural features of both (II) and (III). Pharmacological tests are being carried out to determine their effectiveness and usefulness.

HISTORICAL

Part I

Antipyretics and Analgesics

During the latter part of the nineteenth century the search for synthetic substitutes of quinine was intensified. A large number of compounds were introduced into medicine as a result of this intensive search. Although many of them were not as effective as antimalarials as quinine, they proved their usefulness as antipyretics and analgesics. The drugs having antipyretic and analgesic properties can be divided into three classes (3), as follows:

I The salicylates - cincophen.

II The *para* aminophenol derivatives - acetanilide and acetophenetidine.

III The pyrazolone derivatives - antipyrine and aminopyrine.

The two main actions of the *para* aminophenol derivatives are antipyresis and analgesia. An antipyretic is a drug which reduces the body temperature, particularly when a subject is in a state of fever. The drug acts on the heat regulating centers of the nervous system to bring about a greater dissipation of body heat through cutaneous vasodilitation. The antipyretic action resides in the benzene ring, but benzene itself is not antipyretic, because it cannot react with the body cells. However, this can readily be alleviated by substituting one of the hydrogen atoms with the hydroxyl group as in phenol, or by substituting an amino group as in aniline, or by both as in para aminophenol. The toxicity of para aminophenol is too great for the substance to be useful as an antipyretic. However, the toxicity can be reduced by replacing a hydrogen atom of either the hydroxyl group or the amino group by another radical such as an alkyl or an acetyl group. The liberation of the "parent substance", para aminophenol, is then more gradual, and its action less violent, and easier to control. The pharmacological properties of acetyl p-aminophenoxyethanol, an intermediate also prepared by this author, have been studied and compared with acetophenetidine by Cow (4). The compound, acetyl p-aminophenoxyethanol, sold as "Pertonal", possesses approximately one-half the toxicity of acetophenetidine, and as an antipyretic it produced similar effects in doses approximately double those of acetophenetidine.

As early as 1884 it was observed by Schmiedeberg (5) that certain aniline derivatives break up in the body with the liberation of para aminophenol, which is excreted rapidly by the kidney in the form of conjugation products with glucuronic and sulfuric acids. It has been quite conclusively established that the para aminophenol liberated from its derivatives in the body (6,7) is the portion of the molecule causing the antipyretic and analgesic action.

Analgesia pertains to the alleviation of certain types of pain. The action is probably due to a central depressant action located in the optic thalami. The type of pain relieved is that which usually occurs in headache, and in many muscle, joint and peripheral nerve affections.

Part II

Sympatholytics

Compounds acting peripherally (8) on the autonomic nervous system are referred to as sympatholytic drugs. The name, sympatholytic, means to destroy or block the action of the sympathetic nervous system.

The nervous system consists of two branches, the Autonomic and the Somatic system. The major difference between them is that the motor nerves of the autonomic system supply all structures of the body except skeletal muscle, which is innervated by somatic nerves. Thus, respiration, circulation, digestion, body temperature, metabolism, sweating, and the secretion of certain endocrine glands are regulated by the autonomic nervous system. Physiologically considered, the autonomic nervous system may be divided into two functional divisions: the sympathetic and the parasympathetic which stand as physiological antagonists. If one system inhibits a certain function, the other augments that function. Most viscera are innervated by both divisions, and the level of activity, then, at a given moment is the algebraic sum of the two component influences.

The parasympathetic system is essential to life and is organized for discrete and localized discharge. It slows the heart, lowers blood pressure, stimulates gastro-intestinal movements and secretions, aids absorption, protects the retina from excess light, and empties the bladder and rectum.

The sympathetic system is not essential to life, and animals deprived of it can continue a fairly normal existence. The sympathetic system frequently discharges as a unit and this occurs especially under circumstances of rage and fright. The autonomic structures all over the body are affected at the same time. The heart is accelerated; the blood pressure rises; red blood cells are poured into circulation from the spleen; the blood sugar rises; and, on the whole, the organism is better prepared for fight or flight.

The theory of chemical transmission of nerve impulses holds that nerve impulses effect responses in muscles and glands through liberation of a chemical substance which acts as the major local exciting agent. The parasympathetic mediator has been identified as acetylcholine which, it is believed, exists in the tissues in a form which is physiologically inactive and non-diffusible. The change from the inactive to the active and diffusible form is effected by nerve impulses. The chemical mediator of the sympathetic system at the site of the action is sympathin which bears close resemblance to epinephrine.

