

A FURTHER STUDY OF CHLOROMETHYL INTERMEDIATES IN PREPARATION  
OF SUBSTANCES OF PHARMACOLOGIC INTEREST

by  
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Thesis submitted to the Faculty of the Graduate School  
of the University of Maryland in partial  
fulfillment of the requirements for  
the degree of Doctor of Philosophy

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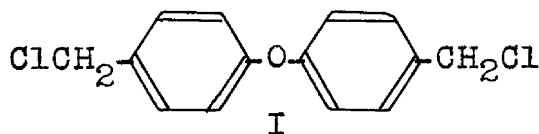
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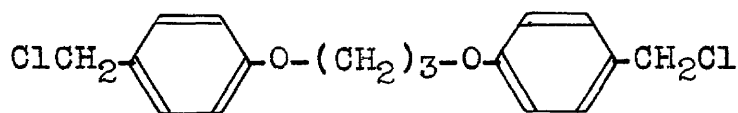
## INTRODUCTION

A study has been made of the use of chloromethylation products in preparation of substances of pharmacologic interest. The bis(chloromethylation)-derivatives of polynuclear aromatic hydrocarbons, viz., naphthalene, biphenyl and bibenzyl have been prepared and converted to diamidines and basic ethers. Two of these diamidines, 4,4'-bis(amidinomethyl)biphenyl dihydrochloride and 4,4'-bis(amidinomethyl)-biphenyl dihydrochloride were found to possess a high order of antibacterial activity when tested in vitro using cultures of *Mycobacterium tuberculosis*, H37Rv (13). Because of the availability of chloromethyl derivatives of aromatic hydrocarbons through the chloromethylation reaction and the ease of their reactions with nucleophilic reagents, the conversion of chloromethyl intermediates to various pharmacodynamically active substances deserves further study.

In the present investigation, the bis(chloromethyl)-derivatives of diphenylether (I), 1,3-diphenoxypropane (II) and 1,5-diphenoxypentane (III) have been prepared for use as intermediates in preparation of substances of possible pharmacologic interest.

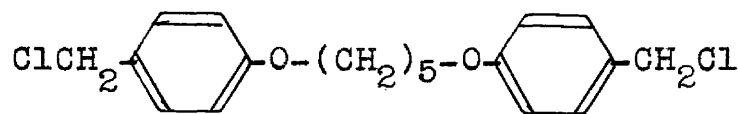


4,4'-bis(chloromethyl)diphenyl ether



II

1,3-bis(4-chloromethylphenoxy)propane



III

1,5-bis(4-chloromethylphenoxy)pentane

From these intermediates, the corresponding amidines (IV), aralkylamines (V), imidazolines (VI) and basic ethers (VII) have been prepared as indicated schematically in Figure 1.

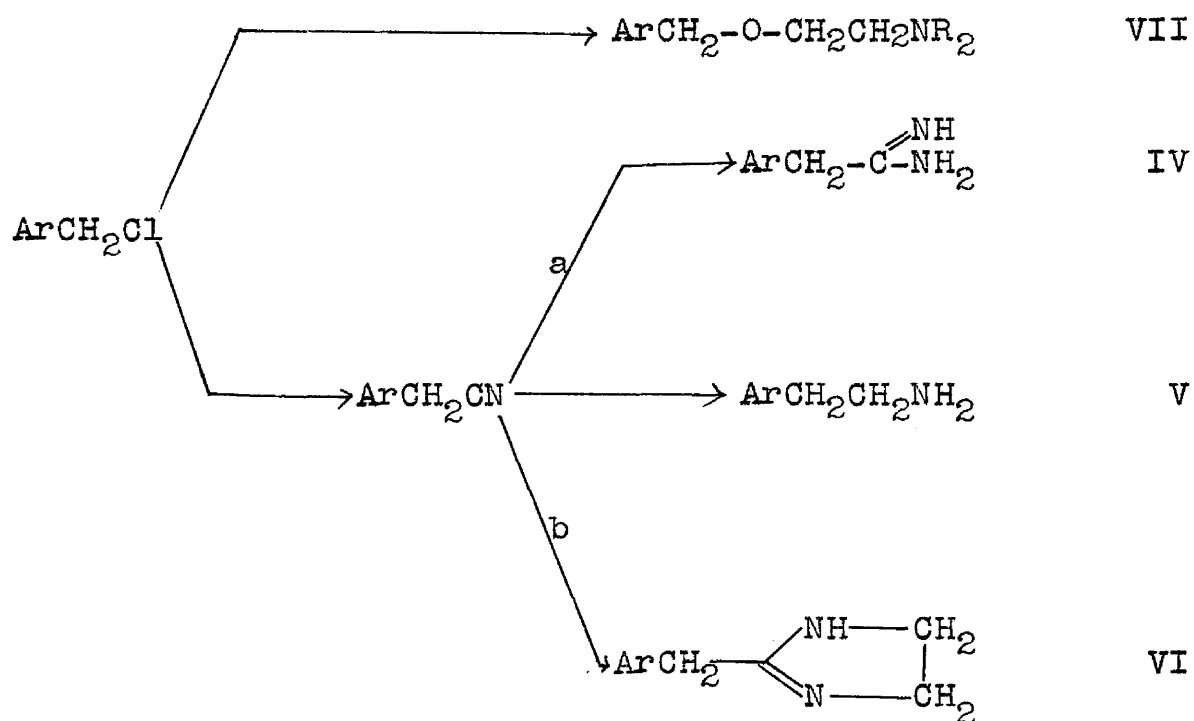
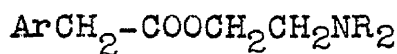


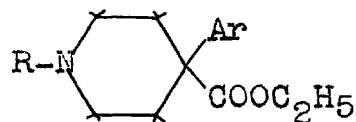
Figure 1

<sup>a</sup>By way of imidoester hydrochloride. <sup>b</sup>By way of carboxylic acid and ethyl ester thereof.

