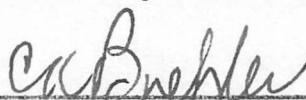


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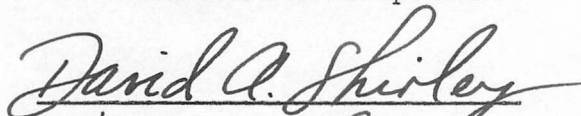


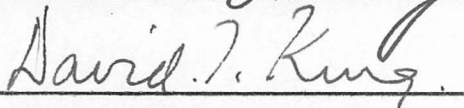
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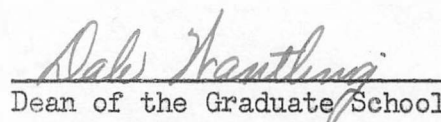
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PREPARATION OF COMPOUNDS OF POTENTIAL PHYSIOLOGICAL ACTIVITY:

DERIVATIVES OF BENZILIC, SUBSTITUTED ACETIC

AND SUBSTITUTED GLYCOLIC ACIDS AND

SUBSTITUTED BUTANONES

A DISSERTATION

Submitted to
The Graduate Council
of
The University of Tennessee
in
Partial Fulfillment of the Requirements
for the Degree of
Doctor of Philosophy

by

Thomas Alexander Magee

December, 1957

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To Ruby

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CHAPTER I

INTRODUCTION AND HISTORY

A. Introduction

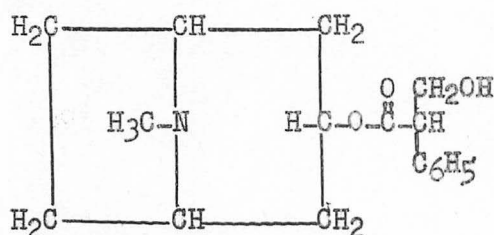
The continuing search of chemists, physiologists and medical researchers for natural and synthetic compounds which will alleviate or cure the illnesses of mankind constitutes a fascinating episode in the history of scientific endeavor. One chapter of this history is necessarily concerned with efforts to synthesize better, more useful antispasmodics. To present a comprehensive critical review of these efforts would require an extensive treatise and will not be attempted here. Several reviews are available which cover the literature to around 1950.^{1,2,3} The present survey will be a brief resume of the more pertinent material to the present time. It is hoped that this resume will afford to the reader some background in and appreciation of the field, together with an understanding of the synthetic approaches involved.

1. Spasm and Antispasmodics

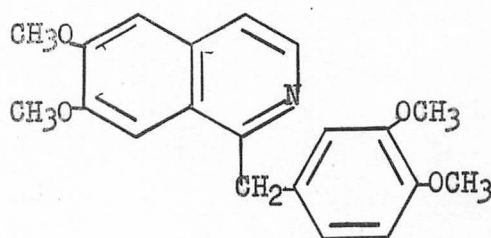
Spasm may be defined as a violent, involuntary contraction due to muscular action, usually accompanied by pain and interference with function. An antispasmodic or spasmolytic is a substance that is capable to producing specific relaxation of such spasticity. For internal medicine the most valuable property possessed by an antispasmodic is the ability to inhibit spasm of the smooth muscles, that is, the mus-

cles which surround the alimentary canal, the blood vessels, and other tubes of the viscera.⁴ It has been recognized that such smooth muscle spasm may be caused either by direct stimulation of the muscle or by indirect stimulation through the nerve endings. On the basis of this distinction, antispasmodics may be divided into two classes: (1) the musculotropic or direct acting and (2) the neurotropic, which act to prevent or abolish neural excitation mediated by acetyl choline. The neurotropic drugs (or anticholinergics) may be further subdivided according to whether they act on the sympathetic or the parasympathetic nervous system. The antispasmodics of greatest practical importance are the musculotropic and the parasympathetic neurotropic compounds.

Nature has supplied useful drugs in each of these categories in atropine (I-1) and papaverine (I-2). However, both of these natural



I-1



I-2

antispasmodics suffer from certain limitations and undesirable side effects. Atropine is ineffective against spasm of entirely muscular origin; papaverine has little effect against neurotropic spasm. In addition, papaverine tends to relax all of the smooth muscles equally, so that when relaxation of the intestinal tract is produced, there also results a prolonged fall in arterial blood pressure. Atropine affects all of the organs activated by the autonomic nervous system, thereby

causing cyclopegia, mydriasis, dryness of the mouth, tachycardia, delayed gastric emptying time, and occasionally a rise in arterial blood pressure.¹

Obviously from a clinical point of view, it would be of great advantage to be able to prescribe an antispasmodic without needing to determine the mechanism by which the particular spasm had been produced. It would also be of definite advantage to possess more selective drugs. These factors plus economic considerations have inspired a tremendous amount of research during the past twenty-five years. All of this research has had a common goal: the preparation of a commercially competitive antispasmodic which will possess both musculotropic and neurotropic activity and in which the activity will be less general, that is, the compound will have a selective activity on the smooth muscles of the hollow viscera, but no, or slight, effect on the pupils of the eye, the salivary glands, and the circulation. To date, this goal has not been achieved, although a number of synthetic antispasmodics have been placed in clinical use.

2. Evaluation of New Antispasmodics

Before the development of synthetic antispasmodics is discussed further, it would seem to be of value to take a brief look at methods of testing and evaluating new compounds. The clinical utility of a spasmolytic depends on its antispasmodic activity, its side effects, and its toxicity. To be evaluated properly, all of these factors must be considered. Unless there is a considerable difference between the

dose required for the desired spasmolytic action and that producing undesirable peripheral effects, there is little point in the clinical investigation of the compounds. Only methods for determining the anticholinergic and musculotropic activity will be touched upon. For a detailed discussion of the entire testing procedure, the reader is referred to the review article in Research Today.³

There are essentially two different methods of testing for spasmolytic activity. The first of these employs an isolated muscle strip as testing agent. This strip is immersed in a bath containing a stimulating agent. The new compound is then compared to atropine or some other reference standard with respect to its ability to block or reduce the spasm. Experimental variables have a profound effect on the test and the results are frequently in disagreement. For example, the published values for the anticholinergic activity of Trasentin determined in this manner ranged from 1 per cent⁵ to 20 per cent⁶ of that of atropine.

The second method employs the whole, live animal as the testing agent. By means of a balloon inserted through a small incision into the intestine of the animal or through use of trained dogs with Thiry fistulas, measurements of the activity may be obtained. There is frequently a considerable variation in activity as measured on the isolated muscle strip (in vitro) and as measured using the intact animal (in vivo). The latter test seems to approximate clinical usefulness more closely, and a good correlation exists between results obtained with this type of test and clinical effectiveness. However, in vivo test-

ing is considerably more expensive and time consuming than in vitro testing and is probably used less.

Because of the large number of factors which must be considered and tested, the evaluation of a new antispasmodic demands a greater pharmacological effort than is required for the study of most types of drug action. If one test is omitted or relied on too heavily, useful compounds may be overlooked or time wasted on unusable materials. It is often quite difficult for the pharmacologist to maintain a proper balance between the screening of many new compounds and the thorough study of a few active drugs.

3. General Approach to the Synthesis of Antispasmodics

The general approach to the synthesis of pharmaceutical materials has been applied to the preparation of antispasmodics. This approach consists of preparing modifications and variations of the structure of a naturally occurring drug and is thus essentially an empirical one. The present knowledge of the physiological modes of action of most drugs is not sufficient to provide many theoretical concepts on which to base the synthesis of pharmaceuticals. Until such understanding is obtained, an empirical method would seem to be the only procedure available. This approach has proved surprisingly successful as may be seen by the number of synthetic drugs in use today. Of course, greater knowledge of the mechanisms of physiological activity would undoubtedly hasten the development of desirable drugs.

A majority of the investigations in the field of synthetic antispasmodics have been concerned with modifications of atropine. The

present survey will consider primarily this work rather than the development of papaverine type structures. In developing permutations of the molecular structure of atropine (the tropine ester of tropic acid) two fundamental assumptions were made. First, since tropine itself has no noteworthy spasmolytic activity, its bicyclic structure was regarded as incidental and it was considered functionally as an aminoalcohol. The second assumption was to view tropic acid as essentially a branched chain phenylacetic acid. Some of the modifications have been fairly close analogues of atropine, but others bear only a superficial resemblance to the prototype.

The majority of synthetic antispasmodics reported to date may be divided into two broad classifications on the basis of their chemical structure. One group is comprised of derivatives of carboxylic acids in the form of esters, amides, and related types. The second group includes amines, aminoalcohols, aminoethers, and other compounds which are not acid derivatives. For obvious reasons it would be desirable to discuss these materials systematically according to their structural relationships. The widely varied methods used in reported pharmacological data make strict adherence to such an arrangement almost impossible. However, an attempt will be made to classify the compounds on a structural basis. These will be divided into three large groups: (1) derivatives of carboxylic acids in which the basic function is contained in the non-acidic portion of the derivative*, (2) derivatives of carboxyl-

*The carboxylic acid derivatives may be considered to be composed of two portions: the acid residue and the alcohol, amine, et cetera which reacts with the acid to form the derivative. Either or both of these portions may contain the basic function common to the antispasmodics.

ic acids in which the basic group is contained in the acid residuum, and (3) compounds other than derivatives of carboxylic acids. No attempt will be made to follow chronological order.

B. History

1. Derivatives of Carboxylic Acids in Which the Basic Group is Contained in the Non-acidic Portion of the Molecule

a. Esters. (1) Esters of simple disubstituted acetic acids.

The series of esters of 3-diethylamino-2,2-dimethylpropanol described by Fromherz⁷ in 1933 constitutes the earliest detailed publication in the antispasmodic field. His results revealed that compounds may simultaneously exhibit neurotropic and musculotropic activity. They also showed that the presence of tropic acid was not an essential factor; relatively simple disubstituted acetic acids were effective. The most potent member of the series was the benzilic acid ester but it was apparently too highly toxic. The tropic acid ester was ultimately selected for clinical use and was marketed under the name Syntropan.

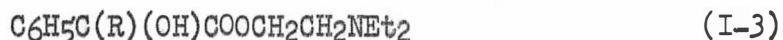
In 1938 Halpern⁸ described a series of esters of alpha alkyl phenylacetic acids in which the alkyl group ranged from ethyl to heptyl. Maximum activity was obtained in esters of α -n-propylphenylacetic acid. Its diethylaminoethyl ester showed a remarkably low toxicity, being approximately one-third as toxic as atropine. This compound was introduced into clinical use in Europe under the name Propivan.

Diethylaminoethyl diphenylacetate hydrochloride (Trasentin) was first described in a patent in 1936.^{9,10} Tripod¹¹ reported that, on

the isolated rabbit intestine, the relative antispasmodic activities of atropine, trasentin, and trasentin-H (the corresponding ester of phenylcyclohexylacetic acid) were 1:0.054:0.14 while the relative toxicities to mice were 1:1.98:2.37. The compound also possessed approximately two-thirds of the musculotropic activity of papaverine.¹ It has been used by a number of investigators as a secondary reference standard for correlating activities.

In line with the previously mentioned results of Fromherz,⁷ diethylaminoethyl benzilate was considerably more active than Trasentin. Kloss¹² reported it to be ten times as active and also more toxic. Burtner and Cusic¹³ found the activity against acetyl choline to be 20 (atropine = 100) and against barium chloride, 142 (papaverine = 100). The analogous dimethylaminoethyl ester, first described by Blinks and Kaplan¹⁴ and later studied by Lee, Scott, and Chen¹⁵ and by Astrom¹⁶ was more active. Lee, Scott and Chen reported its anticholinergic activity as one-half that of atropine. They also said it was twice as effective as papaverine against histamine induced spasm. Astrom stated that the compound was similar to and nearly equal to atropine in its spasmolytic activity and possessed considerable musculotropic activity. He reported it to be more effective than trasentin in relaxing histamine induced spasm in the isolated intestine. In addition the toxicity of the ester was surprisingly low. Kloss¹² stated that both the diethyl- and dimethylaminoethyl benzilate were mydriatics but did not give undesirable dryness of the mouth and had no effect on the blood pressure or pulse rate.

A study of alpha disubstituted phenylacetic acids where the substituents were either hydrogen, methyl, or ethyl groups gave compounds whose activity ranged from 1.5 to 15 (Trasentin = 1).¹⁷ Buchel, Levy, and Pernot¹⁸ reported that esters of type (I-3) had important



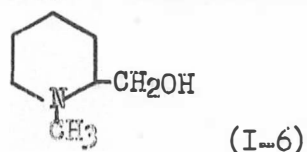
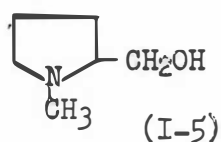
spasmolytic, parasympatholytic and local anesthetic properties. Those compounds where R was hexyl, cyclohexyl or phenyl were the most potent of the group studied. Basic esters of phenylcyclohexylacetic acid, β -phenylacrylic acid, diphenylacetic acid, and α -ethylphenylacetic acid were prepared by Cope¹⁹ who claimed that they were useful as anti-spasmodics of low toxicity.

(2) Effect of varying the aminoalcohol substituents. Numerous variations of the aminoalcohol using diphenylacetic and benzilic acids as the acid function were reported. Munoz-Mena and Mavil Bueno²⁰ said that 2-N-piperidinoethyl diphenylacetate was equal in activity to Trasentin while possessing favorable hygroscopicity. The activity of the analogous benzilic acid ester was found to resemble that of atropine.^{21,22} Blicke²³ prepared compounds of type (I-4) and stated that

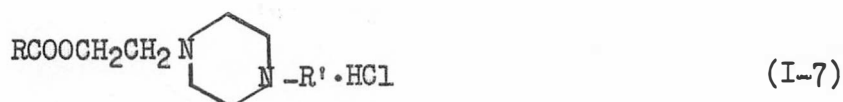


they were useful as antispasmodics. Several groups investigated esters of 3(1-alkylpiperidyl) carbinols. Feldkamp²⁴ found the activity of the 3(1-methylpiperidyl) benzilate hydrochloride to be 9 (atropine = 100). Quaternization with methyl bromide increased the activity to 33. Chen and Beckman²⁵ studied 3(1-ethylpiperidyl) diphenylacetate. They reported that it was at least as active as Trasentin and papaverine on the sphincter of the Oddi, the duodenum, and the ureter. It was relatively

free from undesirable side effects and was no more toxic than Trasentin. Chen²⁶ also studied the benzoic acid ester of the same alcohol. He found that the compound was about equal to atropine in activity while less mydriatic. Its oral toxicity was approximately equal to that of atropine but when given intravenously, it was four times as toxic. Blicke and Lee²⁷ prepared a series of esters of the aminoalcohols (I-5) and (I-6). 2-(1-Methylpyrrolidyl)-methyl diphenylacetate was



effective against spasm at a dilution of 1:870,000 while the analogous benzoate was effective at 1:54,000,000. Under the same conditions atropine was effective at a dilution of 1:50,000,000, again illustrating the generally greater activity of the benzoates as compared to the diphenylacetic acid esters. A series of substituted piperazyl-alkyl esters of type (I-7) was reported by Ide, Lorz, and Baltzly²⁸



where RCOO- was benzoic acid, diphenylacetic acid or related types and R' was a lower alkyl group. None of these compounds showed more than 5 per cent of the activity of atropine as an anticholinergic.