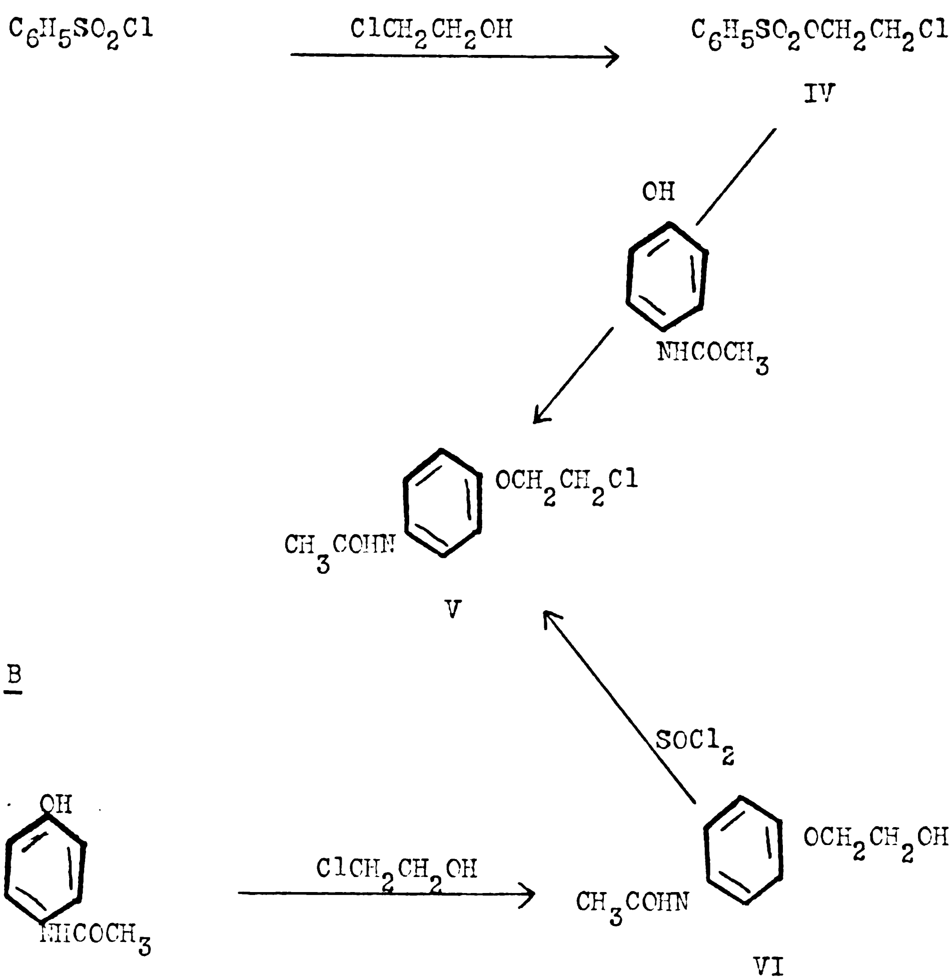
The mechanism of action of the autonomic drugs is the stimulation or depression of effector cells, not nerve endings. The autonomic blocking agents do not prevent nerve impulses from releasing the chemical mediator, rather their locus of action is always peripheral to the site of release of chemical mediator at nerve endings. Two recent opinions on the manner of blockage have been expressed. One suggests that the sympatholytics act as adrenaline antagonists, replacing adrenaline in some enzyme system, while the other suggests that the sympatholytics act by accelerating the enzymatic destruction of adrenaline.

Tertiary amines derived from phenolic ethers have been investigated and many were found to have sympatholytic activity (1,9). The benzyl substituted phenoxyethyl dimethylamines prepared by Cheney, Smith, and Binkley (10) possess considerable antihistaminic activity.

DISCUSSION

In an effort to obtain the tertiary amines related structurally to acetophenetidine (III), the intermediate acetyl p-aminophenyl-β-chloroethyl ether was first prepared by two independent methods. Although other methods of formation of phenolic ethers are available as outlined in "Richter's Organic Chemistry", volume III, page 191, the two methods utilized are as follows:

Method A



Method B

Of the two methods utilized to prepare the intermediate acetyl p-aminophenyl-β-chloroethyl ether (V), the steps involved in method B gave a much better overall yield than those in method A.