The use of certain of the intermediates shown in Figure 1 for preparation of basic esters (VIII) and iso-nipecotic acid derivatives (IX) has also been considered and work on these compounds is currently in progress.

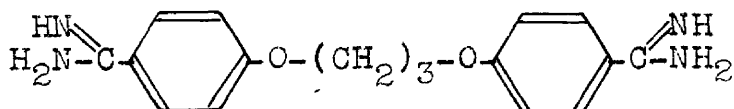


VIII

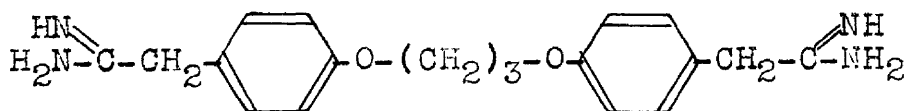


IX

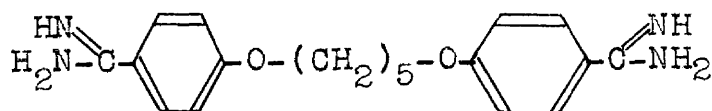
Interest in the substituted acetamides (IV) was stimulated by the success obtained in the use of propamide (X), pentamide (XII) and related compounds in treatment of various tropical diseases (2) (3) (4) (14) (15). Examination of the structures of two of the amides which have been prepared, (XI) and (XIII), reveals their homologous relationship to propamide (X) and pentamide (XII).



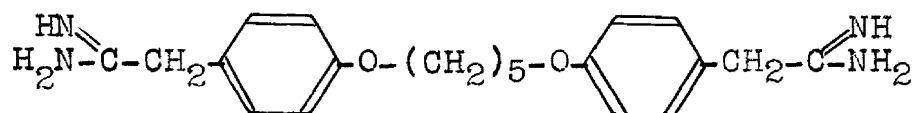
X



XI



XII

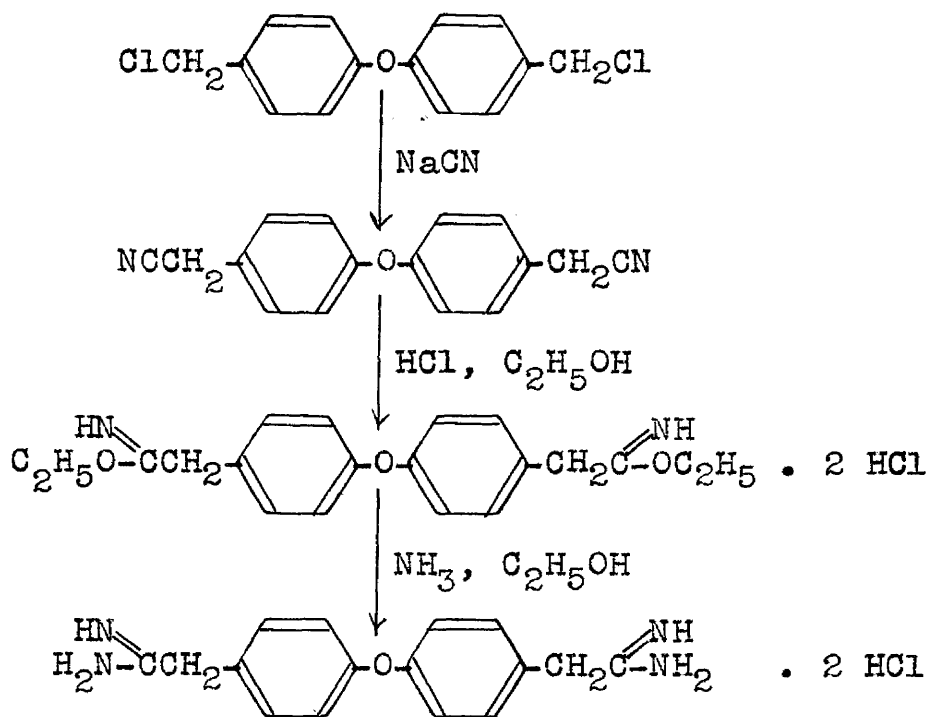


XIII

Since related monoamidines have been shown to possess no trypanocidal activity, it is clear that the symmetrical structure with the polar amidino groups at each extremity is the key to activity in this series. The most active compounds if depicted in their most extended forms are grouped within certain length limits, stilbamidine being the shortest and pentamidine the longest. Longer or shorter molecules are generally less active (20). The three amidines which have been prepared from products of chloromethylation of diphenyl ether (XIV), 1,3-diphenoxypropane (XI) and 1,5-diphenoxypentane (XIII) possess the structural qualifications for chemotherapeutic activity as regards the spatial relationship of the two amidine groups.

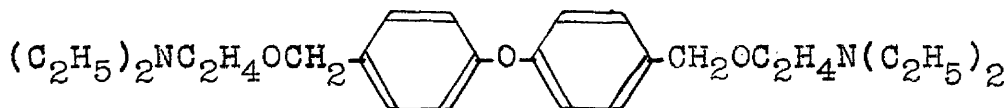
The amidines were prepared from the chloromethyl intermediates by way of the nitriles and imido-ester hydrochlorides as indicated by the equations for the reactions by means of which 4,4'-bis(amidinomethyl)diphenyl ether dihydrochloride (XIV) was prepared. A number of alternate procedures for conversion of nitriles to amidines could probably also be used (21).