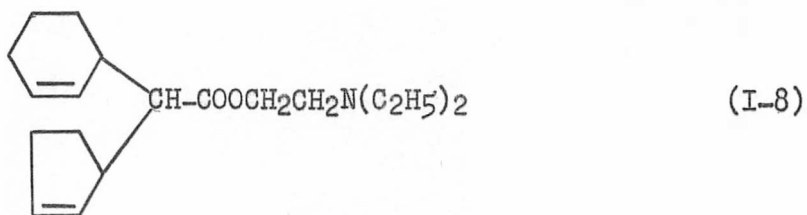
(3) Effect of varying the alpha substituent. Several groups have studied the effect of varying the substituents on the alpha carbon of diphenylacetic acid. Buchel, Levy, and Pernot¹⁸ found that acetylation of the hydroxyl group in benzoic acid esters sharply reduced the activity of the compounds. In 1954, Blicke, Faust and

Raffelson²⁹ reported the preparation of a series of compounds in which the alpha carbon was substituted with chlorine, bromine, ethoxyl, and basic groups. Only weak activity was shown by all of these substances except the α -chloro and α -bromo esters. The potency in these cases was attributed to the fact that such substituents were readily hydrolyzed to give the analogous hydroxy compounds. Thus the physiological activities found were actually those of the benzilic acid esters. Other workers¹³ have also observed that α -halodiphenylacetates and benzilates displayed identical activities. The preparation of compounds where phenoxy, 2-dimethylaminoethoxy, thiocyanate, and related groups were attached to the α carbon was reported in 1955.³⁰ These compounds showed marked spasmolytic activity.

(4) Effect of nuclear hydrogenation. Hydrogenation in the benzene nuclei of diphenylacetic and benzilic acids generally produced compounds of greater activity than was possessed by their precursors. The synthesis of diethylaminoethyl phenylcyclohexylglycolate and the analogous dicyclohexylglycolate was reported by Miesher and Hoffmann in two patents in 1941.^{31,32} Meier and Hoffmann³³ published the results of work which included a study of the effects of nuclear hydrogenation. These results indicated that hydrogenation in the acid portion of the molecule generally increased the activity with little if any change in the toxicity. The stepwise transformation of diphenylacetic acid esters to the dicyclohexylacetate was of particular interest. The maximum activity was possessed by the phenylcyclohexylacetate which was approximately ten times as potent as the parent compound against

acetyl choline. Saturation of both rings resulted in a sharp drop in the neurotropic activity. When tested on the isolated rat duodenum, the relative activities of diethylaminoethyl diphenylacetate and diethylaminoethyl dicyclohexylacetate were 100:200.³⁴ In 1953 Plummer, Barrett, Rutledge, and Yorkman³⁵ reported the results of a pharmacological study of 2-N,N-diethylaminoethyl phenylcyclohexylglycolate methyl bromide (Antrenyl). They found the compound to be readily absorbed and a stable, orally active anticholinergic. Its antispasmodic activity on visceral smooth muscle was comparable to that of atropine while Antrenyl possessed less marked mydriatic and salivary activity than the natural spasmolytic. Its toxicity was low. In addition to its anticholinergic activity, the ester strongly antagonized the action of barium chloride and histamine on the isolated ileum of the guinea pig. The compound was placed in clinical use. In 1942 Blicke and Maxwell³⁶ prepared 2-N-piperidinoethyl dicyclohexylglycolate as part of a study of synthetic mydriatics.

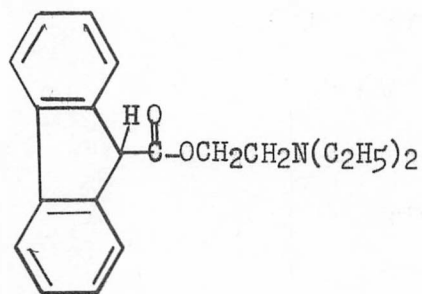
A series of articles beginning in 1947 reported the preparation of compounds in which one or both of the alpha substituents were partially saturated rings.³⁷⁻⁴¹ Among this group of esters, 2-diethylaminoethyl- Δ^2 -cyclopentenyl- Δ^2 -cyclohexenylacetate (I-8) appeared



to have very desirable pharmacological activity. Moffett, Hart, and Hoehn³⁷ gave it their highest rating. Unfortunately, no reference

standard was reported. Several compounds among a series of phenyl- Δ^2 -cyclohexenylacetic acid esters had activities of the order of one-eighth or better than that of atropine sulfate on the isolated rabbit intestine.⁴² Moffett⁴³ patented esters of phenylcyclopentylacetic acid, claiming that they were useful antispasmodics which acted upon the involuntary muscle tissues to relieve spasm induced by the autonomic nervous system. Levy, Rajzman, and Tchoubar⁴⁴ stated that the diethyl-aminoethyl esters of alpha-substituted 1-cyclopentenylacetic acids had atropine and papaverine like properties in general more marked than those of the correspondingly substituted cyclohexylacetic acid and phenylacetic acid esters.

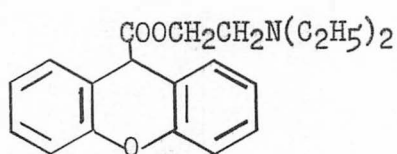
(5) Effect of bridging. Work on anesthetics involving binuclear systems had indicated that bridging two aromatic nuclei to form a condensed polycyclic structure sometimes enhanced the activity and decreased the toxicity. With the hope that such a transformation would likewise afford a beneficial effect in antispasmodic activity, several groups studied modifications of this type. Burtner and Cusic¹³ prepared a series of esters of fluorene-9-carboxylic acid with various basic alcohols. They found that diethylaminoethyl fluorene-9-carboxylate (I-9) was approximately six times as active against acetylcholine in-



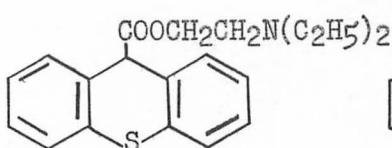
(I-9)

duced spasm as the analogous diphenylacetate. The musculotropic effect was also substantially increased and the toxicity was decreased by about 30 per cent. Unfortunately such an increase was not general; compounds of lower activity also resulted. Burtner and Brown⁴⁵ reported that in a series of esters of pyridyl and piperidylalkanols, the diphenylacetates were generally more active than the corresponding esters of fluorene-9-carboxylic acid, particularly against spasm induced by acetylcholine and barium chloride. The fluorene derivatives were less toxic, however. An analogous fusing of the phenyl rings of aminoalkyl esters of benzoic acid produced a somewhat surprising drop in activity.¹³

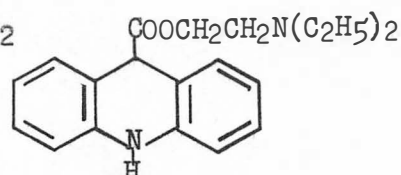
Expansion of the nuclear bridge in fluorene to include oxygen, sulfur, and nitrogen gave erratic results.⁴⁶ The activity of diethylaminoethyl xanthene-9-carboxylate (I-10) was at least twice that of the analogous fluorene ester. Replacement of the oxygen by sulfur (I-11) caused a slight rise in the musculotropic potency and a marked decrease in the neurotropic activity while the dihydroacridine derivative (I-12) was even less effective. All of the heterocyclic compounds were



(I-10)



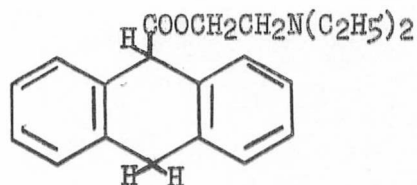
(I-11)



(I-12)

more toxic than the corresponding fluorene-carboxylates. Cusic and Robinson⁴⁷ also reported a series of basic esters of xanthene-9-carboxylic acid, of which some appeared to be more potent than atropine.

The introduction of a methylene group between the two benzene nuclei resulted in a remarkable increase in musculotropic activity.⁴⁶ Diethylaminoethyl 9,10-dihydroanthracene-9-carboxylate (I-13) was



(I-13)

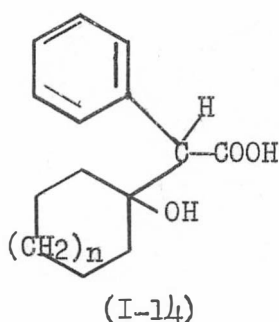
twenty times as active as papaverine against spasm induced by histamine. However, the compounds of this series were characterized by weak neurotropic activity and relatively high toxicity.

(6) Effect of quaternization. The tertiary amino compounds reported as synthetic spasmolytics have for the most part been tested in the form of their hydrochlorides. It was found that conversion of the esters into their quaternary salts by means of relatively simple alkyl halides generally enhanced the neurotropic activity at the expense of the musculotropic effect.^{24,33,48} The toxicity sometimes remained unchanged but more commonly was significantly increased. However, the weakness of generalizations such as this has been emphasized by numerous exceptions.⁴⁹

(7) Effect of nuclear substitution. The effect of nuclear substitution on activity has not been evaluated comprehensively. In a series of para-substituted phenylcyclohexylacetic acid esters, Hoffmann⁵⁰ found the effect to be variable. In general, esters of the para nitro acid were less potent; those of the para amino acid, more potent than the unsubstituted compounds. Several groups studied the effect of

alkoxyl substituents. Introduction of a para methoxyl group in benzilic acid esters greatly reduced both types of activity.^{13,51} Bockstahler and Wright⁵² prepared a series of alkoxyl substituted benzilates in which the size of the alkoxyl groups was varied systematically. None of these surpassed the activity of the unsubstituted esters while most were less potent. A group of para xenylacetic acid esters was reported by Blicke and Grier.⁵³ The results of spasmolytic tests, given for seven of these compounds, indicated that all produced relaxation of the untreated, isolated intestine although detailed information was not listed. In 1945, Faust, Feldkamp, and Moore⁵⁴ prepared a similar series of alpha alkyl para xenylglycolic acid esters. They found, somewhat surprisingly, that the activities of the glycolates were about the same as those of the corresponding acetates.

Beginning in 1951, the synthesis and testing of aminoesters of Δ (1-hydroxycycloalkyl) Δ -phenylacetic acid (I-14) were reported.^{55,57}



Several of these were stated to possess neurotropic activity comparable to that of atropine and musculotropic activity of the order of magnitude of papaverine.

(8) Aralkyl alpha substituents. In 1937 Wagner-Jauregg, Arnold, and Born⁴⁹ reported the properties of twenty-four esters of diethylaminoethanol with a variety of disubstituted acetic acids. Starting with diphenylacetic acid, the workers progressively introduced one to three methylene groups between one or both of the benzene nuclei and the alpha carbon atom. In most cases this resulted in a sharp drop in the neurotropic activity along with a rise in the musculo-tropic potency. From this and other investigations^{13,58} it appears that for maximum activity the aryl group in a disubstituted acetic acid derivative should be closely joined, if not directly attached, to the alpha carbon atom.

(9) Substituted cycloalkylcarboxylic acid esters. Rubin and Wishinsky⁵⁹ reported an interesting series of esters in which the alpha carbon atom of the acid was an integral part of a cyclohexane or cyclohexanone nucleus (I-15). Several investigators have extended this



(I-15)

study to include other cycloalkyl rings.^{37,60-62} A number of these compounds have proved to be active. Diethylaminoethyl-1-phenylcyclopentane-1-carboxylate (Panparmit) possessed one-thirteenth of the activity of atropine and was about three times as potent as papaverine against barium chloride.⁶¹ Its toxicity approached that of atropine. Levy and Tchoubar⁶³ reported that, on the isolated rat duodenum, diethylaminoethyl-1-phenylcyclohexane-1-carboxylate and the analogous 1-

cyclohexylcyclohexane compound possessed twice the spasmolytic activity of atropine.

(10) Sulfonium and phosphonium compounds. In a most interesting study, Protiva and Exner replaced the quaternary nitrogen common to almost all antispasmodics with sulfur and with phosphorus.⁶³⁻⁶⁵ These compounds (I-16) and (I-17) were claimed to be much more active than



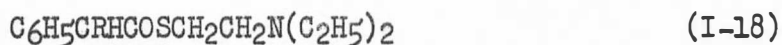
analogous nitrogen compounds. (R_1 and R_2 were alkyl or aryl groups; X was hydrogen or hydroxyl.) Indeed, the authors stated that 2-methylmercaptoethyl phenylcyclohexylacetate methyl iodide exceeded all of the known and used nitrogen compounds in its anti-acetylcholine effects. Protiva and Adlerova⁶⁶ prepared the analogous ester of phenylcyclohexylglycolic acid. They reported that in vivo in rabbits this compound was equal in activity to atropine but was considerably less toxic.

b. Amides. In the modification of the atropine molecule, several groups investigated the effect of replacing the ester function by other acidic derivative linkages. Meier and Hoffmann compared the activity of diethylaminoethyl esters with that of the corresponding amides.³³ In three out of five examples which they gave, the esters possessed ten to one hundred times the neurotropic activity of the amides. The antispasmodic activity and the toxicity of the two groups were essentially identical. Others who carried out work in this field included Miescher, Meisel, and Hoffmann who reported that dialkylaminoalkyl amides of benzoic, tropic, and mandelic acids possessed thera-

peutic properties similar to atropine.⁶⁷ Fromherz and Spiegelberg stated that beta picolinylamides of diphenylacetic, benzilic, and tropic acids exhibited antispasmodic activity.⁶⁸ Other amides of tropic acid were reported to show excellent spasmolytic properties.⁶⁹⁻⁷¹ Some of these showed a relatively wide margin between the therapeutic and toxic dosages.⁷⁰

In 1955 Krapcho, Turk, and Pribyl showed that alkylating the amide nitrogen appreciably increased the activity of dialkylaminoalkyl benzilamides.⁷¹ Among a wide variety of substituents, they found the methyl group to be most effective. Some of these had atropine indices as high as 0.5-0.7.

c. Thiol esters. In many pharmaceuticals, the replacement of an oxygen atom by a sulfur atom has produced a more favorable activity-toxicity ratio. For instance, Thiocaine, 2-N-N-diethylaminoethyl p-aminothiobenzoate, was four to six times as active as Procaine, the analogous oxygen ester, while the toxicity was not proportionately increased.⁷² Extensions of this concept into the antispasmodic field produced erratic results. In a series of compounds of type (I-18)



Dupre, Levy, and Tchoubar⁷³ found that, except where R was the phenyl group, no increase in activity was observed. Diethylaminoethyl diphenylthioacetate possessed desirable antispasmodic properties and was twice as active as the corresponding oxygen compound.^{73,74} For the same replacement, a twenty-fold increase in activity has also been claimed.⁷⁵ Hunter⁷⁶ and Woodruff⁷⁷ prepared aminoalkyl thioesters of diphenylacetic and phenylcycloalkylacetic acids. Some of these were

reported to possess both musculotropic and neurotropic antispasmodic activity.⁷⁶ Preliminary pharmacological screening of a series of thioesters of disubstituted acetic acids indicated that they were less active than the analogous oxygen esters.⁷⁸ In 1949 a series of dialkylaminoalkyl thiobenzilates were described in a patent.⁷⁹ The results of a pharmacological study of these compounds were reported in 1955.⁸⁰ The compounds were not outstanding anticholinergic agents but higher activities against barium, potassium, and nicotine than had been previously known were claimed. However, none of the compounds was more active than papaverine on the uterus, bronchial muscles or coronary vessels. Because of this apparent inconsistency, the author suggested that the generally accepted correlation between anti-barium activity and musculotropic potency was not valid. Thioesters of types (I-19), (I-20), and (I-21) were also prepared.⁸¹ In (I-20) X is either hydro-

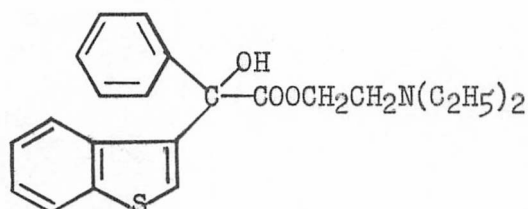


gen or a chloro or bromo substituent. No report of their spasmolytic activity was given but two of the group showed excellent anesthetic powers with low irritation and toxicity. Other thioesters were described by Oegerholm and Ekelund⁸² and by Weston.⁸³

d. Esters with heterocyclic alpha substituents. The replacement of one or both of the benzene rings in diphenylacetic acid with heterocyclic groups proved rewarding. The group of esters of phenyl-2-thienylglycolic acid prepared by Blicke and Tsao⁸⁴ were quite in-

teresting. Diethylaminoethyl phenyl-2-thienylglycolate was three times as potent as the analogous diphenyl ester as a neurotropic spasmolytic. A slight decrease in the antidiarrhoeal activity was observed. The gamma diethylaminopropyl ester of cyclohexyl-2-thienylglycolic acid was found to be approximately equal to atropine and five times as potent as papaverine. Replacement of the alpha hydroxyl group by a hydrogen atom reduced the activity in the phenyl-2-thienyl substituted esters. Campaigne and Burgeois⁸⁵ also prepared diethylaminoethyl phenyl-2-thienylglycolate. They reported that it possessed 63 per cent of the activity of atropine. The N-piperidino analogue was said to be a spasmolytic with marked anti-acetylcholine activity and low toxicity.⁸⁶ A number of aminoesters of alpha cycloalkenyl- α -2-thienylacetic acids were prepared.⁸⁷⁻⁹¹ Several of these compounds were claimed to possess excellent spasmolytic properties.