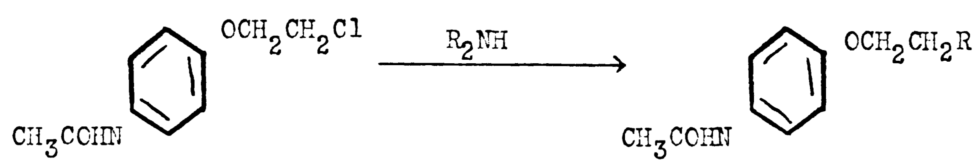
β-Chloroethyl benzenesulfonate (IV) was prepared by the method of Földi (15) to obtain a colorless liquid boiling at 155-157° C. at 2 mm. in 65 percent yield.

Acetyl p-aminophenyl-β-chloroethyl ether (V) was obtained in 71 percent yield by heating β-chloroethyl benzenesulfonate (IV), with acetyl p-aminophenol in sodium hydroxide solution on a water bath. The product is a colorless solid which melts at 126-127° C. Clemo and Perkin (14) obtained the same compound by interaction of β-chloroethyl p-toluenesulfonate and acetyl p-aminophenol.

In method B, acetyl p-aminophenyl-β-hydroxyethyl ether (VI) was obtained in 88 percent yield by the interaction of the sodium salt of acetyl p-aminophenol and ethylene chlorohydrin. The compound is a colorless solid which melts at 119-120° C. The alcohol, under the trade name "Pertonal", has previously been described by Cow (4).

Application of the Darzens reaction (12,13) using thionyl chloride and pyridine for the conversion of acetyl p-aminophenyl-β-hydroxyethyl ether (VI) to the chloride was attempted with little success. The yields were poor and the crude product contained considerable amounts of dark products making purification by recrystallization difficult. However, this was alleviated by adding thionyl chloride dissolved in chloroform to a solution of the alcohol in chloroform. The crude product obtained by this procedure could be easily purified and the yield was over 90 percent. The chloroform acts as a diluent and thereby moderates the localized action of the thionyl chloride as each drop comes in contact with the solution containing the alcohol.

The tertiary amines were obtained by the interaction of acetyl p-aminophenyl-β-chloroethyl ether (V) and a variety of secondary amines in a high boiling solvent such as toluene.



V VII

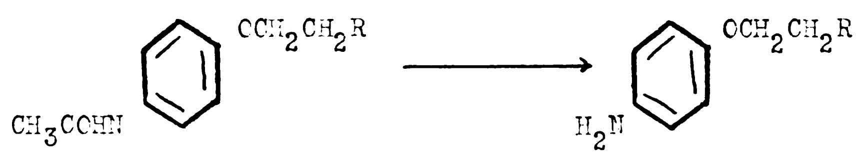
R = a, morpholino
b, piperidino
c, dimethylamino
d, diethylamino

After completion of the reaction, the mixture was neutralized and the excess secondary amine and solvent were separated from the tertiary amine by evaporation under reduced pressure. This technique was utilized because of the comparatively large difference in the molecular weights of the secondary amine and the tertiary amine.

Because of the individual differences in the properties of the secondary amines used, modifications of the general method of preparation of the tertiary amines were necessary. For example, reactions with dimethyl and diethyl amine were carried out in sealed combustion tubes in an oven at 150° C. Morpholine and piperidine, on the other hand, reacted readily with the chloride in toluene solution on boiling under reflux at atmospheric pressure.

The tertiary amines were converted into the hydrochlorides which could be isolated as colorless crystalline solids. The free bases obtained from the purified hydrochlorides crystallized as colorless needles. The only exception was acetyl p-aminophenyl-β-diethylaminoethyl ether (VII-d) which could not be induced to crystallize.

The hydrolysis of the hydrochlorides of acetyl p-aminophenyl-β-morpholinoethyl ether (VII-a), acetyl p-aminophenyl-β-piperidinoethyl ether (VII-b), acetyl p-aminophenyl-β-dimethylaminoethyl ether (VII-c), and acetyl p-aminophenyl-β-diethylaminoethyl ether (VII-d) was accomplished by heating with concentrated hydrochloric acid.