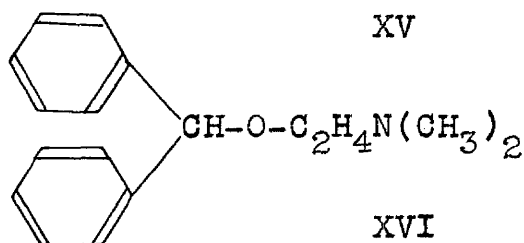


XIV

Virtually all the compounds grouped under antihistaminic drugs contain the structural unit  $\text{R}_2\text{N-C-C-X}$  in which X is an aralkoxy group, disubstituted amino group or an aralkyl group. They counteract many manifestations of histamine toxicity, even in conditions (dermal allergies) in which the role of histamine is relatively insignificant (8). The basic ether (XV) was prepared for testing for antihistaminic activity because of its structural relationship to Benadryl (XVI).

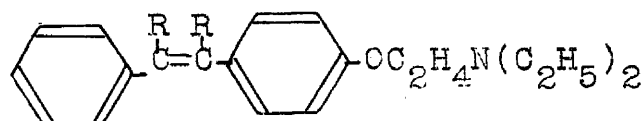


XV

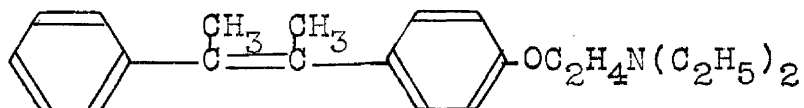


XVI

Further interest in the basic ethers, such as (XV) of this series arises from their structural relationship to a number of basic ethers found by Marinopoulo (16) to possess coronary dilating and antifibrillatory activity. In the series of 4(2-diethylaminoethoxy)- $\alpha,\alpha'$ -dialkyl-stilbenes (XVII), 4(2-diethylaminoethoxy)- $\alpha,\alpha'$ -dimethyl-stilbene (XVIII) was found to possess sufficient coronary dilating and anti-fibrillatory activity and to be of sufficiently low toxicity, to be of further interest.

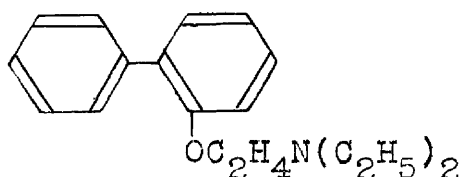


XVII



XVIII

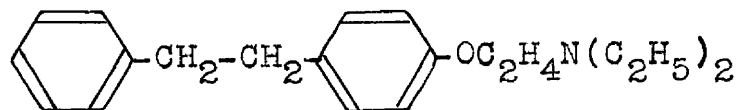
A similar effect on coronary circulation and the heart was observed in 2(2-diethylaminoethoxy)biphenyl (XIX) (25) (26); 4(2-diethylaminoethoxy)-stilbene (XX) and 4(2-diethylaminoethoxy)bibenzyl (XXI) (9).



XIX

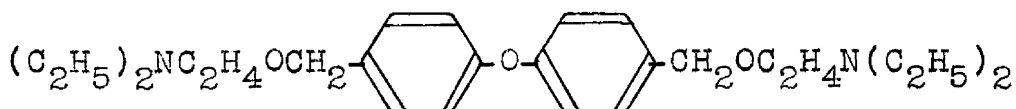


XX

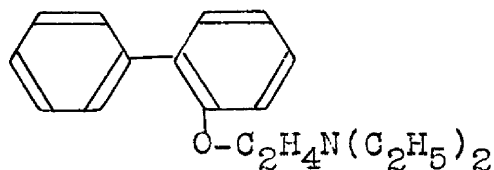


XXI

The close structural relationship of compound (XXII) described in this paper and compounds (XXIII) and (XXIV) respectively, justifies the pharmacologic study of its effects on coronary circulation and the heart.



XXII



XXIII



XXIV

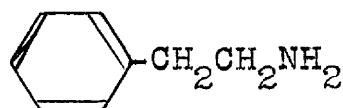
It has been known since the early observations of Vulpinus (1856) that a secretion of adrenal medulla can raise the blood pressure in laboratory animals and in man. After the isolation, purification and the elucidation of the structure of its main component, epinephrine, shortly after 1900, the similarity of its chemical properties and those of certain putrefactive amines attracted the attention of Barger and Dale (6). In a comprehensive investigation, they synthesized a series of compounds having in common the phenylethylamine grouping and with substituents at  $\alpha$  or  $\beta$  -carbon atoms as

well as in the benzene ring. These amines were tested as vasopressors. That the aromatic ring is not absolutely essential for pressor activity is attested by the weak pressor action of isoamylamine which is found naturally as a putrefaction product of leucine. Other aliphatic amines share in this property, and some, for instance 2-aminoheptane, have found therapeutic use. Nevertheless, the arylethylamines possess a much higher order of sympathomimetic activity (8).

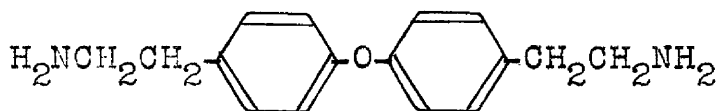
Of further interest is the fact that during the past few years aralkylamines have received considerable attention as potential analgesic agents. The term aralkylamine is applied, in general, to compounds of the type  $\text{Ar}-(\text{CH}_2)_n-\text{NR}_2$ , where  $n$  may vary from 1 to 6 and the chain may be substituted or unsubstituted;  $-\text{NR}_2$  is a primary, secondary or a tertiary amino group. Major attention has been given to those compounds that may be considered as derivatives of  $\beta$ -phenyl-ethylamine, higher or lower homologs of this basic structure and various substitution products thereof. A number of reports have been made to the effect that epinephrine and ephedrine manifest an analgesic action in human subjects (10) (17) (18) (22).