Ludueno and Lands⁹² conducted a study of the pharmacology of the hydrochloride and methyl bromide of 2-N,N-diethylaminoethyl- α -cyclopentyl- α -2-thienylglycolate. They found that on the isolated rabbit intestine stimulated with acetylcholine both compounds were twice as active as atropine sulfate. A basic ester of α -phenyl- α -3-thianaphthenylglycolic acid (I-22) was reported to be valuable as an anti-



(I-22)

spasmodic and antihistaminic.⁹³

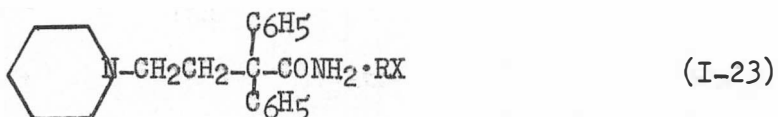
Khromov-Borisov and Zakharova⁹⁴ claimed to have prepared the diethylaminoethyl ester of α -phenyl- α -2-furylglycolic acid. No details of the preparation of the acid and no pharmacological data were given.

2. Derivatives of Carboxylic Acids in Which the Basic Group is Contained in the Acidic Portion of the Molecule

The compounds discussed thus far have been rather closely related to atropine in structure. A more dissimilar group of synthetic spasmolytics is that in which either a or the basic group is contained in the acid portion of the molecule.

Two of these types still bear a formal resemblance to the compounds previously described. In 1953 Duschinsky⁹⁵ reported a series of esters, thioesters, and amides of α -amino- α , α -diphenylacetic acid. These compounds were useful analgesics, hypnotics, and antispasmodics. Brender⁹⁶ stated that diethylaminoethyl α -phenyl- α -N-piperidylacetate possessed one thirty-sixth of the activity of atropine and twice that of papaverine. It was said to act selectively on the smooth muscles of the stomach, intestine, and urinary tract.

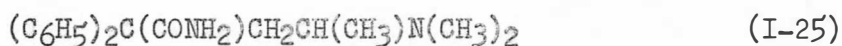
Compounds less closely related to atropine have been studied. A British patent in 1954 described a series of compounds similar to (I-23).⁹⁷ An atropine index of one-thirtieth was shown by (I-23) itself.



A group of similar compounds of the structure (I-24) was reported.⁹⁸

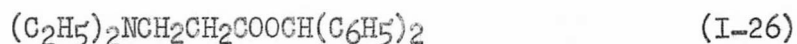


Some of these had atropine indices of five-tenths or more. An interesting study concerning the relative activity of optical isomers was conducted on a compound of this type.⁹⁹ The investigators resolved the d and l isomers of (I-25). The racemate had been found to possess



high anticholinergic activity. After resolution it was shown that the levo isomer was four times as potent as the dextro against acetylcholine in an isolated muscle strip.

In 1950 Vejdelek and Protiva¹⁰⁰ reported the preparation of a compound in which the positions of the dialkylaminoalkyl and diphenylmethyl groups had been reversed from the usual ones (I-26). This com-



ound, a spasmolytic of the papaverine type, possessed 1 per cent of the activity of atropine and was 10 per cent as effective as benadryl as an antihistaminic. Numerous other groups reported synthetic antispasmodics which contained the basic function in the acidic portion of the molecule, but none of these possessed outstanding activity.¹⁰¹⁻¹¹¹

3. Antispasmodics Other Than Carboxylic Acid Derivatives

a. Aminoketones. Other groups of compounds which have been investigated for spasmolytic activity include aminoketones and aminoalcohols and alkenes derived from them. The first of a large series of papers reporting work in this area was published in 1949.¹¹² In this paper the authors described the preparation and testing of a group

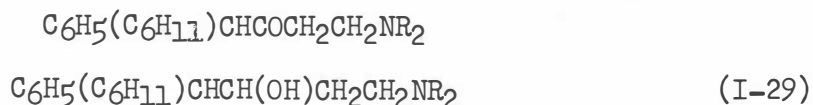
of aminoketones of type (I-27) where R was phenyl, naphthyl or a



heterocyclic group. R' was hydrogen or phenyl and R²R³ were alkyl or together with the nitrogen formed a ring. Some of these were said to be as active as Trasentin. The work was later extended to include more complex amino and aromatic functions.¹¹³ All of these were of lower activity than their more simple prototypes. 1,1-Diphenyl-4-N-piperidino-butanone-2 was prepared by Katz and Karger in 1952.¹¹⁴ In the same year Wilson and Kyi¹¹⁵ prepared materials of the same type but varied the amino function (I-28). These compounds were not tested as antispasmodics



but were reported to be potent local anesthetics which were unstable in neutral or alkaline solution. 1,1-Diphenyl-1-alkyl-4-dialkylamino-2-butanones were synthesized by Zaugg, Freifelder, and Horrom.¹¹⁶ They were also tested not for spasmolytic potency but as analgesics. Sprague and Schultz¹¹⁷ reported ketones and alcohols of type (I-29).



No statement of their physiological activity was given.

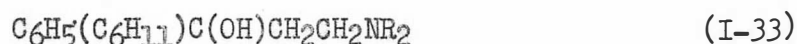
b. Aminoalcohols and aminoalkenes. In a patent in 1952, Barrett and Wilkinson¹¹⁸ reported that 1,1-diphenyl-~~4~~-amino-1-alkanols and 1-alkenes were of value as spasmolytic agents. Similar but somewhat more complex substances were also claimed to possess antispasmodic properties.¹¹⁹ Adamson¹²⁰ reported in more detail on the preparation and properties of a group of compounds of the types given below (I-30 to

I-32). Preliminary pharmacological data indicated that the compounds



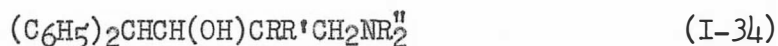
were surface anesthetics, and in some cases comparable to atropine.

A group of 1,1-diacyl-3-dialkylamino-1-propanols where the dialkylamino groups were substituted piperazines were claimed to exhibit anti-spasmodic properties.¹²¹ Phenyl-cyclohexyl carbinols of type (I-33)



also showed spasmolytic activity. Harferist and Magnien¹²² stated that these compounds had substantial activity though somewhat lower than atropine in maximum activity. When the propane skeleton was methyl-branched, their potency was decreased severely. 1-Phenyl-1-cyclohexyl-3-N-piperidino-1-propanol methyl bromide was reported to be more active than atropine sulfate against acetylcholine induced spasm.⁹²

The effect of dehydration on the activity of aminoalcohols proved somewhat erratic. Kjaer and Petersen¹²³ prepared a number of 1,1-diaryl-3-dialkylamino-1-propanols plus the analogous 1-propenes. The alkenes showed marked spasmolytic activity; the alcohols did not. 1,1-Diphenyl-3-methyl-3-dimethylamino-1-propene strongly antagonized the action of acetylcholine and barium chloride on the isolated intestine.¹²⁴ Katz, Karger, and Cohen¹²⁵ reported butanols of type (I-34). Of these,



1,1-diphenyl-3,3-dimethyl-4-N-piperidino-2-butanol was claimed to be twice as active as Trasentin against acetylcholine and barium chloride.

In this case dehydration to the substituted butene decreased the activity three fold. The authors also stated that 1,1-diphenyl-4-N-piperidino-1-butene was 5-10 times as active as Trasentin in vitro, but showed no activity in vivo. It was felt that this somewhat surprising difference was due to decomposition of the compound into 1,1-diphenylbutadiene and piperidine when injected into the live animal. Other workers have noted similar cleavages in beta aminoketones.^{126,127}

The importance of chain length in producing activity was illustrated by the work of Morrison, Long, and Konigstein¹²⁸ who found that a series 1,1-diphenyl-1-hydroxy-2-dialkylaminoethanes possessed no outstanding spasmolytic properties. Several workers prepared α -2-thienylalkanols and alkenes.¹²⁹⁻¹³³ These were reported to possess favorable spasmolytic activity, but no detailed statements of their pharmacology were given.

An extensive series of aminoalcohols was prepared by the reduction of the corresponding aminoketones.¹³⁴⁻¹⁴² These compounds possessed the general structure (I-35), where R,R' were aryl, cyclo-



alkyl, or hydrogen, R'' was alkyl or hydrogen, and R''' was a tertiary amino function. The results of this study are somewhat difficult to evaluate since in most cases a reference standard was not given. A number of the alcohols were said to be moderately active however. Some generalizations can be drawn from this work. The investigators found that: (1) the greatest activity resulted from a 1,3 relationship of the hydroxyl and dialkylamino groups, (2) the alkanols were

generally more active than their ketonic precursors, (3) the piperidyl group was the most active amine function of those tested, and (4) increasing the complexity of the compounds lessened the activity.

c. Miscellaneous types. Numerous other types of structures were tested as antispasmodics. Aminoethers of type (I-34) were claimed

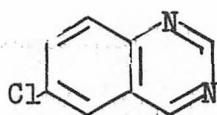


to show antispasmodic activity comparable to atropine.¹⁴³⁻¹⁴⁵

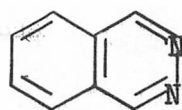
Rieveschl¹⁴⁶ extended the aminoethyl chain to aminopropyl and reported that the compounds were powerful antihistamines. They were also said to be useful in preventing smooth muscle spasm induced by histamine, acetylcholine, or barium chloride. Ethers of structure (I-35) were



claimed to possess antispasmodic activity, especially for the smooth muscles of the intestine.¹⁴⁷ Some dialkylaminoalkyl ethers of the heterocycles (I-36) and (I-37) were found to be central nervous system



(I-36)



(I-37)

depressors and also showed appreciable musculotropic activity.¹⁴⁸

Aminothioethers were reported to be antispasmodics.¹⁴⁹ Fahlen, Huber, Laskowski, and Clinton¹⁵⁰ combined ester and thioether functions in compounds of type (I-38) where RCOO was diphenylacetic, benzilic, or



related type acids and m and n were two or three. None of these exhibited high activity against acetylcholine although all were equal

to or slightly more active than papaverine against barium chloride.

Substituted amines were shown to possess spasmolytic activity. Benoit, Jacob, and Eliopoulo¹⁵¹ found that some members of a series of ω -diphenyl-dialkylaminoalkanes were as active or slightly more active than Trasentin. Other workers have reported that compounds of this and related types were stable, useful antispasmodics.¹⁵²⁻¹⁵⁵ Cyclic amines were tested. 4-Substituted-N-alkylpiperidines possessed spasmolytic activity as well as antihistaminic and analgesic potency.¹⁵⁶ N,N'-Disubstituted piperazines were reported to be active especially against neurotropic spasm.¹⁵⁷

Antispasmodics which contained no basic function have been prepared. Sperber, Papa, and Schwenk¹⁵⁸ claimed that acids of type (I-39)



showed spasmolytic properties when they totaled 12-17 carbon atoms and the R groups were of approximately equal length. Koninklijke^{159,160} reported non-basic antispasmodic esters. He said that esters of mandelic acid where the alcohol was aliphatic or cycloaliphatic and contained from five to nine carbon atoms possessed activity similar to that of papaverine.

C. Conclusion

As was stated previously, the scope of the synthetic antispasmodic field is limited only by the ingenuity, endeavor, and patience of the chemist. It may readily be seen that such ingenuity, endeavor, and patience have led to the preparation of a vast number of compounds

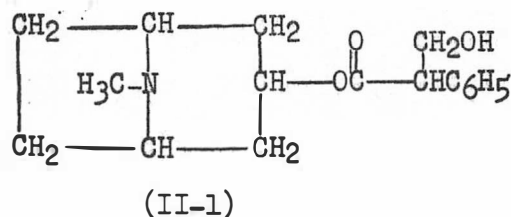
of many and varied structures. As yet, however, no compound has been reported which completely satisfies the requirements of the ideal spasmolytic. Until such a compound is found, work in the field must be continued. There are yet many areas not touched upon, which may provide the desired antispasmodic. The work to be reported here was undertaken to investigate some of these areas.

CHAPTER II

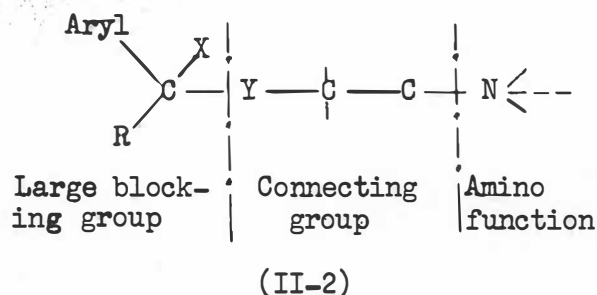
DISCUSSION OF RESULTS

A. Introduction

As previously related, the generally followed approach to the synthesis of new pharmaceuticals has consisted primarily of preparing modifications of a compound of known activity. In view of this fact, it is not surprising that the majority of synthetic anticholinergics possess certain structural features in common with one another and with atropine, the potent naturally-occurring anticholinergic (II-1). These



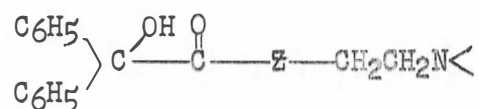
compounds are made up of a large blocking group linked by a short connective group to a strongly basic amino function as shown in (II-2).



Within the limits of these broad similarities, however, the number of different compounds appears almost limitless. In the search for better anticholinergics, chemists have varied each of the three portions, systematically or at random, producing a multitude of modifications.

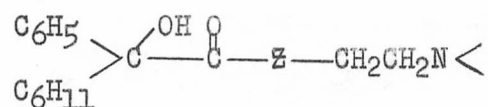
In spite of the tremendous amount of work done in the field, no correlation between structure and physiological activity has as yet been established. It was hoped that the present work might assist in the determination of such a correlation by an evaluation of the effect of several systematic structural variations on physiological activity.

The compounds selected to be prepared were all derivatives of benzilic acid or closely related analogues. A number of substances derived from benzilic acid have been reported to possess high anti-cholinergic activity. These compounds all fit the generic formula (II-3). In the present work it was proposed to vary the nature of Z

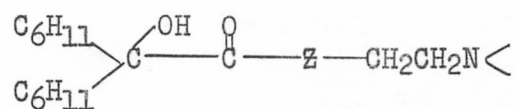


(II-3)

and for each such variation to prepare the partially hydrogenated (II-4) and completely hydrogenated (II-5) analogues of the benzilic acid deriv-



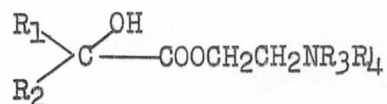
(II-4)



(II-5)

atives. Such a study, combined with the results of other workers, could provide sufficient information to establish the presence or absence of a correlation between these structural factors and physiological activity.