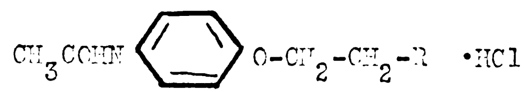
VII VIII

R = a, morpholino
b, piperidino
c, dimethylamino
d, diethylamino

The diamines were isolated as faintly colored solids the physical properties of which are tabulated in Table III. Here again the diethylamino derivative was not a solid and was, therefore, converted into the dihydrochloride. The other three diamines were also converted into the dihydrochlorides. The physical properties of the dihydrochlorides are tabulated in Table IV.

TABLE I

ACETYL P-AMINOPHENYL-β-DIALKYLAMINOETHYL ETHER HYDROCHLORIDES

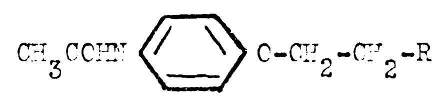


R	Formula	M.p., °C.*	Yield %	Analysis % N ** Calc'd	Found
Morpholino	$C_{14}H_2ClN_2O_3$	229-230°C.	85%	9.2	9.1
Piperidino	$C_{15}H_{23}ClN_2O_2$	255-256°C.	87%	9.3	9.2
Dimethylamino	$C_{12}H_{19}ClN_2C_2$	223-224°C.	77%	10.8	10.7
Diethylamino	$C_{14}H_{23}ClN_2C_2$	214-215°C.	83%	9.7	9.6

* All melting points are uncorrected.
** Nitrogen determined by Kjeldahl-Gunning Method.

TABLE II

ACETYL P-AMINOPHENYL-β-DIALKYLAMINOETHYL ETHERS

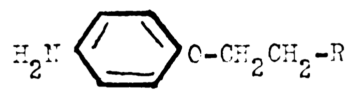


R	Formula	M.P., °C.*	Analysis % N ** Calc'd	Found
Morpholino	$C_{14}H_{20}N_2O_2$	111.5-113°C.	10.6	10.4
Piperidino	$C_{15}H_{22}N_2O_2$	100-101°C.	10.6	10.6
Dimethylamino	$C_{12}H_{18}N_2O_2$	105-107°C.	12.6	12.8
Diethylamino	$C_{14}H_{22}N_2O_2$	Heavy oil	----	----

* All melting points are uncorrected.
** Nitrogen determined by Kjeldahl-Gunning Method.

TABLE III

P-AMINOPHENYL-β-DIALKYLAMINOETHYL ETHERS

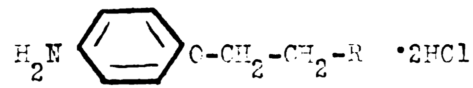


R	Formula	M.p., °C.*	Yield %	Analysis % N ** Calc'd	Found
Morpholino	$C_{12}H_{18}N_2O_2$	69.5-70.5°C.	87%	12.6	12.5
Piperidino	$C_{13}H_{20}N_2O$	65-66.5°C.	69%	12.7	12.5
Dimethylamino	$C_{10}H_{16}N_2O$	53.0-54.5°C.	76%	15.5	15.4
Diethylamino	$C_{12}H_{20}N_2O$	Heavy oil	--	----	----

* All melting points are uncorrected.
** Nitrogen determined by Kjeldahl-Gunning Method.

TABLE IV

P-AMINOPHENYL-β-DIALKYLAMINOETHYL ETHER DIHYDROCHLORIDES

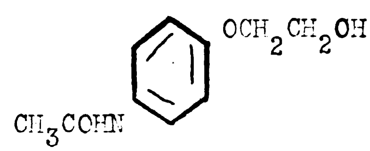


R	Formula	M.p., °C.*	ANALYSIS Calculated Cl	N	Found Cl**	N***
Morpholino	$C_{12}H_{20}Cl_2N_2C_2$	201-202°C.	24.3	9.5	24.2	9.3
Piperidino	$C_{13}H_{22}Cl_2N_2O$	216-217°C.	24.2	9.5	24.1	9.4
Dimethylamino	$C_{10}H_{18}Cl_2N_2O$	230-232°C.	28.0	11.1	28.1	11.3
Diethylamino	$C_{12}H_{22}Cl_2N_2O$	196-198°C.	25.2	9.9	25.3	9.8

* All melting points are uncorrected.
** Chloride determined by gravimetric method.
*** Nitrogen determined by Kjeldahl-Gunning Method.