The apparent structural similarity between phenylethylamine (XXV) and the compound (XXVI) described in this study justifies the pharmacologic study of the possible

vasopressor and analgesic action of this compound (XXVI).

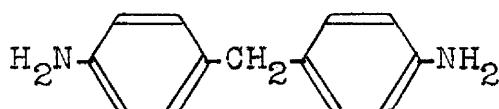


XXV

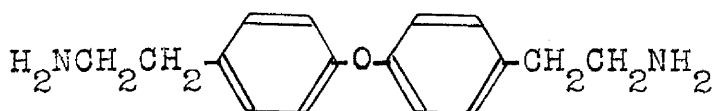


XXVI

Aminobenzene derivatives were found to possess anti-thyroid activity. The most potent compounds encountered in the aminobenzene series were 4,4'-diaminodiphenylmethane and its tetramethyl derivative, these were about one fourth as active as thiouracil and thus about twice as active as thiourea (5). A comparison of the structures of 4,4'-diaminodiphenylmethane (XXVII) and the compound (XXVIII) described in this study shows clearly that the two compounds are related in a homologous sense. Since the oxygen linkage is isosteric with a methylene linkage, the major difference in the structures of these two compounds is the intramolecular distance separating the amino groups. Such a configurational similarity justifies the pharmacologic study of the possible antithyroid activity of this compound (XXVIII).

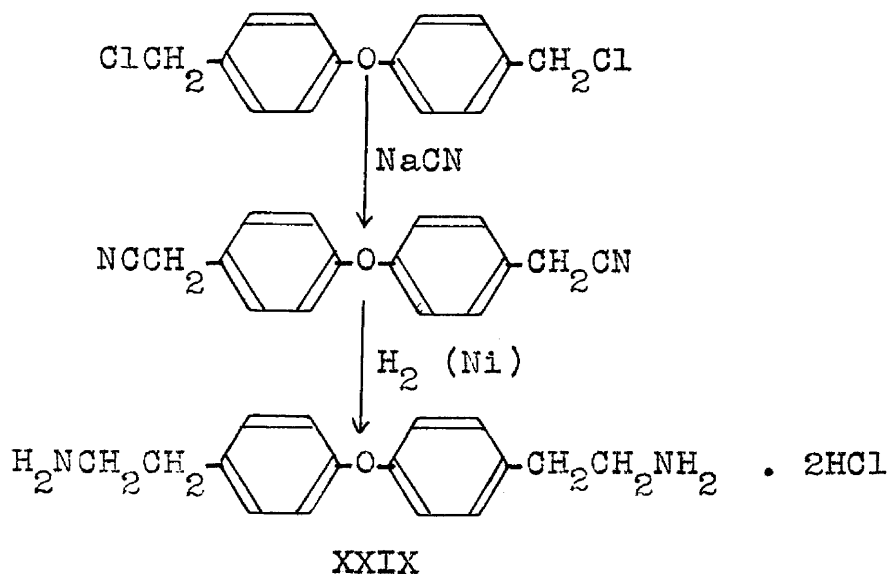


XXVII

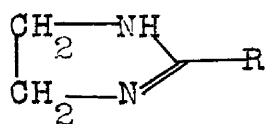


XXVIII

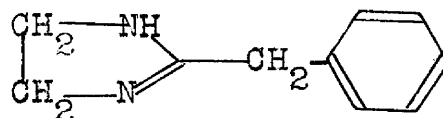
The chloromethyl intermediates (I, II and III) can be used as starting materials for preparation of arylethylamines useful in the above indicated studies. The preparation of 4,4'-bis(2-aminoethyl)diphenyl ether dihydrochloride (XXIX) has been carried out by use of the following reactions:



Guided by the thought that nature produces many physiologically active alkaloids, amino acids and biogenic amines containing the imidazole ring (pilocarpine, histidine, histamine), simple derivatives of imidazoline (XXX) had been tested repeatedly for pharmacologic activity (8) (19). Several of the derivatives in which R is benzyl or hydrogenated benzyl possessed definite vasodilator and hypotensive activity in laboratory animals and stimulated further research in this field. It is noteworthy that 2-benzyl-imidazoline, Priscoline (XXXI) is, in a sense, a substituted phenylethylamine; a fact that may serve as a basis for understanding its vasomotor properties.



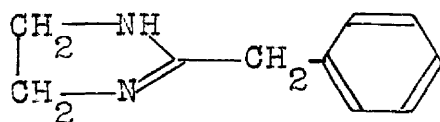
XXX



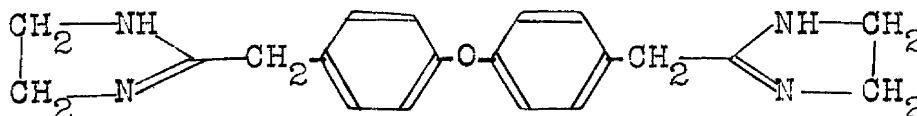
XXXI

Priscoline has been used in the treatment of the arthritis, and the clinical evidence indicates that Priscoline acts as an adjuvant to conventional therapeutic measures of established value (26).

The close resemblance between the structure of Priscoline (XXXII) and a compound (XXXIII) prepared in this investigation justifies the pharmacologic study of its possible vasomotor effect. Furthermore, the oxygen bridge at the para position may have an important influence on its pharmacologic effects.