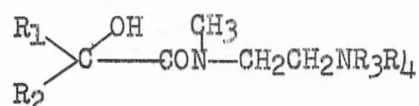
Five types of compounds were to be prepared for this study. These were esters (II-6), amides (II-7), N-methyl amides (II-8), thiol esters (II-9) and ketones (II-10). To minimize error due to differences



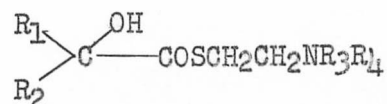
(II-6)



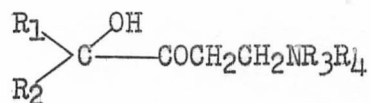
(II-7)



(II-8)



(II-9)

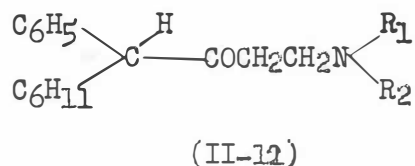
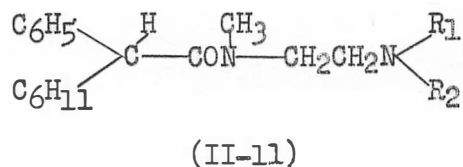


(II-10)

in activity associated with variation of the alkyl substituents on the amine function, three simple dialkyl amino groups were to be used with each type of compound.

In the course of the research, it was found necessary to modify the original aims somewhat. For some of the types it proved impossible to prepare the reduced analogues of the benzilic acid derivatives by any of the methods used. In certain of these cases, where the compounds

had not been previously reported, the non-hydroxy compounds were prepared (II-11 and II-12).



A total of twenty-two compounds was prepared of which seven were esters, five were amides, four were N-methylamides, three were thiol esters and three were ketones. All of these were obtained in the form of their hydrochlorides; the methyl bromides of two of them were also prepared.

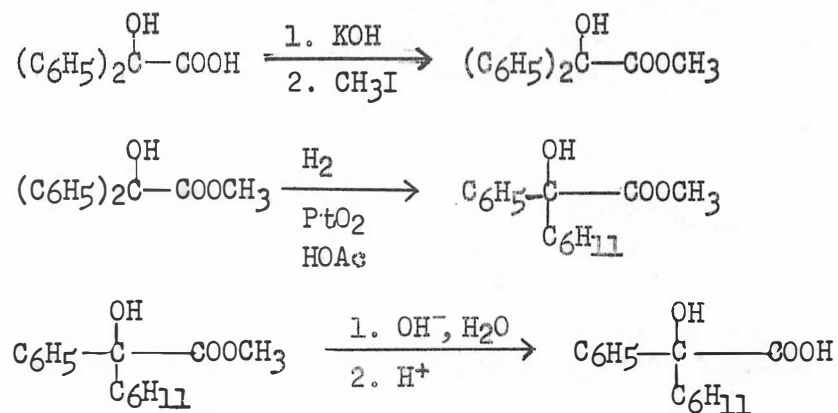
The synthesis of these compounds constituted the major interest of this research. The preliminary results of physiological testing, although incomplete, will be discussed following a consideration of the preparative methods employed.

B. Synthetic Methods

1. Acids

a. Phenylcyclohexylglycolic acid. For the preparation of all of the compounds by the originally proposed methods, a supply of phenylcyclohexylglycolic acid and its methyl ester was required. Three different methods of preparation were attempted. Of these, two were successful.

(1) Method A. Shacklett¹⁶¹ reported the preparation of phenylcyclohexylglycolic acid from benzilic acid by the partial reduction of methyl benzilate. This series of reactions is given in (II-12).

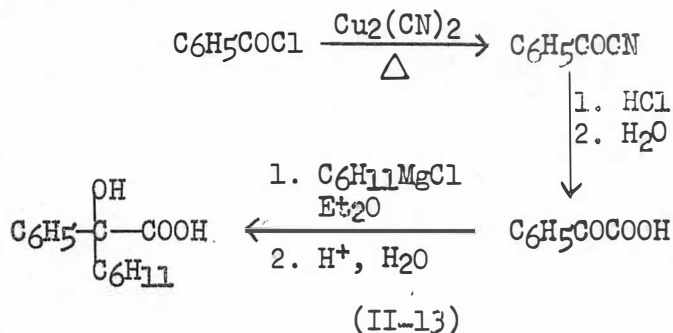


(II-12)

The author reported that when hydrogenation of the ester was stopped at a point corresponding to 50 per cent of complete reduction, a mixture was obtained which consisted of approximately 17.5 per cent methyl benzilate, 17.5 per cent methyl dicyclohexylglycolate and 65 per cent methyl phenylcyclohexylglycolate. These products could be separated by distillation. In the present work, it was found that an easier separation was obtained when the reduction was carried out only to 45 per cent of complete hydrogenation. Methyl benzilate was prepared from benzilic acid in 97 per cent yield by the method of Merritt, Levy and Cutter.¹⁶² This compound was reduced in approximately 100 g. batches by shaking an acetic acid solution of the ester with Adams' platinum catalyst under initial hydrogen pressures of 64 psi. Shaking was continued until a pressure drop corresponding to 45 per cent of complete hydrogenation was noted. The combined acetic acid solutions from

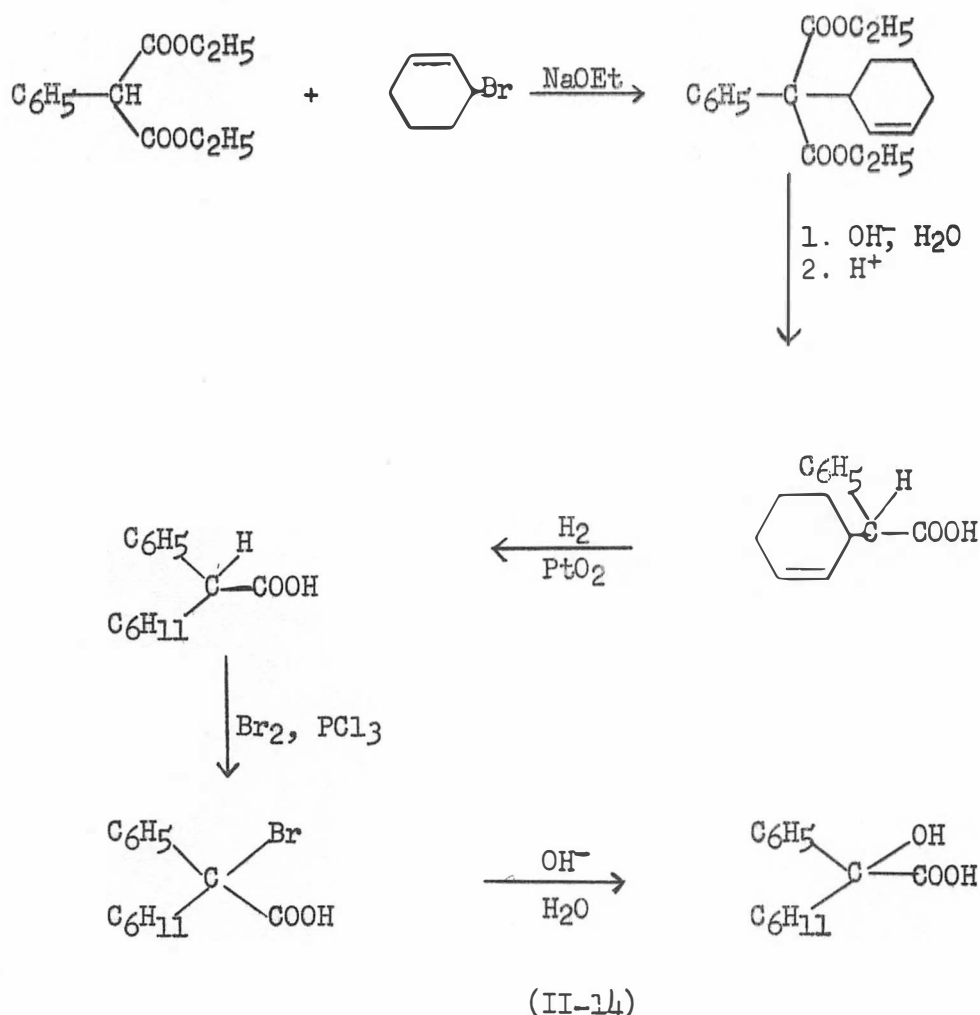
several runs were placed in a pot attached to an eight-foot Vigreux column. The acetic acid was removed by distillation under reduced pressure from a water pump and the residue was fractionated under reduced pressure from a vacuum pump. Portions of the fractions were hydrolyzed to the acids by heating with base in aqueous-ethanol solution. The purity of the fractions was determined by the melting points of the acids and their mixed melting points with authentic phenylcyclohexylglycolic acid. It was found that the middle seven fractions were fairly pure methyl phenylcyclohexylglycolate. Material of this purity was used for the major portion of the preparative work. Phenylcyclohexylglycolic acid was obtained from the ester by hydrolysis as described above.

(2) Method B. An alternative method of preparation which gave the acid directly was also used. This procedure was essentially a modification of the procedure of Smith, Alderman, Shacklett and Welch¹⁶³ for the synthesis of phenylcyclohexylglycolic acid. Benzoyl cyanide was prepared from benzoyl chloride by the procedure of Oakwood and Weisgerber.¹⁶⁴ By hydrolysis in concentrated hydrochloric acid, benzoylformic acid was obtained. Addition of cyclohexylmagnesium chloride across the carbonyl function then gave the desired acid (II-13).



The yields from this series of reactions were not generally very high. Some difficulty was experienced both in the hydrolysis of benzoyl cyanide and in the addition of the Grignard reagent. Because of these factors this method of synthesis was used to prepare only a small amount of the acid employed in the research.

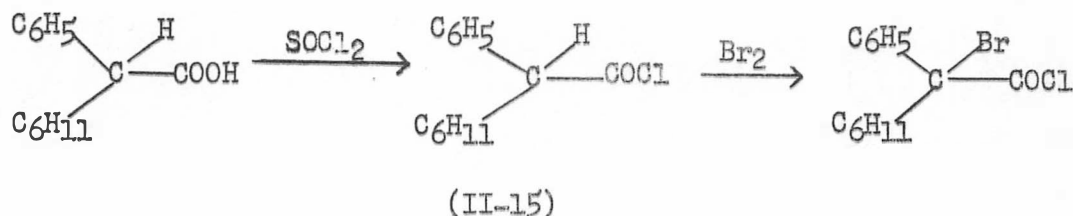
(3) Method C. It was planned to prepare the acid by the series of reactions outlined below (II-14).



A similar procedure through step three had been used previously by Kolloff, Hunter, Woodruff and Moffett⁴² to prepare phenylcyclohexyl-acetic acid.

In the present work the substituted acetic acid was obtained in good yield with no difficulty. Bromination of this acid was attempted under the conditions of the Hell-Volhard-Zelinsky reaction using phosphorus trichloride as catalyst. The only product was a hard polymeric material which was insoluble in base even after extended heating.

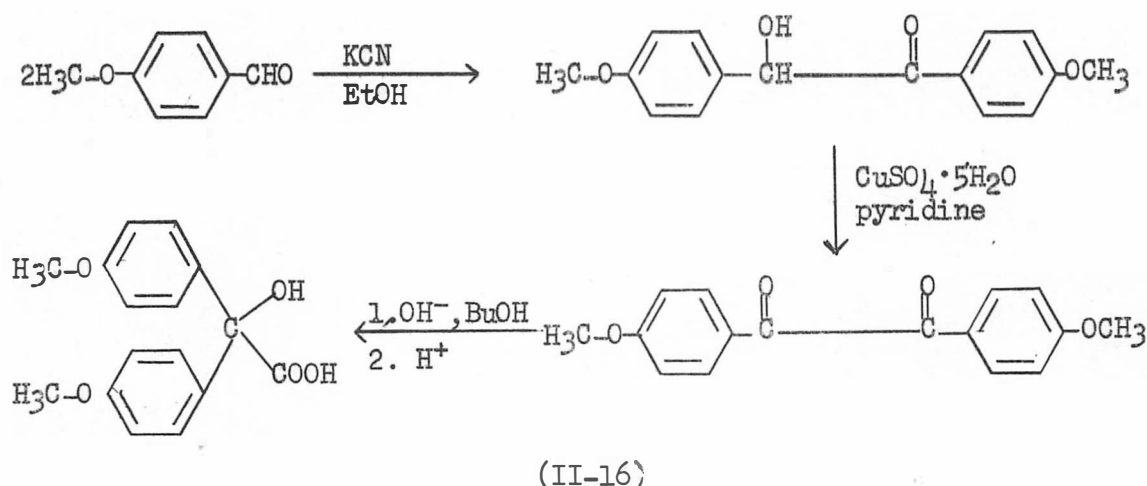
Since, in general, the acid chloride brominates more easily than the acid itself, a modification of the above procedure was tried (II-15).



Schwenk and Papa¹⁶⁵ have reported the successful bromination in this way of a number of acid chlorides, including those of phenylacetic acid and cyclohexylacetic acid. The acid chloride was prepared by heating the acid with an excess of thionyl chloride for two hours. An equimolar quantity of bromine was then added to the gently refluxing solution over one and one-half hours. A copious evolution of hydrogen bromide was observed. The product of this reaction, after removal of the excess thionyl chloride, was a dark liquid. It was refluxed for several hours with a solution of dioxane and excess base. After removing the dioxane the bulk of the material was found to be base-insoluble. Only a trace of organic acid could be obtained. A similar phenomenon has been noted by Shacklett¹⁶¹ in an attempt to prepare dicyclohexylglycolic acid by an analogous procedure. Since the successful preparation of benzilic acid from diphenylacetic acid by bromination and hydrolysis has been

reported by Symons and Zincke,¹⁶⁶ it would appear that the difficulties in the reaction are associated with the cyclohexyl group. However, the nature of the product has not been determined and no explanation of the reaction has been proposed. This method of preparation of the acid was abandoned.

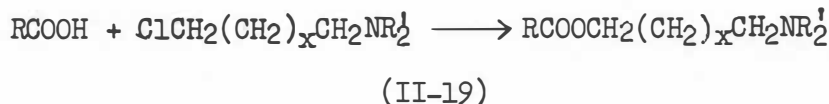
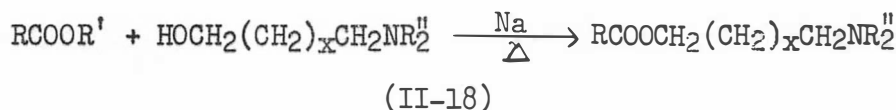
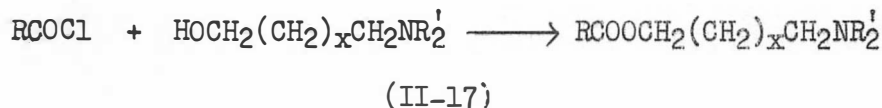
b. 4,4'-Dimethoxybenzilic Acid. This acid was prepared by a benzilic acid rearrangement as outlined below (II-16). This procedure



gave the acid in good yield with no difficulty.

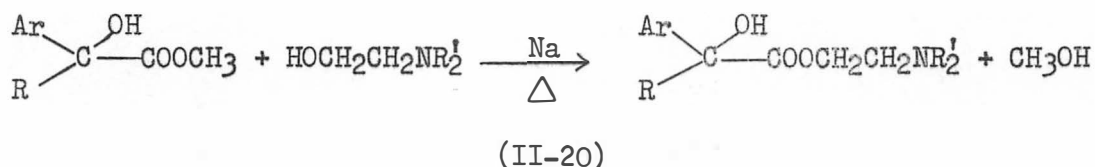
2. Aminoesters

Three general methods have been reported for the synthesis of aminoesters of the type to be discussed. These are: (1) the reaction of an acid chloride with an aminoalcohol (II-17), (2) the reaction of a lower alkyl ester of the acid with an aminoalcohol (Method A) (II-18), and (3) the reaction of an acid with an aminoalkyl chloride (Method B) (II-19).