EXPERIMENTAL

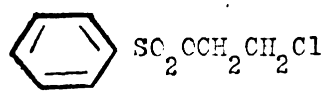
Preparation of Acetyl p-aminophenyl-β-hydroxyethyl ether (VI)



In a one liter, three-necked flask fitted with a stirrer, and two separatory funnels was placed 151.2 g. (1.0 mole) of acetyl p-aminophenol. A solution of 80 g. of sodium hydroxide in 700 ml. of water was added dropwise through one separatory funnel. At the same time 160 g. (2 moles) of ethylene chlorohydrin was added dropwise through the other separatory funnel. The sodium hydroxide solution and the ethylene chlorohydrin were added dropwise at proportionate rates that would result in complete addition simultaneously. The stirred mixture was kept cool until all the sodium hydroxide solution and ethylene chlorohydrin were added, at which time, the mixture was heated so that the temperature of the reaction mixture did not exceed 40° C. After about one and one-half hours the product separated from the solution to form a thick sludge. The solid was broken up and washed with water until the filtrate was free of chloride ion. The crude product was dissolved in 1,4-dioxane and decolorized with charcoal (Norite A), filtered and allowed to crystallize. The product weighed 167 g., (86% of theoretical).

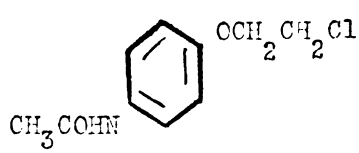
A second run was made using the same amounts except for the concentration of the sodium hydroxide solution which was 80 g. of sodium hydroxide in 175 ml. of water. The product which melted at 119-120° C. (uncor.), after recrystallization from 1,4-dioxane, weighed 171 g., (88% of theoretical).

Preparation of β-chloroethyl benzene sulfonate (IV)



In a 250 ml. three-necked flask, fitted with stirrer and dropping funnel were placed 17.6 g. (0.1 mole) of benzene sulfonyl chloride and 12.8 g. (0.16 mole) of ethylene chlorohydrin. To the stirred mixture, kept below 15° C., was added dropwise 35 ml. of 20% sodium hydroxide solution. After stirring the mixture for twelve hours, it was extracted with benzene and washed with water and dilute sodium hydroxide. The extract was dried over anhydrous potassium carbonate. The product distilled at 155-157° C. at 2 mm. and had a refractive index of 1.5283 at 25° C. and specific gravity of 1.3422 at 25° C. The yield was 14.4 g., (65% of theoretical).

Preparation of Acetyl p-aminophenyl-β-chloroethyl ether (V)



Method A

In a 250 ml. three-necked flask fitted with a stirrer, separatory funnel, and reflux condenser were placed 25 g. (0.16 mole) of acetyl p-aminophenol and a solution of 7.5 g. of sodium hydroxide in 15 ml. of water. The stirred mixture was heated in a water bath and 39 g. (0.16 mole) of β-chloroethyl benzenesulfonate was added dropwise through the separatory funnel. After about one hour, the reaction mixture was poured into ice water. The insoluble oil solidified and was filtered. The product was then washed with dilute sodium hydroxide and finally with water. The crude product was dissolved in benzene and the solution was decolorized with "Norite A", filtered and cooled. The product weighed 22.1 g., (68% of theoretical).

A second run was made using 100 g. (0.66 mole) of acetyl p-aminophenol and proportionately larger amounts of all reagents. The product, which melted at 126-127° C. after recrystallization from benzene, weighed 103 g., (71% of theoretical).

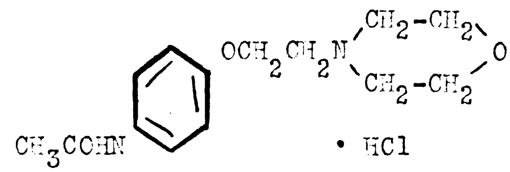
Method B

A mixture of 39 g. (0.2 mole) of acetyl p-aminophenyl-β-hydroxyethyl ether, 75 ml. of 1,4-dioxane, and 23.7 g. (0.25 mole) of pyridine was placed in a 250 ml. three necked flask fitted with stirrer, separatory funnel, and reflux condenser. Thionyl chloride (35.4 g., 0.25 mole) was added dropwise with cooling to the stirred mixture. The mixture was then warmed to 50° C. for 15 minutes and immediately poured into ice water. The product, recrystallized from benzene, melted at 126-127° C. weighed 42.6 g., (75% of theoretical).