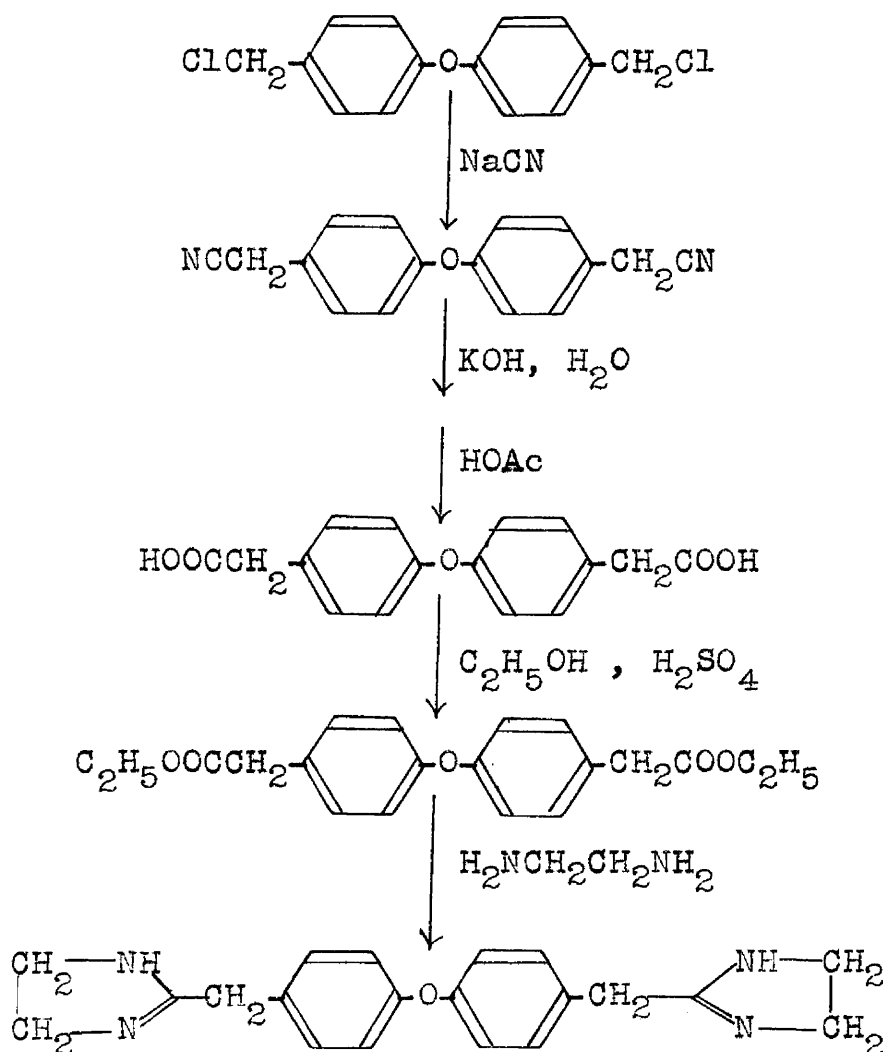


XXXII



XXXIII

The chloromethyl intermediates can also be used as starting materials for preparation of imidazolines, by reactions indicated by the following equations:



By this means, 4,4'-bis(2-methylene-2-imidazoline)-diphenyl ether dihydrochloride has been prepared. Pharmacologic testing of the compound along the lines indicated in the above discussion, is currently in progress.



## EXPERIMENTAL

### Preparation of 4,4'-Bis(chloromethyl)diphenyl Ether.-

The method described by Tomita and Kimura was employed with some modifications (23). Diphenyl ether 10 g. (0.059 mole) was mixed with 15 g. of glacial acetic acid, 15 g. of 40% aqueous solution of formaldehyde and 13.7 g. of 85% phosphoric acid. The mixture was stirred mechanically for five hours while a rapid stream of dry hydrogen chloride was introduced. At the end of five hours, the mixture was poured into 300 ml. of ice water and shaken with ether. The ether layer was separated and thoroughly washed with 20% sodium carbonate solution. The ether layer was dried with anhydrous sodium sulfate and concentrated by complete distillation of the ether. The residual oil was distilled under reduced pressure at 1.5 mm. and the fraction boiling at 165-175° was collected. The distillate solidified on cooling to a white solid. After recrystallization from Skelly-solve B or 95% ethanol, 6.8 g. of 4,4'-bis(chloromethyl)diphenyl ether (42.7% of theoretical yield) m.p.<sup>1</sup> 62-4° (reported 61-3°), was obtained (23).

### Preparation of 1,3-Bis(4-chloromethylphenoxy)propane.-

1,3-Diphenoxypropane, 45.7 g. (0.2 mole), was mixed with 200 ml. of petroleum ether, 50 g. of glacial acetic acid,

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<sup>1</sup>All melting points were determined on Fisher melting point block and were uncorrected.

50 g. of 40% aqueous solution of formaldehyde and 46 g. of 85% phosphoric acid. The mixture was stirred mechanically for eight hours while a rapid stream of dry hydrogen chloride was introduced and the temperature was kept at 90-95°. At the end of the eight-hour period, the mixture was poured into 1 l. of ice water. The solid mass was carefully ground to powder form in a mortar and suspended in 200 ml. of petroleum ether. The suspension was shaken for one hour and then filtered. The solid material on the filter was washed thrice with 20 ml. portions of petroleum ether and then twice with 50 ml. of water. The residue was then recrystallized from carbon tetrachloride, -a white powder, 22.8 g. (35% of theoretical yield), m.p. 126-7°, was obtained.