Two of these methods, the second and third, were utilized to prepare the esters of interest in this research.

a. Method A. It was originally proposed to prepare all of the esters by an ester interchange reaction between the methyl ester of the appropriate acid and the desired 2-N,N-dialkylaminoethanol (II-20).



The procedure described by Hill and Holmes¹⁶⁷ was used.

When the reactants were refluxed at atmospheric pressure for ten hours, none of the desired product was obtained. The alternate procedure of Hill and Holmes¹⁶⁷ was then employed. This consisted of heating the reaction mixture, at controlled temperatures, under reduced pressure. Methanol was removed continuously as it was formed in the reaction. By this method the aminoesters were obtained, although in poor yield. Besides the low yields, the procedure has the disadvantage of being manip-
ulatively difficult and tedious. The compounds prepared by this method are listed in Table I.

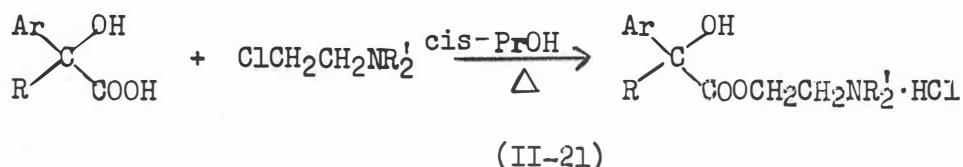
TABLE I

2-N,N-DIALKYLAMINOETHYL ESTERS OF DISUBSTITUTED GLYCOLIC ACIDS

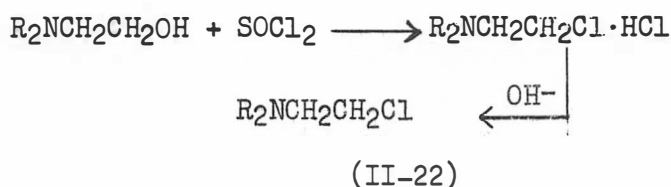
$ \begin{array}{c} \text{R} \quad \text{OH} \\ \diagdown \quad / \\ \text{C} - \text{COOCH}_2\text{CH}_2\text{N} \begin{array}{l} \text{R}'' \\ \text{R}''' \end{array} \cdot \text{X} \\ / \\ \text{R}' \end{array} $								
	R	R'	R''	R'''	X	Method of Preparation	Per Cent Yield	Melting Point °C
1.	C ₆ H ₅	C ₆ H ₁₁	CH ₃	CH ₃	HCl	A	47	219-220
2.	C ₆ H ₅	C ₆ H ₁₁	C ₅ H ₁₀ ^a		HCl	A	47	223-224
3.	C ₆ H ₅	C ₆ H ₁₁	C ₅ H ₁₀ ^a		CH ₃ Br	B	24	176-177
4.	C ₆ H ₁₁	C ₆ H ₁₁	CH ₃	CH ₃	HCl	B ^b	72	258-259
5.	C ₆ H ₁₁	C ₆ H ₁₁	C ₅ H ₁₀ ^a		HCl	A ^b	35	212-213
6.	4-CH ₃ OC ₆ H ₄	4-CH ₃ OC ₆ H ₄	C ₅ H ₁₀ ^a		HCl	B	92	181-182
7.	4-CH ₃ OC ₆ H ₄	4-CH ₃ OC ₆ H ₄	C ₅ H ₁₀ ^a		CH ₃ Br	B	53	147-148

^aPiperidino^bFollowed by hydrogenation

b. Method B. The procedure of Horenstein and Pahlicke¹⁶⁸ was followed in the preparation of some of the esters. The reaction of the acid and the substituted ethyl chloride was conducted by refluxing equimolar amounts of the two in isopropyl alcohol for twelve hours (II-21). The hydrochloride of the aminoester is obtained directly in the



reaction. The N,N-dialkylaminoethyl chlorides were obtained from the analogous ethanol. Treatment with thionyl chloride by the procedure of Slotta and Behnisch¹⁶⁹ gave the hydrochlorides of the desired compounds in quantitative yield. The free N,N-dialkylaminoethyl chloride was obtained by treatment of this amine salt with excess base by the method of Gilman and Shirley¹⁷⁰ and subsequent distillation (II-22).



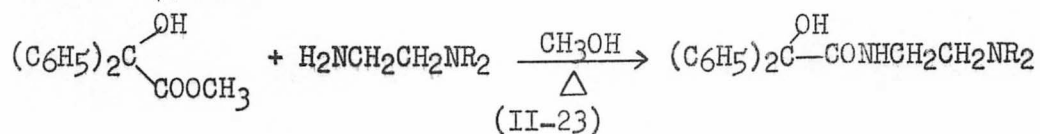
In general, Method B was found to be much superior to Method A in yield, time required, and ease of manipulation. The esters prepared by this procedure are listed in Table I.

c. Preparation of dicyclohexylglycolates. These esters were prepared from the analogous benzoic acid esters by the complete hydrogenation of the ester hydrochlorides in glacial acetic acid using Adams' platinum catalyst at room temperature. The reaction was essentially quantitative and afforded the desired esters with no difficulty. These

compounds are listed in Table I.

3. Amides

a. Method A. Phillips¹⁷¹ has reported the preparation of eight amine salts of benzilamides which he obtained in yields of better than 90 per cent from the reaction of methyl benzilate and the appropriately substituted ethylene diamine (II-23). The reaction conditions



consisted of a twenty-four hour reflux period in methanol solution followed by evaporation of the solvent and work-up of the residue through its amine salt.

In the present work, the use of this procedure gave only low yields of the benzilamides and essentially none of the analogous phenyl-cyclohexylglycolamides. The method was therefore discontinued in favor of a slightly different procedure.

b. Method B. Miescher, Meisel and Hoffmann⁶⁷ also reported a group of benzilamides prepared by the reaction of methyl benzilate with the appropriate amine. However, these workers used an excess of the amine itself as a solvent rather than methanol as Philips¹⁷¹ had done. By this procedure it was possible to obtain the desired glycolamides although the yields were not high. These compounds are listed in Table II.

c. Preparation of dicyclohexylglycolamides. The dicyclohexyl substituted compounds were again prepared by the complete hydrogenation of the corresponding benzilamide hydrochlorides. The procedure de-

TABLE II

2-N,N-DIALKYLAMINOETHYL AMIDE HYDROCHLORIDES
OF DISUBSTITUTED GLYCOLIC ACIDS

$\begin{array}{c} \text{R} \diagup \text{C} \begin{array}{l} \text{OH} \\ \text{CONHCH}_2\text{CH}_2\text{N} \begin{array}{l} \text{R}'' \\ \text{R}''' \end{array} \end{array} \diagdown \text{R}' \end{array} \cdot \text{HCl}$						
	R	R'	R''	R'''	Per Cent Yield	Melting Point °C
8.	C ₆ H ₅	C ₆ H ₁₁	CH ₃	CH ₃	12	215-216
9.	C ₆ H ₅	C ₆ H ₁₁	C ₅ H ₁₀ ^a		18	222-223
10.	C ₆ H ₁₁	C ₆ H ₁₁	CH ₃	CH ₃	29	233-234
11.	C ₆ H ₁₁	C ₆ H ₁₁	C ₂ H ₅	C ₂ H ₅	50	231-232
12.	C ₆ H ₁₁	C ₆ H ₁₁	C ₅ H ₁₀ ^a		35	260-261

^aPiperidino

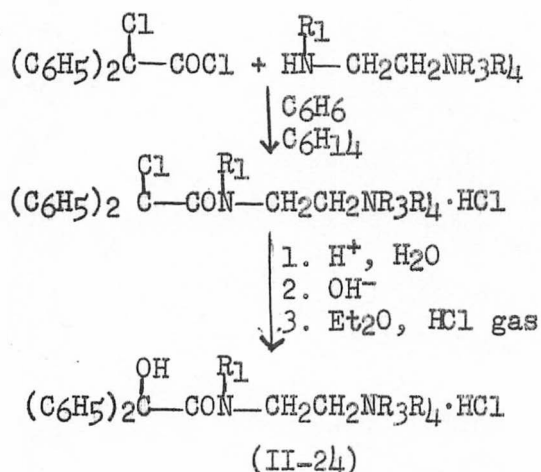
scribed for the preparation of the dicyclohexylglycolates was followed. These amides are also listed in Table II.

4. N-Methylamides

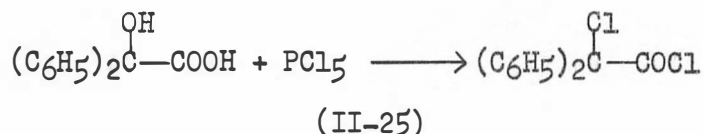
In general, it has been found that amides are much weaker antispasmodics than the corresponding esters. In 1956, Krapcho, Turk and Pribyl⁷¹ reported the preparation of a number of N,N-dialkylaminoalkylbenzilamides which possessed alkyl substituents on the amide nitrogen. These investigators stated that such substitution increased markedly the antispasmodic activity over that of the unsubstituted amides. Among a wide variety of substituents, the methyl group was found to be the most effective substituent in increasing the physiological activity.

In view of this report, it was decided to prepare several additional N-methylamides to see if a similar increase in activity was obtained.

a. Method A. Krapcho, Turk and Pribyl⁷¹ prepared their amides by the reaction of the acid chloride with the appropriate amine followed by hydrolysis of the α -chloro group (II-24). The compounds were obtained in 80-90 per cent yield.

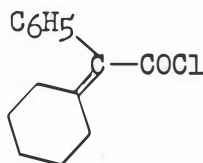


(1) Acid chlorides. The intermediate α, α -diphenyl- α -chloroacetyl chloride was prepared from benzilic acid by the method of King and Holmes¹⁷² (II-25). The acid chloride was obtained in 45-

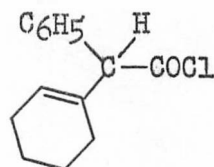


50 per cent yield.

Attempts to prepare α -phenyl- α -cyclohexyl- α -chloroacetyl chloride by treatment of phenylcyclohexylglycolic acid with phosphorus pentachloride or thionyl chloride were unsuccessful. When amides prepared from the product obtained did not give the correct elemental analyses, a closer study of the purity of the supposed α -phenyl- α -cyclohexyl- α -chloroacetyl chloride was made. A sample prepared by treatment of the acid with thionyl chloride possessed unsaturation as evidenced by positive bromine and Baeyer tests. It is possible that it is a mixture of α -phenyl- α -cyclohexyl- α -chloroacetyl chloride, α -phenyl- α -cyclohexylideneacetyl chloride (II-26) and α -phenyl- α - Δ^1 -cyclohexenylacetyl chloride (II-27). A *p*-toluidide prepared from



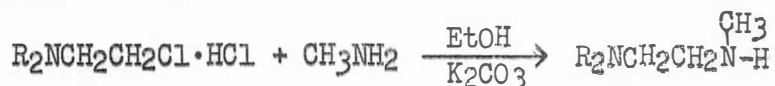
(II-26)



(II-27)

the reaction product did not give a sharp melting point even after several recrystallizations. The nature of the product has not been established. It does not appear possible, however, to prepare the desired acid chloride by this procedure.

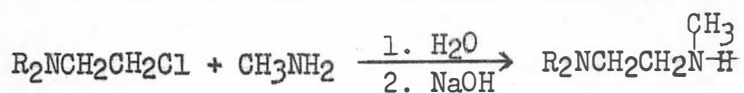
(2) 2-N,N-Dialkylaminoethyl methylamines. Two methods were employed to prepare these substituted ethylene diamines. Both procedures involved the reaction of the appropriate N,N-dialkylaminoethyl chloride with methylamine. The method of Kermack and Wight,¹⁷³ which consisted of refluxing the hydrochloride of the substituted ethyl chloride with a saturated ethanolic solution of methylamine in the presence of anhydrous potassium carbonate (II-28), gave the desired amine in 15-



(II-28)

30 per cent yields. A major difficulty in this procedure was in the preparation of the saturated solution of methylamine in ethanol since the anhydrous amine was not available and had to be generated.

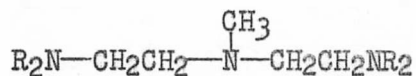
The second procedure used was that of Damiens.¹⁷⁴ This method consisted essentially of shaking a four-fold excess of 40 per cent aqueous methylamine solution with the free N,N-dialkylaminoethyl chloride (II-29). The shaking was conducted in a pressure bottle equipped



(II-29)

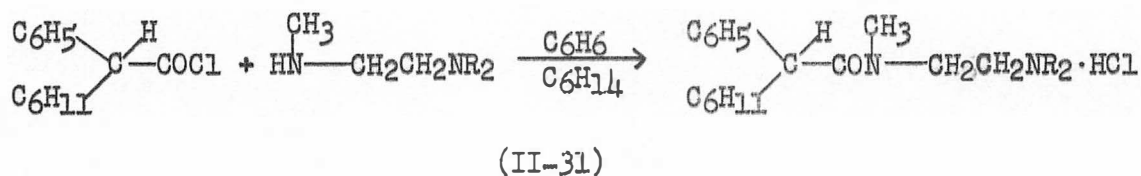
with a thermometer and a stopcock. The yields from this procedure were uniformly in the range of 30 per cent.

With both methods, a large amount of high boiling residue was obtained. This was presumably the tertiary amine dicondensation product (II-30), but in no case was an effort made to isolate it.



(II-30)

(3) N-Methylamides. The procedure of Krapcho, Turk and Pribyl⁷¹ gave the amides listed in Table III in good yield. Two of these were previously reported by Krapcho, Turk and Pribyl.⁷¹ However, the melting points given by these authors differ from those found in the present work. In view of the apparent impossibility of obtaining pure α -phenyl- α -cyclohexyl- α -chloroacetyl chloride, it was decided to prepare the analogous acetamides (II-31) to determine



whether the reported increase in activity for the benzilamides would also be observed for the acetamides. These compounds were also obtained in good yield and are listed in Table III.

b. Method B. Since α -phenyl- α -cyclohexyl- α -chloroacetyl chloride could not be obtained by the procedures used, the preparation of the phenylcyclohexylglycolamides by the ester interchange method was attempted. (This procedure has been previously described in connection with the preparation of the unsubstituted glycolamides.) Equimolar quantities of the methyl ester and the amine were refluxed with no solvent and with isopropyl alcohol, benzene, toluene and cyclohexanone. In no case was more than a trace amount of the hydrochloride obtained. Therefore, work on this procedure was not continued further.

c. Attempted preparation of dicyclohexylglycolamides. It was proposed to prepare these compounds by the complete hydrogenation of the benzilamide hydrochloride analogues as described previously for

TABLE III

2-N,N-DIALKYLAMINOETHYLMETHYLAMIDE HYDROCHLORIDES
OF SUBSTITUTED ACETIC ACIDS

$ \begin{array}{c} \text{R} \quad \text{X} \quad \text{CH}_3 \\ \diagdown \quad \diagup \quad \\ \text{C} - \text{CON} - \text{CH}_2\text{CH}_2\text{N} \begin{array}{l} \diagup \text{R}'' \\ \diagdown \text{R}''' \end{array} \cdot \text{HCl} \\ \diagup \\ \text{R}' \end{array} $							
	R	R'	R''	R'''	X	Per Cent Yield	Melting Point °C
13.	C ₆ H ₅	C ₆ H ₅	CH ₃	CH ₃	OH	26	272-274 ^b
14.	C ₆ H ₅	C ₆ H ₅	C ₅ H ₁₀ ^a		OH	46	226-227 ^c
15.	C ₆ H ₅	C ₆ H ₁₁	CH ₃	CH ₃	H	89	206-207
16.	C ₆ H ₅	C ₆ H ₁₁	C ₅ H ₁₀ ^a		H	85	208-209

^aPiperidino^bKrapcho, Turk and Pribyl⁷¹ give 252-253°.^cKrapcho, Turk and Pribyl⁷¹ give 212-214°.