A second run was made as follows: In a 250 ml. three-necked flask fitted with a stirrer, separatory funnel, and reflux condenser were placed 9.7 g. (0.05 mole) of acetyl p-aminophenyl-β-hydroxyethyl ether and 15 ml. of chloroform. To the stirred mixture a solution of 7.0 g. (0.06 mole) of thionyl chloride in 10 ml. of chloroform was added dropwise from a separatory funnel. The mixture was kept cool during the addition after which it was warmed to 40° C. for two hours. The mixture was then placed on the steam bath and evaporated to dryness. The solid residue was dissolved in benzene, decolorized with charcoal (Norite A), filtered, and allowed to cool. The product weighed 8.0 g., (74% of theoretical).

A third run was made using 97 g. (0.49 mole) of acetyl p-aminophenyl-β-hydroxyethyl ether in 200 ml. of chloroform. To the stirred mixture was added dropwise a solution of 67 g. (0.56 mole) of thionyl chloride in 50 ml. of chloroform. The mixture was stirred for several hours after which the excess thionyl chloride was distilled under reduced pressure. The flask was placed on the steam bath to dry the solid product completely. The product was dissolved in benzene and decolorized with "Norite A", filtered and allowed to crystallize. The product weighed 100 g., (94% of theoretical).

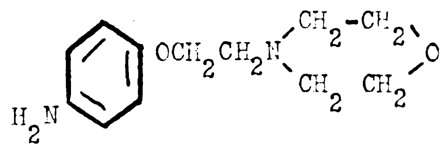
Preparation of Acetyl p-aminophenyl-β-morpholinoethyl ether (VII-a) hydrochloride



In a 250 ml. flask fitted with condenser, were placed 26 g. (0.12 mole) of acetyl p-aminophenyl-β-chloroethyl ether, 50 ml. of toluene as solvent and 31 g. (0.36 mole) of morpholine. The solution was boiled under reflux for eight hours at which time the amine was liberated with sodium carbonate. The toluene and excess morpholine were evaporated on a hot water bath at 20 mm. pressure. After the last traces of morpholine had been removed, the residue was taken up in dilute hydrochloric acid. To the clear solution was added enough sodium carbonate to liberate the tertiary amine which was then taken up in benzene and the aqueous layer was extracted with benzene three times. The solvent was evaporated and this time a residue of solid amine remained. Some of it was saved for analysis. The hydrochloride was prepared by dissolving the base in a small volume of absolute isopropyl alcohol, and passing in dry hydrogen chloride. The hydrochloride weighed 31.2 g., (85% of theoretical), m.p. 229-230° C.

One gram of the pure hydrochloride was dissolved in water and enough sodium carbonate was added to liberate the amine. The amine was taken up in benzene and the aqueous layer was extracted twice from benzene. The solution was decolorized with "Norite A" and filtered. The solvent was evaporated on the steam bath and upon cooling and scratching the heavy oil solidified. The solid amine recrystallized from high boiling ligroin as colorless needles melting at 111.5-113° C.

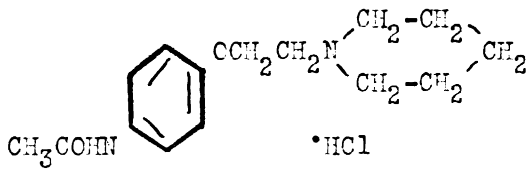
Preparation of p-aminophenyl-β-morpholinoethyl ether (VIII-a)



In a 100 ml. flask were placed 5 g. of acetyl p-aminophenyl-β-morpholinoethyl ether hydrochloride and 50 ml. of concentrated hydrochloric acid. The mixture was boiled under reflux for five and one half hours. The solution was poured into a beaker and treated with enough sodium carbonate to liberate the base. The organic layer formed was taken up in benzene and the aqueous layer was extracted with benzene. The benzene solution was decolorized with "Norite A". The benzene was evaporated on the steam bath and upon cooling and scratching the residue solidified. The solid amine recrystallized from cyclohexane as long needles melting at 69.5-70.5° C. and had a pink color.