Anal. Calcd. for  $C_{17}H_{18}Cl_2O_2$ : Cl, 21.80; Found:  
Cl, 22.05

Preparation of 1,5-Bis(4-chloromethylphenoxy)pentane.-

The 1,5-diphenoxypentane was prepared by the method described by von Braun and Steindorff (7). 1,5-Dichloropentane, 14 g. (0.1 mole), was mechanically stirred under reflux for 30 hours with sodium phenolate 58 g. (0.5 mole) in 580 ml. of 95% ethanol. The unreacted 1,5-dichloropentane in the resulting mixture was removed by steam distillation. The residue was cooled and 1,5-diphenoxypentane began to crystallize out as white crystals. It was filtered and recrystallized from 95% ethanol, -19.2 g. (75% of theoretical yield), m.p. 48-9° (reported m.p. 48-9°) (7).

1,5-Diphenoxypentane, 25.6 g. (0.1 mole), was mixed with 25 g. of glacial acetic acid, 25 g. of 40% aqueous solution of formaldehyde, and 23 g. of 85% phosphoric acid. The mixture was stirred mechanically for five hours while a rapid stream of dry hydrogen chloride was introduced and the temperature was kept at 90-5°. At the end of five hours, the mixture was poured into 1 l. of ice water. The aqueous layer was decanted and the pasty mass was stirred with a fresh 500 ml. portion of ice water. The aqueous layer was again decanted. In a similar way, 500 ml. of 10% sodium carbonate solution was used twice and then water was again used. The pasty mass was then dissolved in warm Skelly-solve B and filtered. The white crystals that formed on cooling were recrystallized twice from Skelly-solve B, -7.8 g. (22% of theoretical yield), m.p. 65.5-66.5°.

Anal. Calcd. for  $C_{19}H_{22}Cl_2O_2$ : Cl, 20.07; Found;  
Cl, 20.06

Preparation of 4,4'-Bis(cyanomethyl)diphenyl Ether.-

The method described by Tomita and Kimura was used (23). 4,4'-Bis(chloromethyl)diphenyl ether, 10 g. (0.059 mole), was refluxed with a mixture of 40 ml. of 95% ethanol, 7 g. of sodium cyanide and 20 ml. of water. After boiling under reflux for four hours, the alcohol and water were distilled off under reduced pressure. The residue was taken up in water and extracted with nitrobenzene. The nitrobenzene layer was separated and dried with 10 g. of anhydrous sodium sulfate. The nitrobenzene was then removed

by distillation under reduced pressure. The residue was distilled at 3 mm. pressure and the fraction boiling between 200-227° was collected. The distillate solidified into a white mass and was recrystallized from 95% ethanol, -8 g. (54.7% of theoretical yield), m.p. 53-55° (reported m.p. 53-6°) (23).

Preparation of 1,3-Bis(4-cyanomethylphenoxy)propane.--

(Method I) 1,3-Bis(4-chloromethylphenoxy)propane, 6.5 g. (0.02 mole), was refluxed with a mixture of 95% ethanol, 3.5 g. of sodium cyanide, and 10 ml. of water. After boiling under reflux for four hours, the alcohol and water were distilled off under reduced pressure. The residue was taken up in 50 ml. of water, filtered and the resulting crystalline material was washed with water. It was then dissolved in absolute ethanol and decolorized with activated carbon. Upon cooling, white crystals formed and were recrystallized from absolute ethanol, -m.p. 112-3°, 2.9 g. (41% of theoretical yield).

Preparation of 1,3-Bis(4-cyanomethylphenoxy)propane.--

(Method II) 1,3-Dichloropropane, 11.3 g. (0.1 mole), was mechanically stirred under reflux for 30 hours with sodium ethoxide 13.6 g. (0.2 mole) and p-hydroxyphenylacetonitrile, 26.6 g. (0.2 mole), in 270 ml. of absolute ethanol. The resulting mixture was then cooled and sodium chloride and crystalline 1,3-bis(4-cyanomethylphenoxy)propane separated. The mixture was filtered and the precipitate suspended in 70 ml. of water. The suspension was then filtered and the precipitate was dissolved in 95% ethanol and decolorized

with activated carbon. Upon cooling, white crystals formed and were recrystallized from 95% ethanol, -m.p. 113-4°, 18.4 g. (60% of theoretical yield).

The p-hydroxyphenylacetonitrile used in this procedure was prepared by method described by Fourneau (12).

Anal. Calcd. for  $C_{19}H_{18}N_2O_2$ : N, 9.15; Found:  
N, 9.06

Preparation of 1,5-Bis(4-cyanomethylphenoxy)pentane.-

(Method I) 1,5-Bis(4-chloromethylphenoxy)pentane, 7.1 g. (0.02 mole), was refluxed with a mixture of 40 ml. of 95% ethanol, 3.5 g. of sodium cyanide and 10 ml. of water. After boiling under reflux for four hours, the alcohol and water were distilled off under reduced pressure. The residue was taken up in 50 ml. of water, filtered and the resulting crystalline material was washed with water. It was then dissolved in absolute ethanol and decolorized with activated carbon. White crystals formed upon cooling, and were recrystallized from absolute ethanol, - 3.1 g. (45% of theoretical yield), m.p. 93-4°.