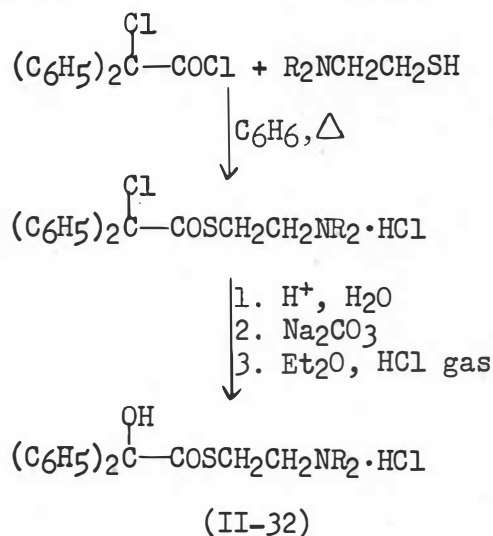
the preparation of the dicyclohexylglycolates. The products from these hydrogenations did not possess the correct elemental composition. The percentage of hydrogen found was consistently low even after repeated exhaustive hydrogenations. No explanation for this phenomenon has been found. However, in view of these results, it seems impossible to prepare the desired dicyclohexylglycolamides by this procedure.

5. Thiol Esters

It has been observed by Clinton, Salvador, Laskowski and Suter¹⁷⁵ that replacement of an oxygen atom by a sulfur atom in compounds possessing physiological activity results in a decrease in toxicity without a corresponding decrease in activity. Since one of the detractions of the N,N-dialkylaminoalkylbenzylates is their relatively high toxicity, it was decided to prepare a group of thiolbenzylates and related compounds. Morrison and Königstein⁷⁹ reported the preparation of several such compounds, including 2-N,N-diethylaminoethyl thiolbenzylate and 2-N-piperidinoethyl thiolbenzylate. They did not give any melting point data on the hydrochlorides although their preparation was claimed. The results of physiological testing of these compounds was reported by Parkes⁸⁰ in 1955. These tests showed an anti-barium and anti-potassium activity so much higher than ever before observed that it seemed worthwhile to repeat the preparation of these compounds in order to verify their activity.

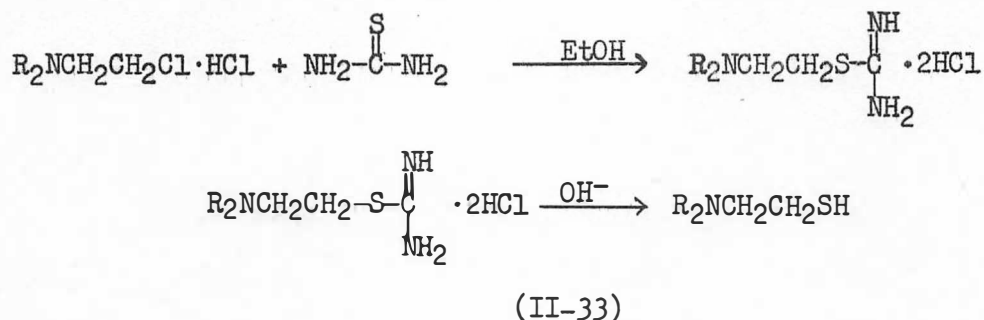
The procedure of Kolloff, Hunter, Woodruff and Moffett⁷⁸ was followed. The reaction of α, δ -diphenyl- α -chloroacetyl chloride with the appropriate 2-N,N-dialkylaminoethanethiol, followed by hydrolysis

of the alpha chloro group gave the desired compounds (II-32). These



compounds are listed in Table IV. It was not possible to prepare the desired reduced analogues of the thiolbenzylates because of the lack of the requisite acid chlorides. Preparation of these compounds by hydrogenation was not attempted since the sulfur present would probably have poisoned the platinum catalyst used in the reduction.

The 2-N,N-dialkylaminoethanethiols were prepared by the method of Albertson and Clinton⁷² from the corresponding β -N,N-dialkylaminoethyl chloride hydrochlorides (II-33). The mercaptans were not iso-



lated but were used as their ether solutions to lessen the amount of oxidation to the sulfide.

TABLE IV

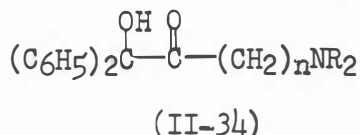
2-N,N-DIALKYLAMINOETHYL THIOLBENZILATE HYDROCHLORIDES

$ \begin{array}{c} \text{C}_6\text{H}_5 \quad \text{OH} \\ \diagdown \quad \diagup \\ \text{C} - \text{COSCH}_2\text{CH}_2\text{N} \begin{array}{l} \text{R}' \\ \text{R} \end{array} \cdot \text{HCl} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_5 \end{array} $				
	R	R'	Per Cent Yield	Melting Point °C
17.	CH ₃	CH ₃	7	153 - 154
18.	C ₂ H ₅	C ₂ H ₅	23	138 - 139
19.	C ₅ H ₁₀ ^a		17	185 - 187

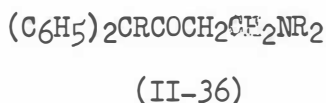
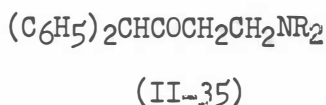
^aPiperidino

6. Ketones

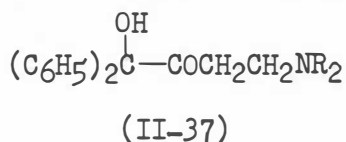
The preparation and physiological testing of aminoketones has been reported by a number of investigators. However, no report of a ketone of the structure (II-34) has been noted in the literature.



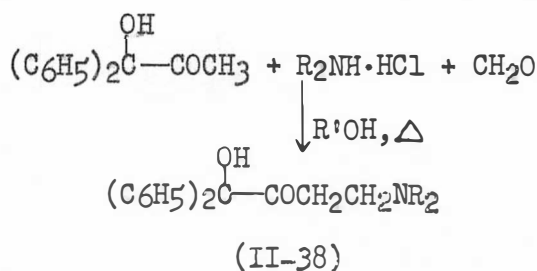
Wilson and Kyi¹¹⁵ and Zaugg, Freifelder and Horrom¹¹⁶ have prepared related compounds, (II-35) and (II-36) respectively, but these were tested as anesthetics rather than as antispasmodics.



a. 1,1-Diphenyl-1-hydroxy-4-N,N-dialkylaminobutanone-2-hydrochlorides. In view of the generally increased activity of alpha hydroxy compounds over their alpha hydrogen analogues, it was decided to attempt the preparation of a group of ketones of the structure (II-37)



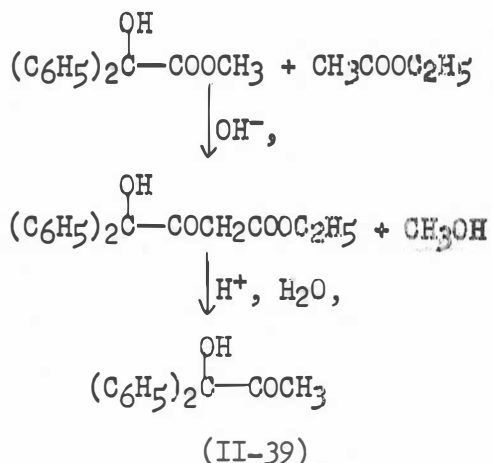
plus their reduced analogues. It was proposed to prepare these compounds by a Mannich reaction (II-38). The first problem to be faced



was the preparation of the 1,1-diphenyl-1-hydroxypropanone-2 intermediate.

(1) 1,1-Diphenyl-1-hydroxypropanone-2. Several methods of preparation of this ketone were investigated. Of these, three were successful. All of the attempts are discussed below.

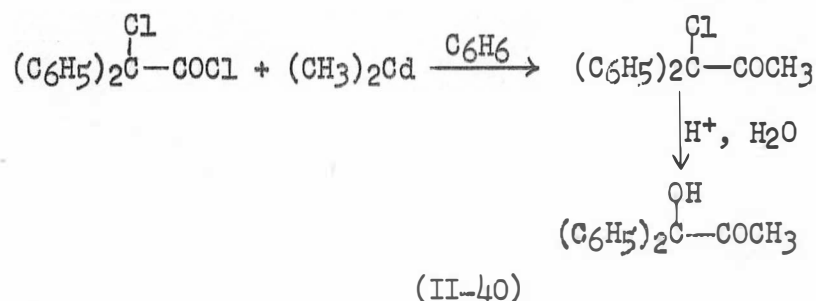
(a) Method A. A Claisen condensation between methyl benzilate and ethyl acetate, followed by hydrolysis and decarboxylation, should have given the desired compound (II-39). The product, a viscous



orange liquid, possessed a carbonyl function as evidenced by the formation of a 2,4-dinitrophenylhydrazone and an oxime. The melting point of this oxime was 15° lower than that reported by Stevens and Sherr¹⁷⁶ for 1,1-diphenyl-1-hydroxypropanone-2 oxime. The correct carbon and hydrogen percentages were obtained on analysis, however. The product of the Claisen condensation was used in several attempts to prepare the aminoketones by the Mannich reaction. The failure of these attempts led to a search for other ways to prepare the intermediate. This work was done in the earlier stages of the research when proper conditions for the Mannich reaction had not yet been determined. It is possible

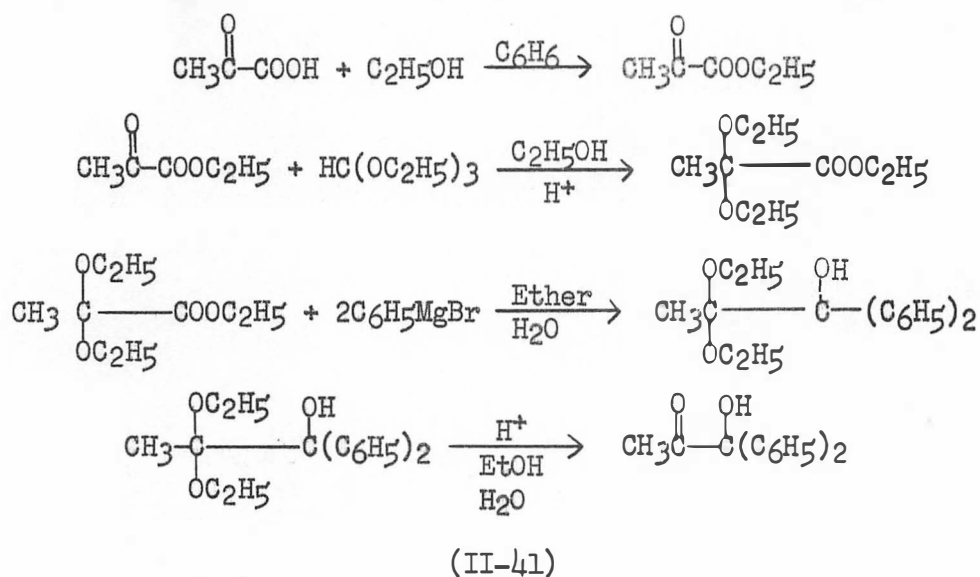
that the Claisen product was the desired ketone and that improper reaction conditions were the cause of the failure of the Mannich reactions.

(b) Method B. A modification of the procedure of Cason¹⁷⁷ was employed. The reaction of 1,1-diphenyl-1-chloroacetyl chloride with dimethyl cadmium (II-40) gave no ketonic product, however, as indicated



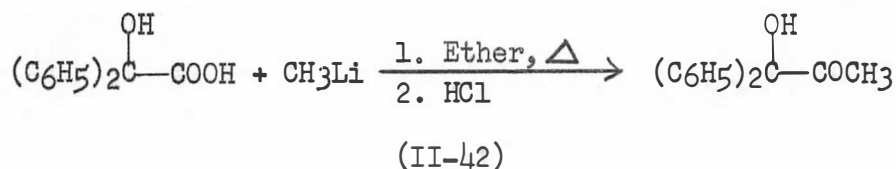
by the failure of the material to form any carbonyl derivatives.

(c) Method C. The procedure of Stevens and Sherr¹⁷⁶ was employed to prepare the bulk of the material used in the research. This series of reactions is outlined below (II-41). The desired ketone was



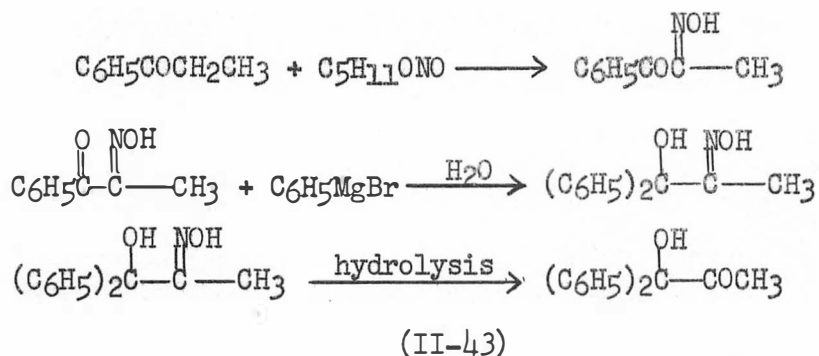
was obtained, but the method was time consuming and tedious, especially since the last step could be run conveniently only on a small scale.

(d) Method D. The procedure of Tegner¹⁷⁸ for the preparation of methyl ketones was followed. This involved the reaction of the organic acid with methyl lithium (II-42). The present attempts



were not successful; the starting benzilic acid was recovered quantitatively in each case.

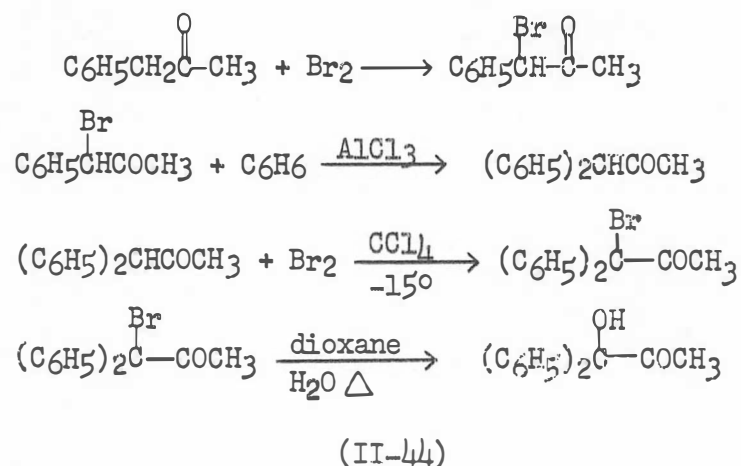
(e) Method E. The substituted propanone was to be prepared by hydrolysis of its oxime which could be obtained by isonitrosation of propiophenone followed by the addition of phenylmagnesium bromide to the carbonyl group (II-43). The procedure was quite success-



ful up to the hydrolysis of the oxime. A wide variety of conditions were employed in attempts to effect this hydrolysis, but none of these proved successful. The method, therefore, had to be abandoned.

(f) Method F. The directions of Stevens and Lenk¹⁷⁹ were followed. 1,1-Diphenylpropanone was prepared by a Friedel-Crafts reaction. Bromination of this product followed by hydrolysis of the

alpha bromo group gave the desired compound (II-44). This reaction



proceeded nicely and in good yield. It appears to be the best method to prepare the propanone in large amounts.