The dihydrochloride was prepared by dissolving the base in methyl alcohol and passing in dry hydrogen chloride. The solution was decolorized with "Norite A" and a small piece of mossy zinc. Dry ethyl ether was added dropwise to the warm, filtered solution until a slight turbidity was induced after which the dihydrochloride crystallized on standing, m.p. 201-202° C.

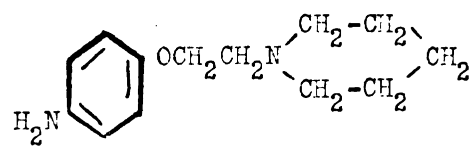
Preparation of Acetyl p-aminophenyl-β-piperidinoethyl ether (VII-b) hydrochloride



A solution of 23.3 g. (0.1 mole) of acetyl p-aminophenyl-β-chloroethyl ether, 100 ml. of toluene and 25.2 g. (0.3 mole) of piperidine was boiled under reflux for eight hours. To the mixture was added 400 ml. of water and enough sodium carbonate to liberate the base. The excess piperidine and toluene were evaporated under reduced pressure. More water was added and again evaporated to insure complete removal of the secondary amine. The residue in the flask was dissolved in dilute hydrochloric acid and to the clear solution was added enough sodium carbonate to liberate the tertiary amine. The organic layer formed was taken up in benzene and the aqueous layer was extracted three times with benzene. The solvent was then removed on the steam bath. The yield of amine, a heavy oil, was 26 g. The hydrochloride was prepared by dissolving the amine in absolute isopropyl alcohol and passing in dry hydrogen chloride. The yield was 28 g., (87% of theoretical). The hydrochloride was recrystallized from ethyl alcohol-ether, m.p. 255-256° C.

One gram of the pure hydrochloride was dissolved in water and the amine was liberated with sodium carbonate. The organic layer was taken up in benzene and the aqueous layer extracted twice with benzene. After the benzene solution was decolorized with "Norite A", and filtered, the solvent was evaporated on the steam bath. The heavy oil solidified upon cooling and scratching. The amine crystallized from high boiling ligroin as needles and melted at 100-101° C.

Preparation of p-aminophenyl-β-piperidinoethyl ether (VIII-b)



A mixture of 5 g. of acetyl p-aminophenyl-β-piperidinoethyl ether hydrochloride and 50 ml. of concentrated hydrochloric acid was boiled under reflux for six hours. The solution was poured into a beaker and enough sodium carbonate was added to liberate the amine. The amine was taken up in benzene and the aqueous layer was extracted three times with benzene. The solvent was evaporated on the steam bath and upon cooling and scratching the residue solidified. The amine, recrystallized from "Skellysolve B", melted at 65-66.7° C. and had a pink color.

The dihydrochloride was prepared by dissolving the amine in methyl alcohol and passing in dry hydrogen chloride. The solution was decolorized with "Norite A" and filtered. Dry ethyl ether was added dropwise to the warm solution until a slight turbidity persisted after which the dihydrochloride crystallized on standing, m.p. 216-217° C.

Preparation of Acetyl p-aminophenyl-β-dimethylaminoethyl ether (VII-c) hydrochloride

Acetyl p-aminophenyl-β-chloroethyl ether (6.5 g., 0.03 mole) was dissolved in 50 ml. of 1,4-dioxane. This solution was combined with 20 ml. of 25% aqueous dimethylamine and placed in a long combustion tube and sealed. Four tubes each charged in this manner were heated in an oven at 150° C. for five days. At the end of this time, the tubes were opened and the contents poured into a one liter round bottom flask. Water (400 ml.) and enough sodium carbonate was added to liberate the base. The tertiary amine was isolated as in the previous example. The yield of the amine was 25 g. The hydrochloride was prepared by dissolving the amine in ethyl alcohol and passing in dry hydrogen chloride. The yield was 77% of theoretical, m.p. 223-224° C.

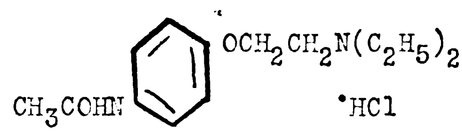
One gram of the pure hydrochloride was dissolved in water and the amine was liberated by the addition of sodium carbonate. The amine was taken up in benzene and the aqueous layer was extracted with benzene. The solution was decolorized with "Norite A" and filtered. The solvent was evaporated on the steam bath and the heavy oily residue solidified on scratching. The solid amine was recrystallized from high boiling ligroin from which it separated as colorless needles melting at 105-107° C.