Preparation of 1,5-Bis(4-cyanomethylphenoxy)pentane.-

(Method II) 1,5-Dichloropentane, 14.1 g. (0.1 mole), was mechanically stirred under reflux for 30 hours with sodium ethoxide, 13.6 g. (0.2 mole), and p-hydroxyphenylacetonitrile, 26.6 g. (0.2 mole), in 270 ml. of absolute ethanol. The resulting mixture was cooled and sodium chloride and 1,5-bis(4-cyanomethylphenoxy)pentane separated as a crystalline mass. The mixture was filtered and the precipitate was

then suspended in 70 ml. of water. The suspension was filtered and the precipitate was dissolved in 95% ethanol and decolorized with activated carbon. Upon cooling, white crystals formed and were recrystallized from 95% ethanol, -m.p. 93-4°, 18.3 g. (55% of theoretical yield).

Anal. Calcd. for  $C_{21}H_{22}N_2O_2$ : N, 8.38; Found:  
N, 8.14, 8.18

Preparation of 4,4'-Bis(amidinomethyl)diphenyl Ether Dihydrochloride.- Dry hydrogen chloride was passed into a solution of 15 g. (0.06 mole) of thoroughly dried 4,4'-bis(cyanomethyl)diphenyl ether in 8.3 g. of absolute ethanol and 20 ml. of nitrobenzene contained in a one-liter tared suction flask surrounded by a freezing mixture of ice and salt, until an increase in weight of 5.5 g. (0.15 mole) was obtained. The mixture was transferred to a pressure bottle, stoppered tightly and allowed to stand at room temperature for seven days. A part of the mixture set to a solid mass.

The solid crystalline mass of imidoester hydrochloride was filtered, placed in a sealed tube with 100 ml. of 14% ethanolic ammonia and shaken for 5 hours at a temperature of 35-45°. The resulting solution was evaporated under reduced pressure to about one-half of its original volume. After decolorization with activated carbon and filtration, the solution was treated with anhydrous ether while warm until it became cloudy. On cooling, a crystalline powder separated. The crystals were dissolved in hot absolute

ethanol and reprecipitated with anhydrous ether,- white crystalline solid, m.p. 292-4° with decomposition, yield 5.5 g. (27% of theoretical yield).

The free amidine was obtained by treating the amidine hydrochloride with 10% sodium hydroxide,- white solid, m.p. 155-6°.

Anal. Calcd. for  $C_{16}H_{18}N_4O_2$ : N, 19.85; Found:  
N, 19.32

Preparation of 1,3-Bis(4-amidinomethylphenoxy)propane Dihydrochloride.- Dry hydrogen chloride was passed into a solution of 22 g. (0.072 mole) of thoroughly dried 1,3-bis-(4-cyanomethylphenoxy)propane in 10 g. of absolute ethanol and 20 ml. of nitrobenzene contained in a one-liter tared suction flask surrounded by a freezing mixture of ice and salt, until an increase in weight of 6.6 g. (0.18 mole) resulted (1). The mixture was transferred to a pressure bottle, stoppered tightly and allowed to stand at room temperature for seven days. A part of the mixture set to a solid mass.

The solid crystalline mass of imidoester hydrochloride was filtered, placed in a sealed tube with 100 ml. of 14% ethanolic ammonia and shaken for 5 hours at a temperature of 35-45°. The resulting solution was evaporated under reduced pressure to about one-half of its original volume. After decolorization with activated carbon and filtration, the solution was treated with anhydrous ether while warm until it became cloudy. On cooling, a crystalline solid

separated. The crystals were dissolved in hot absolute ethanol and reprecipitated with anhydrous ether,- white crystalline solid, m.p. 288-290° with decomposition, yield 8.3 g. (28% of theoretical yield).

The free amidine was obtained by treating the amidine hydrochloride with 10% sodium hydroxide,- white solid, m.p. 215-7°.

Anal. Calcd. for  $C_{19}H_{24}N_4O_2$ : N, 16.46; Found:  
N, 16.30

Preparation of 1,5-Bis(4-amidinomethylphenoxy)pentane Dihydrochloride.- Dry hydrogen chloride was passed into a solution of 18 g. (0.054 mole) of thoroughly dried 1,5-bis-(4-cyanomethylphenoxy)pentane in 7.5 g. of absolute ethanol and 20 ml. of nitrobenzene contained in a one-liter tared suction flask surrounded by a freezing mixture of ice and salt, until an increase in weight of 4.9 g. (0.135 mole) resulted. The mixture was transferred to a pressure bottle, stoppered tightly and allowed to stand at room temperature for seven days. A part of the mixture set to a solid mass.

The solid crystalline mass of imidoester hydrochloride was filtered, placed in a sealed tube with 100 ml. of 14% ethanolic ammonia and shaken for 5 hours at a temperature of 35-45°. The resulting solution was evaporated under reduced pressure to about one-half of its original volume. After decolorization with activated carbon and filtration, the solution was treated with anhydrous ether while warm



until it became cloudy. On cooling, a crystalline powder separated. The crystals were dissolved in hot absolute ethanol and reprecipitated with anhydrous ether,- white crystalline solid, m.p. 295-7° with decomposition, yield 6.2 g. (26% of theoretical yield).

The free amidine was obtained by treating the amidine hydrochloride with 10% sodium hydroxide,- white solid, m.p. 166-7°.