(2) Mannich reaction. A number of different reaction conditions were used in an attempt to prepare the aminoketones by the Mannich reaction. All of the methods consisted essentially of refluxing an alcoholic solution of 1,1-diphenyl-1-hydroxypropanone-2 with a secondary amine and formaldehyde. However, they differed in respect to the time of reflux, the alcohol used as solvent, and the presence or absence of water in the reaction mixture. Only the procedure of Zaugg, Freifelder and Horrom¹¹⁶ gave the desired compounds. This set of conditions is described in the experimental section of this report. The compounds prepared by this method are listed in Table V.

b. 1-Phenyl-1-cyclohexyl-4-N,N-dialkylaminobutanone-2 hydrochlorides. It was proposed to prepare these compounds by a Mannich reaction employing 1-phenyl-1-cyclohexylpropanone-2. Three methods were employed to prepare the hitherto unknown propanone. Two of these were successful.

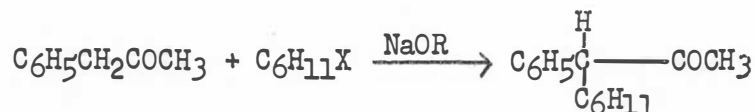
TABLE V

SUBSTITUTED 4--N,N-DIALKYLAMINO-2-BUTANONE-2 HYDROCHLORIDES

$\begin{array}{c} \text{R} \quad \text{X} \\ \diagdown \quad \diagup \\ \text{C} - \text{COCH}_2\text{CH}_2\text{N} \begin{array}{l} \text{R}'' \\ \text{R}''' \end{array} \\ \diagup \quad \diagdown \\ \text{R}' \end{array} \cdot \text{HCl}$							
	R	R'	R''	R'''	X	Per Cent Yield	Melting Point °C
20.	C ₆ H ₅	C ₆ H ₅	CH ₃	CH ₃	OH	19	163.5 - 165
21.	C ₆ H ₅	C ₆ H ₁₁	CH ₃	CH ₃	H	22	181.5 - 182
22.	C ₆ H ₅	C ₆ H ₁₁	C ₅ H ₁₀ ^a		H	25	214 - 215

^aPiperidino

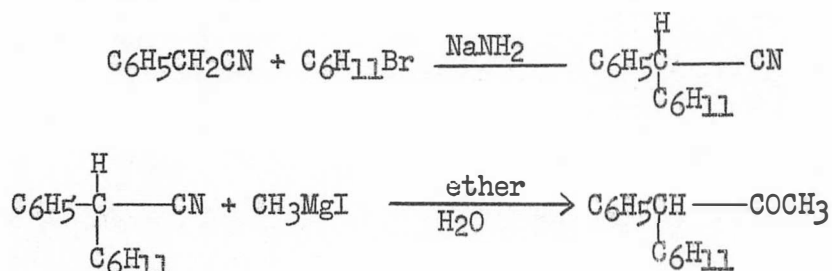
(1) 1-Phenyl-1-cyclohexylpropanone-2. (a) Method A. The simplest way to obtain the desired ketone seemed to be by the alkylation of phenyl acetone using a cyclohexyl halide (II-45). A number of



(II-45)

investigators have alkylated phenylacetone with a variety of alkyl halides in good yield. The attempts reported here were unsuccessful, however. In every case, some phenylacetone was recovered together with a high boiling residue. In view of the reported success with other alkyl halides, the difficulty must be associated with the cyclohexyl group in some way. As will be discussed in Method B, the analogous alkylation of phenylacetone nitrile with bromocyclohexane gave the desired product. Why the reaction with phenylacetone did not give similar results is not as yet clear.

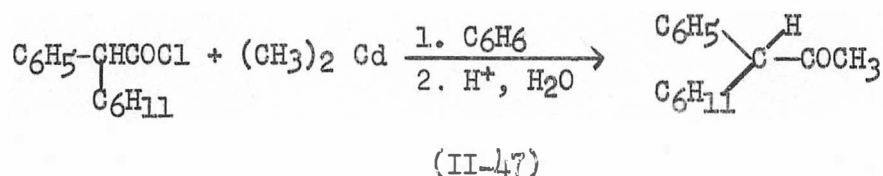
(b) Method B. A modification of the procedure of Hauser and Humphlett¹⁸⁰ was used. The action of methyl magnesium iodide on phenylcyclohexylacetone nitrile gave the desired compound although the yield was not satisfactory (II-46). The identity of the ketone was



(II-46)

verified through the elemental analyses of its 2,4-dinitrophenylhydrazone and oxime.

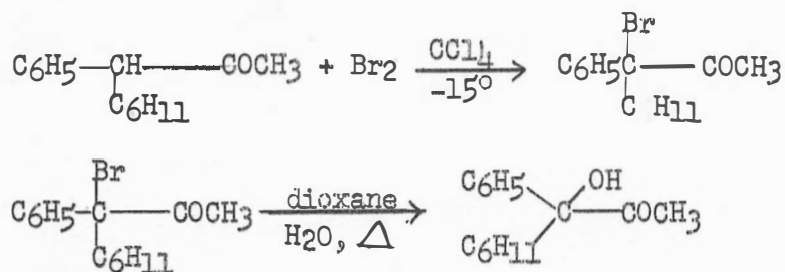
(c) Method C. The reaction of phenylcyclohexylacetyl chloride and dimethyl cadmium (II-47) by the procedure of Cason¹⁷⁷ gave



the ketone. The yields from this method were somewhat better than those from Method B. This, combined with the relatively more simple experimental conditions, makes Method C the preferred method of preparation.

(2) Mannich reaction. For the aminoketones prepared from 1-phenyl-1-cyclohexylpropanone-2, the reaction conditions of Wilson and Kyi¹¹⁵ were used. These differ from those employed for the hydroxyketones primarily in the time of reflux and the nature of the alcohol used as solvent. The conditions are described in the experimental section. The compounds prepared by this method are listed in Table V.

(c) Attempted preparation of 1-phenyl-1-cyclohexyl-1-hydroxy-4-N,N-dialkylaminobutanone-2 hydrochlorides. A Mannich reaction employing 1-phenyl-1-cyclohexyl-1-hydroxypropanone-2 was to be used to prepare these aminoketones. An attempt was made to prepare the propanone intermediate by bromination of 1-phenyl-1-cyclohexylpropanone-2 followed by hydrolysis (II-48). The product of this reaction possessed unsaturation as evidenced by positive bromine and Baeyer tests. (Compare these results with those obtained from the bromination of phenyl-



(II-48)

cyclohexylacetic acid under different conditions. In both cases, unsaturation was noted.) The extent of unsaturation was not determined, but since the material was not pure 1-phenyl-1-cyclohexyl-1-hydroxypropanone-2, the method was abandoned. Since no alternate synthesis of the propanone seemed promising, the preparation of the aminoketones had to be abandoned.

C. Physiological Testing

The compounds were tested for physiological activity in the Pharmacology Branch of the Chemical Corps Medical Laboratories in Army Chemical Center by Drs. Gerald Groblewski and J. H. Wills. The results reported here are of a preliminary nature and are not by any means complete. In addition, test results on a number of the compounds have not yet been received. The tables to follow will summarize the data which are available.

The following tests were made:

1. Ability to prevent mortality from a standard dose of an anticholinesterase compound.
2. Ability to block blood pressure fall produced by a standard dose of acetylcholine.

3. Ability to block blood pressure fall produced by a standard dose of histamine.

4. Ability to stimulate gut and decrease tracheal air exchange.

5. Ability to produce changes in diameter of the pupil of the eye.

6. Ability to produce anesthesia of the cornea.

All of these tests were conducted in the live, whole animal. In test (1) the compounds were compared to atropine in ability to prevent mortality from an anticholinesterase compound. A standard dose of the latter compound was given to six rabbits, which were then treated with the test compound. The effectiveness of the test compound is reported in terms of the mortality rate among animals treated with it as compared to those treated with atropine. The compounds are classified as less active, more active, or equal in activity to atropine.

Tests (2) and (3) were run on cats. Injections of acetylcholine or histamine produce a marked fall in the animal's blood pressure. The activity of the compounds is reported in terms of their ability to block this fall.

Test (4) was run on animals in which a balloon had been inserted through a slit into the duodenum. The movement of the gut was then recorded on a chymograph. The ability of the compounds to block excitation of the gut by a standard dose of acetylcholine was recorded.

Tests (5) and (6) were conducted on rabbits. In test (5) the diameter of the pupil was measured before and after administering a dose of the compound undergoing testing. The degree of anesthesia of the cornea (test 6) was determined by pressing the cornea with a rod

before and after the dose of the compound and observing how much pressure was required to produce blinking.

The results of these tests are summarized in Tables VI-VIII. Of the compounds for which results have been obtained, the most active in preventing mortality from a standard dose of an anticholinesterase is compound 14. Compound 2 appears to be the most active antispasmodic.

TABLE VI

ANTICHOLINESTERASE SCREENING

(Tests on Rabbits With Standard 2.0 Mg./Kg. Dose Unless Otherwise Indicated)		
Less Active Than Atropine	Equally as Active as Atropine	More Active Than Atropine
7	1	14
	2	
	3	
	5	
	6	
	9	
	10	
	11	
	12	

TABLE VII

DIRECT EFFECTS OF CHEMICALS ON FUNCTION

No.	Dose (Mg./Kg.)	Per Cent Block of Blood Pressure Fall After		Effect of Compound on:			
		Acetyl Choline	Histamine	Blood Pressure	Gut	Respiration Depth	Rate
1.	2.0	93 (77 - 0.7 mg.)	18	None		None	None
2.	1.0	78 (68 - 0.5 mg.)	0	None	Blocks spontaneous activity and response to acetyl choline and histamine	None	None
	1.0	100 (63 - 0.5 mg.)	6				
4.	7.0	63	39	-40%	-100%	+	+
5.	2.0	74 (54 - 0.5 mg.)	25 (0.5 mg.)	None		None	None
						Blocks response to acetyl choline	
8.	0.5	None	None	None	Tonus increased	+	None
11.	6.5	Increased 16%	Increased 6%	None	None	+	+
12.	7.0	5	None	-11%	None	+	+

TABLE VIII

EYE EFFECTS

Slight Mydriasis:	1, 4, 11, 12
Slight Miosis:	3, 5, 8
Local Irritation:	11

CHAPTER III

EXPERIMENTAL

All of the reagents used were obtained commercially except where otherwise noted. They were of the highest quality available. The substituted aminoethanols and ethylene diamines were donated by the Carbide and Carbon Chemicals Company. All melting points were taken using a Fischer melting point block.

A. Esters

1. Preparation of Methyl Phenylcyclohexylglycolate

The procedure of Shacklett¹⁶¹ was employed.

a. Methyl benzilate. Potassium benzilate was prepared by adding, with stirring, 100 g. (0.44 m.) of benzoic acid to a solution of 30 g. (0.53 m.) of potassium hydroxide in 700 ml. of absolute ethanol. After filtering and drying, 107 g. (0.4 m., 91 per cent) of an amorphous white solid was obtained. An additional few grams of less pure potassium benzilate could be recovered from the filtrate by evaporation of the alcohol.

This salt was refluxed for one hour with 30 ml. (0.48 m.) of methyl iodide in a solution of 500 ml. of butyl carbitol and 80 ml. of water. The reaction mixture was poured into two and one-half liters of water and allowed to cool. A light yellow oil, which quickly solidified, formed to give, after filtering and drying, 93.5 g. (98 per cent) of a cream-colored solid. Two recrystallizations were performed from

hot ethanol by adding sufficient water to produce cloudiness and chilling the resulting solution. Small snow-white needles were obtained, m.p. 76-76.5°. (Klinger and Standke¹⁸¹ give 74-74.5°.)

b. Reduction. Methyl benzilate was reduced in approximately 100 g. batches by shaking an acetic acid solution of the material with 0.5 g. of platinum oxide at room temperature under initial hydrogen pressures of the order of 64 psi. Shaking was continued until about 45 per cent of the amount of hydrogen required for complete hydrogenation had been taken up (about forty-eight hours). The catalyst was removed by filtration and the filtrate was set aside for subsequent distillation.

c. Distillation. The acetic acid solutions containing the partially reduced ester from 475 g. of methyl benzilate were placed in a pot attached to an eight-foot Vigreux column equipped with a total reflux-variable take-off distilling head. The acetic acid was removed under reduced pressure produced by a water aspirator. Distillation of the residue under reduced pressure from a vacuum pump gave the fractions listed in Table IX. All of the fractions were clear, slightly yellow liquids. Fractions 1-9 were quite viscous; 10-11 flowed freely. To determine which fractions contained sufficiently pure methyl phenylcyclohexylglycolate, samples from each end of the boiling range were hydrolyzed with alcoholic sodium hydroxide. From the melting points of the acids thus obtained and their mixed melting points with an authentic sample of phenylcyclohexylglycolic acid, it was determined that fractions 4-10 were sufficiently pure to be used in further work.

TABLE IX

DISTILLATION OF REDUCED METHYL BENZILATE

Fraction	Volume Ml.	Head Temperature °C	Pressure mm.	Refractive Index
1.	17.0	162-164	7	1.4989
2.	33.0	164-168	7	1.5078
3.	48.5	165	7	1.5097
4.	47.2	166-170	7	1.5120
5.	52.5	168-172	7	1.5174
6.	52.0	170-175	7	1.5218
7.	31.5	173-176	11	1.5270
8.	17.5	175-179	11	1.5295
9.	19.5	177-181	11	1.5269
10.	25.5	177-179	11	1.5314
11.	24.5	184-188	11	1.5705

After standing for several days, fraction 7 spontaneously crystallized. The remaining fractions (4-10) also crystallized after they were seeded. All of the fractions gave small white crystals, melting around 40° . It was not possible to obtain a more definite melting point.

The remaining fractions were completely hydrogenated to methyl dicyclohexylglycolate. This ester was hydrolyzed to give dicyclohexylglycolic acid, m.p. $168-170^{\circ}$.

2. Preparation of Phenylcyclohexylglycolic Acid

a. Method A. Methyl phenylcyclohexylglycolate was hydrolyzed as described (A.1.c) to give the crude acid in quantitative yield.

This was recrystallized several times by dissolving it in hot ethanol, adding sufficient water to produce a slight cloudiness, and chilling. Small white needles, m.p. $160-162^{\circ}$, were obtained. (Smith, Alderman, Shacklett, and Welch¹⁶³ give $167-168^{\circ}$.)

b. Method B. (1) Benzoyl cyanide. This compound was prepared from benzoyl chloride by the method of Oakwood and Weisgerber.¹⁶⁴ In a 500-ml. distilling flask equipped with a thermometer were placed 110 g. (1.2 m.) of cuprous cyanide and 143 g. (1.02 m.) of freshly distilled benzoyl chloride. The flask was shaken thoroughly to moisten all of the cuprous cyanide and placed in a Woods' metal bath previously heated to $145-150^{\circ}$. The temperature of the bath was raised to $220-230^{\circ}$ and maintained between these limits for one and one-half hours. During this time the flask was removed from the bath about every fifteen minutes and the contents were thoroughly mixed by vigorous shaking. At the end of this heating period the flask was connected for distillation.

The temperature was raised slowly to $305-310^{\circ}$ and the distillation was carried out at this temperature until no more product came over. There was obtained 124 g. (93 per cent) of a clear, yellow liquid, boiling from $204-209^{\circ}$. This crystallized into clear, large needles which melted at $31-33^{\circ}$. (Oakwood and Weisgerber¹⁶⁴ give $32-33^{\circ}$.) They were used without further purification.

(2) Benzoylformic acid. The procedure of Oakwood and Weisgerber¹⁸² was followed.