Preparation of p-Aminophenyl-β-dimethylaminoethyl ether (VIII-c)

A mixture of 5 g. of acetyl p-aminophenyl-β-dimethylaminoethyl ether hydrochloride and 50 ml. of concentrated hydrochloric acid was boiled under reflux for six hours. The amine was liberated from the reaction mixture and isolated as a solid by the procedure described previously. The amine crystallized from "Skellysolve B" and melted at 53.0-54.5° C. A pink coloration could not be removed from the product.

The dihydrochloride was prepared by dissolving the amine in methyl alcohol, bubbling dry hydrogen chloride into the solution, and decolorizing with "Norite A". To the hot solution after filtering, ether was added dropwise until a slight turbidity persisted after which the dihydrochloride crystallized on standing, m.p. 230-232° C.

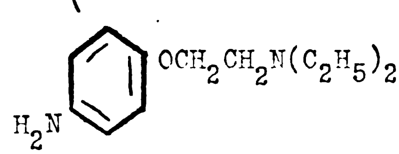
Preparation of Acetyl p-aminophenyl-β-diethylaminoethyl ether (VII-d) hydrochloride



A mixture of 6.5 g. (0.03 mole) of acetyl p-aminophenyl-β-chloroethyl ether, 10 ml. (0.09 mole) of diethyl amine, and 40 ml. of toluene was placed in each of four long combustion tubes and sealed. The tubes were heated for five days at 150° C. At the end of this time, the tubes were opened and the tertiary amine was isolated as described in the previous experiment. The yield of the amine was 27.7 g. The hydrochloride was prepared by dissolving the amine in absolute isopropyl alcohol and decolorizing with "Norite A". After filtering, dry hydrogen chloride was bubbled into the solution. The hydrochloride came out as needles melting at 214-215° C. The yield was 29 g., (83% of theoretical).

The pure hydrochloride was dissolved in water and the amine was liberated as previously described. The amine was taken up in benzene and the aqueous layer extracted with benzene. The solvent was evaporated but the heavy oil could not be induced to solidify.

<u>Preparation of p-aminophenyl-β-diethylaminoethyl ether</u> (VIII-d)



Acetyl p-aminophenyl-β-diethylaminoethyl ether hydrochloride (6.4 g.) and 65 ml. of concentrated hydrochloric acid were boiled under reflux for six hours. The reaction mixture was worked up as before to obtain the diamine. The diamine did not solidify when cooled and scratched as in the previous case.

The dihydrochloride was prepared by dissolving the diamine in methyl alcohol and bubbling in dry hydrogen chloride. The solution of the dihydrochloride was decolorized with "Norite A" and filtered. To the hot solution ether was added dropwise until it was slightly turbid, at which time crystals of the dihydrochloride started to form as plates, m.p. 196-198° C.

SUMMARY

1. The intermediate, acetyl p-aminophenyl-β-chloroethyl ether was prepared by two methods: (a) by the interaction of acetyl p-aminophenol with β-chloroethyl benzenesulfonate and (b) by the interaction of acetyl p-aminophenol with ethylene chlorohydrin followed by treatment of the resulting acetyl p-aminophenyl-β-hydroxyethyl ether with thionyl chloride.

2. A group of previously undescribed β-dialkylaminoethyl ethers of acetyl p-aminophenol was prepared by the interaction of the corresponding β-chloroethyl ethers with a number of secondary amines including dimethylamine, diethylamine, morpholine, and piperidine. The tertiary amino ethers were isolated as hydrochlorides and further characterized by liberation of the free bases. All the bases except acetyl p-aminophenyl-β-diethylaminoethyl ether were solids.

3. The corresponding p-aminophenyl-β-dialkylaminoethyl ethers which were prepared by acid hydrolysis of their acetyl derivatives are also new compounds. Only the diethylaminoethyl ether of p-aminophenol failed to crystallize, and all the diamines were further characterized as dihydrochlorides.

4. The acetyl p-aminophenyl-β-dialkylaminoethyl ether hydrochlorides have been submitted for pharmacological tests to determine their usefulness and effectiveness.

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