Anal. Calcd. for  $C_{21}H_{28}N_4O_2$ : N, 15.21; Found:  
N, 15.16

Preparation of 4,4'-Bis(2-diethylaminoethoxymethyl)-diphenyl Ether Dihydrochloride.- 4,4'-Bis(chloromethyl)-diphenyl ether, 10 g. (0.037 mole), and 10.4 g. (0.074 mole) of sodium diethylaminoethoxide were dissolved in 100 ml. of dry toluene and refluxed for 12 hours. The toluene was removed by distillation under reduced pressure and 20 ml. of 10% sodium hydroxide was added to the residue and the mixture extracted three times with 20 ml. of ether. The ether extract was shaken twice with 20 ml. of 10% hydrochloric acid. Four grams of sodium hydroxide pellets were added to the acid extract and the free basic ether was extracted with two 20 ml. portions of ether. The ether solution was dried with anhydrous sodium sulfate and the ether was removed under reduced pressure. The residue was then distilled under reduced pressure and that fraction distilling over at 230-5°, 2 mm. was collected. The

distillate was taken up with dry absolute ethanol saturated with hydrogen chloride gas. Dry ether was added, a solid hygroscopic precipitate was formed. The precipitate was filtered in a dry atmosphere (using a desiccator), and recrystallized from acetone,- white crystalline solid, m.p. 160-1°, yield 11 g. (59.4% of theoretical yield).

Anal. Calcd. for  $C_{26}H_{42}Cl_2N_2O_3$ : N, 5.59; Found: N, 5.78

Preparation of 4,4'-Bis(2-aminoethyl)diphenyl Ether Dihydrochloride.- 4,4'-Bis(cyanomethyl)diphenyl ether, 6.2 g. (0.025 mole), was dissolved in 75 ml. of methanol containing 15% of ammonia. Raney Nickel 3.1 g. was added to the solution and the mixture was placed in the glass liner of a high pressure reaction vessel. It was shaken for 3 hours at 60-5° under a pressure of hydrogen of 1100 psi. After the bomb had been cooled and opened, the contents were filtered through a layer of active charcoal on filter paper, and washed twice with 25 ml. of methanol. The filtrate was distilled under reduced pressure to remove methanol. The residue was distilled under reduced pressure and the fraction distilling between 170-5° at 3 mm. was collected.

The distillate was taken up with absolute ethanol saturated with dry hydrogen chloride. A white crystalline powder was precipitated upon addition of anhydrous ether. The solid was recrystallized from absolute ethanol and dry ether,- white crystalline powder, m.p. 295-7° with slight

decomposition, yield 6.5 g. (79% of theoretical yield).

The Raney Nickel used in the above procedure was prepared according to the method described by Covert and Adkins (11).

Anal. Calcd. for  $C_{16}H_{22}Cl_2N_2O$ : N, 8.51; Found:  
N, 8.47, 8.54

Preparation of 4,4'-Bis(carboethoxymethyl)diphenyl Ether.- The ester was prepared by refluxing for three hours a mixture of 6 g. (0.021 mole) of 4,4'-bis(carboxymethyl)diphenyl ether, 120 ml. of absolute ethanol and 3 g. of concentrated sulfuric acid. The ester was isolated by distilling off 70 ml. of ethanol under reduced pressure, diluting the residue with 100 ml. of water, separating and extracting the aqueous layer twice with 25 ml. portions of ether. The combined ether layers were washed with 10 ml. of 5% sodium carbonate solution and dried with anhydrous sodium sulfate. After filtration, the ether was removed by distillation and the residue was distilled under reduced pressure, the portion boiling at  $205-8^{\circ}$  at 3 mm. was collected, 5 g. (70% of theoretical yield).

Anal. Calcd. for  $C_{20}H_{22}O_5$ : C, 70.17; H, 6.48.  
Found: C, 71.26; H, 6.90

Preparation of 4,4'-Bis(2-methylene-2-imidazoline)-diphenyl Ether Dihydrochloride.- A mixture of 4 g. (0.0117 mole) of 4,4'-bis(carboethoxymethyl)diphenyl ether and 5.8 g. (0.096 mole) of anhydrous ethylenediamine was heated for 36 hours on a steam bath in a sealed tube.

The excess ethylenediamine was then removed by distillation under reduced pressure. The residue could not be distilled under vacuum without decomposition. It was purified by recrystallization from dry xylene and a white solid, m.p. 163-4°, was obtained, - 2.8 g. (72% of theoretical yield).

Anal. Calcd. for  $C_{20}H_{22}N_4O$ : N, 16.76; Found:  
N, 16.58

The hydrochloride was prepared by saturation of a xylene solution of the imidazoline with dry hydrogen chloride, - white precipitate, m.p. 212-3°.

## SUMMARY

The products of chloromethylation of aromatic hydrocarbons, as expected, undergo a variety of nucleophilic substitution reactions which make possible their conversion to compounds of pharmacologic interest.

The present research is an extension of a previous study of the preparation of substances of pharmacologic interest from products of chloromethylation. The reactions by means of which such chloromethyl derivatives can be converted to amidines have been employed for preparation of the following:

4,4'-bis(amidinomethyl)diphenyl ether dihydrochloride  
1,3-bis(4-amidinomethylphenoxy)propane dihydrochloride  
1,5-bis(4-amidinomethylphenoxy)pentane dihydrochloride

The structures of :

1,3-bis(4-chloromethylphenoxy)propane  
1,5-bis(4-chloromethylphenoxy)pentane

have been proved by synthesis of their corresponding dinitriles by two different methods as well as analysis of the products.

Reactions of the chloromethyl derivative with the sodium salt of an aminoalcohol have been used for the preparation of:

4,4'-bis(2-diethylaminoethoxymethyl)diphenyl ether dihydrochloride.

The conversion of the same intermediate chloromethyl derivative to 4,4'-bis(2-aminoethyl)diphenyl ether dihydrochloride which is of possible interest as sympathomimetic agent has been carried out.

The preparation of 4,4'-bis(2-methylene-2-imidazoline)-diphenyl ether dihydrochloride from the chloromethyl derivative was accomplished by treatment of the 4,4'-bis(carboethoxymethyl)diphenyl ether which was prepared from the chloromethyl intermediate, with ethylenediamine.

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