In a 1-l. flask were placed 50 g. (0.38 m.) of benzoyl cyanide and 500 ml. of concentrated hydrochloric acid. The flask was stoppered and shaken occasionally until all of the material had dissolved (about twelve hours). The stoppered flask was allowed to stand at room temperature for five days. The contents were then poured into a large excess of water and extracted three times with ether. The dried extracts were heated to remove the ether. The viscous liquid residue failed to crystallize on standing in a vacuum desiccator. Cooling the chloroform solution gave colorless crystals which weighed 48 g. (86 per cent) and melted at $63-65^{\circ}$. (Oakwood and Weisgerber¹⁸² give $64-66^{\circ}$.)

(3) Phenylcyclohexylglycolic acid. A Grignard reagent was prepared from 12.4 g. (0.51 m.) of magnesium turnings and 60.4 g. (0.51 m.) of chlorocyclohexane according to the procedure of Gilman and Zoellner.¹⁸³ This reagent was added dropwise to a chilled, stirred solution of 25 g. (0.17 m.) of benzoylformic acid in ether. The mixture was stirred for one hour, refluxed for two hours, cooled and

poured into ice and dilute sulfuric acid. The ether layer was separated and extracted with aqueous sodium carbonate. This alkaline solution was made acidic and the solid thus obtained was separated by filtration. There was obtained 20 g. (50 per cent) of a cream-colored solid, melting from 143 to 148°. A portion of this was recrystallized several times by dissolving the compound in hot ethanol, adding water until the solution became slightly cloudy, and chilling. White needles, m.p. 158-160°, were obtained by this procedure. (Smith, Alderman, Shacklett, and Welch¹⁶³ give 167-168°.)

c. Method C. (1) 3-Bromocyclohexene. This was prepared according to the procedure of Ziegler, Spaeth, Schaaf, Schumann, and Winkelmann.¹⁸⁴ Two hundred grams (1.44 m.) of cyclohexene, 72 g. (0.48 m.) of N-bromosuccinimide and 300 ml. of carbon tetrachloride were refluxed until all the N-bromosuccinimide had reacted (thirty minutes). The insoluble succinimide formed in the reaction was removed by filtration. Distillation of the filtrate under reduced pressure gave 48 g. (62 per cent) of 3-bromocyclohexene, a slightly yellow liquid, b.p. 82-85°/45 mm. (Crossley¹⁸⁵ gives 74°/28 mm.)

(2) Diethyl phenyl- Δ^2 -cyclohexenylmalonate. The method described by Kolloff, Hunter, Woodruff, and Moffett⁴² was followed. To a solution of 7.0 g. (0.305 m.) of sodium in 250 ml. of absolute ethanol was added 70.8 g. (0.3 m.) of diethyl phenylmalonate. The solution was stirred at reflux temperature during the dropwise addition of 49.1 g. (0.305 m.) of 3-bromocyclohexene. The reaction mixture was then refluxed with stirring for six hours. After cooling and making the solution

acidic with acetic acid, most of the solvent was removed by distillation. Water was then added and the organic layer was separated. The aqueous layer was extracted twice with ether. Distillation of the combined organic layers gave 48 g. (51 per cent) of diethyl phenyl- Δ^2 -cyclohexenylmalonate. The product was a faintly yellow liquid, b.p. 155-160°/0.5 mm. (Kolloff, Hunter, Woodruff, and Moffett⁴² give 126°/0.07 mm.)

(3) Phenyl- Δ^2 -cyclohexenylacetic acid. The procedure of Kolloff, Hunter, Woodruff, and Moffett⁴² was again employed. A solution of 48 g. (0.15 m.) of diethyl phenyl- Δ^2 -cyclohexenylmalonate and 53.3 g. (0.95 m.) of potassium hydroxide in 250 ml. of 95 per cent ethanol was refluxed for six hours. Water was added from time to time to dissolve the solid which separated. Most of the alcohol was removed by distillation. The product was dissolved in water, extracted with ether and the aqueous layer cooled and made acidic. An oil, which crystallized after a few minutes, formed. There was obtained 31 g. (95 per cent) of the crude acid, m.p. 109-112°. (Kolloff, Hunter, Woodruff, and Moffett⁴² give 120-122° as the melting point of the pure compound.)

(4) Phenylcyclohexylacetic acid. This compound was prepared by catalytic reduction of the unsaturated acid. Thirty-one grams (0.143 m.) of phenyl- Δ^2 -cyclohexenylacetic acid was dissolved in 100 ml. of 95 per cent ethanol and shaken with 0.2 g. of platinum oxide at an initial hydrogen pressure of 64 psi. until no further drop in pressure was noted. An attempt to remove the catalyst by filtering was unsuccessful because the reduced acid crystallized on the filter.

The solution was therefore poured into an excess of dilute base and filtered to remove the platinum oxide. The filtrate was poured onto ice and dilute hydrochloric acid. After filtering and drying, there was obtained 29 g. (93 per cent) of a white solid, m.p. 143-145°. (Kolloff, Hunter, Woodruff, and Moffett⁴² give 146.5-147.5° as the melting point of the pure acid.)

(5) Attempted preparation of phenylcyclohexylbromoacetic acid. It was proposed to prepare this compound by a Hell-Volhard-Zelinsky type reaction. A mixture of 10.9 g. (0.05 m.) of phenylcyclohexylacetic acid, 8.2 g. (0.051 m.) of bromine, and 0.1 ml. of phosphorus trichloride was heated to 80-90° for one hour. It was found that heating to 140-150° was required to cause the reaction to proceed. (The course of the reaction was followed by the evolution of hydrogen bromide.) After heating at this latter temperature for five hours, the reaction mixture was allowed to cool. The contents of the flask set to a hard polymeric material which was insoluble in base even when heated for several hours. No attempt to identify this material was made. The method of preparation was discarded.

(6) Attempted preparation of phenylcyclohexylbromoacetyl chloride. A modification of the procedure of Schwenk and Papa¹⁶⁵ was followed. A mixture of 21.8 g. (0.1 m.) of phenylcyclohexylacetic acid and 30 ml. (48 g., 0.41 m.) of thionyl chloride was refluxed for two hours. To the gently refluxing solution was added 16.8 g. (0.105 m.) of bromine dropwise over two hours. The reaction mixture was then allowed to stand overnight. A portion was refluxed for three hours

in a dioxane-dilute base solution. The dioxane was removed by distillation under reduced pressure. When the residue was poured into an excess of dilute alkali, a large amount of insoluble material was noted. The mixture was extracted with ether and the aqueous layer was made acidic. Only a trace of organic acid was found. No attempt to identify the insoluble material was made. The reaction was repeated several times, but each time a base insoluble product was obtained. The method of preparation was discarded.

Since the necessary alpha bromo intermediates could not be prepared, this method of synthesis of phenylcyclohexylglycolic acid had to be abandoned.

3. Preparation of 4,4'-Dimethoxybenzilic Acid

This was prepared by the benzilic acid rearrangement according to the procedure described by Shacklett.¹⁸⁶

a. 4,4'-Dimethoxybenzoin. A mixture of 150 g. (1.1 m.) of anisaldehyde, 180 g. of 95 per cent ethanol, 30 g. of potassium cyanide and 120 ml. of water was refluxed for two hours. An additional 30 g. of potassium cyanide was added and refluxing was continued for an additional two hours. The solution was cooled rapidly with vigorous shaking and allowed to stand overnight in the cold room. Since no solid was obtained, small portions of water were added until milkiness occurred. The solution was then chilled again. The crystalline benzoin was filtered, washed with a cold 80 per cent aqueous ethanol solution and then with water and dried. There was obtained 46 g. of white solid melting at 107-109°. (van Alphen¹⁸⁷ gives the melting point

as 113°.) An additional 8 g. was recovered from the filtrate by dilution with water. The total yield was 36 per cent.

b. 4,4'-Dimethoxybenzil. A mixture of 104 g. (0.38 m.) of 4,4'-dimethoxybenzoin, 229 g. of copper sulfate pentahydrate, 229 g. of pyridine and 92 ml. of water was refluxed for two and one-half hours. The solution was poured into a beaker and cooled by the addition of ice and water. The chartreuse colored solid was filtered, washed with dilute hydrochloric acid and water and dried to give 102.5 g. (99 per cent). After recrystallization from carbon tetrachloride and then from ethanol, there was obtained 91 g. of bright yellow needles, m.p. 132-133°. (Klein¹⁸⁸ gives 132-133°.)

c. 4,4'-Dimethoxybenzilic acid. To a boiling solution of 17 g. of potassium hydroxide in 90 ml. of 1-butanol was added 35 g. (0.13 m.) of 4,4'-dimethoxybenzil. Refluxing was continued for ten minutes. The deep purple solution was cooled rapidly and extracted with water with the addition of a little ether to help the separation. The aqueous extract was made acidic with concentrated hydrochloric acid. After filtering and drying, there was obtained 21.5 g. (61 per cent) of a white solid, m.p. 162-164°. The compound was recrystallized from benzene and from hot ethanol solutions to which water had been added until slight cloudiness was produced. This gave small white needles, m.p. 165-167°. (Bosler¹⁸⁹ gives 164°.)

4. 2-N,N-Dialkylaminoethanols

All of the aminoethanols used were obtained commercially except 2-N-piperidinoethanol which was prepared by the procedure of Hazard,

Cheymol, Chabrier, Corteggiani, and Nicolas.¹⁹⁰

2-N-Piperidinoethanol. A mixture of 30 g. (0.37 m.) of ethylene chlorohydrin, 50 g. (0.70 m.) of piperidine and 200 ml. of benzene was refluxed on a steam bath for six hours. After cooling, the solid piperidine hydrochloride which formed was removed by filtration. Distillation of the residue gave 35.5 g. (79 per cent) of 2-N-piperidinoethanol, b.p. 195-196°. (Hazard, Cheymol, Chabrier, Corteggiani, and Nicolas¹⁹⁰ give 198°.)

5. Preparation of 2-N,N-Dialkylaminoethyl Chlorides

The method of Slotta and Behnisch¹⁶⁹ was used to obtain the substituted aminoethyl chloride hydrochlorides. The free bases were prepared from these hydrochlorides by the procedure of Gilman and Shirley.¹⁷⁰

a. β -Diethylaminoethyl chloride. To a chilled (ice bath) solution of 156 g. (1.32 m.) of β -diethylaminoethyl alcohol in 1500 ml. of benzene was added a solution of 321 g. (2.7 m.) of thionyl chloride in 300 ml. of benzene. The mixture was stirred rapidly throughout the reaction. The contents of the flask were refluxed for two hours on a water bath, cooled and filtered. There was obtained 224 g. (100 per cent) of a white solid.

One hundred grams (0.58 m.) of this hydrochloride was treated with 150 ml. of 40 per cent aqueous sodium hydroxide. The liberated chloride was extracted with 500 ml. of ether. The extract was dried with anhydrous magnesium sulfate and distilled. The material boiling at 147-148° was collected. (Slotta and Behnisch¹⁶⁹ give 146-147°.) The 2-N,N- diethylaminoethyl chloride was a colorless liquid which

weighed 58 g. (74 per cent).

b. β -N,N-Dimethylaminoethyl chloride. This was prepared by an analogous procedure in 53 per cent yield. It was a colorless liquid, b.p. 109°. (Slotta and Behnisch¹⁶⁹ give 109°.)

c. β -N-Piperidinoethyl chloride. This was prepared by an analogous procedure in 55 per cent yield. Its boiling point was 189-190°. (Gilman and Woods¹⁹¹ give 36-38°/0.5 mm.)

All of these substituted aminoethyl chlorides tended to dimerize on standing. This was especially true of β -N,N-dimethylaminoethyl chloride, which dimerized completely in twenty-four hours. To retard this reaction, the compounds were diluted with an equal weight of dry xylene and stored in the cold room.

6. Drying of Isopropyl Alcohol

Five hundred ml. of isopropyl alcohol (99 per cent) was mixed with 100 g. of calcium oxide and refluxed for eight hours. The mixture was distilled and the fraction boiling at 82° was collected.

7. Preparation of 2-N,N-Dialkylaminoethyl Esters of Substituted Glycolic Acids

a. Method A. The method of Hill and Holmes¹⁶⁷ was used to prepare several of the esters. The preparation of 2-N,N-dimethylaminoethyl phenylcyclohexylglycolate hydrochloride, which is typical, will be described. Other esters prepared by this method are listed in Table X.

2-N,N-Dimethylaminoethyl phenylcyclohexylglycolate hydrochloride. In a 50-ml. pot attached to a short Vigreux column equipped with a total

TABLE X

2-N,N-DIALKYLAMINOETHYL ESTERS OF DISUBSTITUTED GLYCOLIC ACIDS

$\begin{array}{c} \text{R} \quad \text{OH} \\ \diagdown \quad / \\ \text{C} - \text{COOCH}_2\text{CH}_2\text{NR} \begin{array}{c} \text{R}''' \\ \diagup \quad \diagdown \\ \text{R}'' \end{array} \cdot \text{X} \\ \diagup \\ \text{R}' \end{array}$											
R	R'	R''	R'''	X	Method of Prep- aration	Per Cent Yield	Melting Point °C	Analyses			
								Calculated		Found	
								C	H	C	H
1. C ₆ H ₅	C ₆ H ₁₁	CH ₃	CH ₃	HCl	A	47	219-220	63.24	8.25	63.31	8.46
2. C ₆ H ₅	C ₆ H ₁₁	C ₅ H ₁₀ ^a		HCl	A	47	223-224	66.04	8.45	66.02	8.55
3. C ₆ H ₅	C ₆ H ₁₁	C ₅ H ₁₀ ^a		CH ₃ Br	B	24	176-177	60.00	7.78	59.97	8.00
4. C ₆ H ₁₁	C ₆ H ₁₁	CH ₃	CH ₃	HCl	B ^b	72	258-259	62.14	9.85	62.58	9.58
5. C ₆ H ₁₁	C ₆ H ₁₁	C ₅ H ₁₀ ^a		HCl	A ^b	35	212-213	65.01	9.87	65.03	9.78
6. 4-CH ₃ OC ₆ H ₄	4-CH ₃ OC ₆ H ₄	C ₅ H ₁₀ ^a		HCl	B	92	181-182	63.37	6.94	63.08	7.11
7. 4-CH ₃ OC ₆ H ₄	4-CH ₃ OC ₆ H ₄	C ₅ H ₁₀ ^a		CH ₃ Br	B	53	147-148	58.30	6.52	58.10	6.62

^aPiperidino^bFollowed by hydrogenation

reflux-variable take-off distilling head were placed 17.5 g. (0.2 m.) of 2-N,N-dimethylaminoethanol and 0.02 g. of metallic sodium. After the reaction of the sodium was complete, 11.4 g. (0.046 m.) of methyl phenylcyclohexylglycolate was added. The pressure was reduced to 100 mm. and the pot was heated with an oil bath, the temperature of which was raised slowly to 75°. After three hours the temperature was raised to 120° and maintained there for four hours. During this latter period the contents of the pot turned dark red. The pressure was lowered to 25 mm., at which pressure the excess aminoalcohol distilled. The viscous red-brown liquid residue was withdrawn from the pot while still hot. The pot was washed thoroughly with ether and the combined washings and residue were shaken until a clear solution was obtained. This was washed successively with dilute aqueous sodium chloride and three portions of water and dried over anhydrous magnesium sulfate. The solution was cooled in an ice bath and saturated with dry hydrogen chloride. A white solid formed. This was filtered, washed with cold absolute ethanol, and dried to give 7.5 g. (47 per cent) of a white amorphous solid, m.p. 220-222°. Recrystallization was performed by dissolving the compound in hot ethanol, adding sufficient anhydrous ether to produce cloudiness, and chilling. This gave small needles, m.p. 222-223°.

Anal. Calcd. for $C_{18}H_{28}NO_3Cl$: C, 63.24; H, 8.25

Found: C, 63.31; H, 8.46.

b. Method B. The procedure of Horenstein and Pahlicke¹⁶⁸ was used to prepare several of the aminoesters. For illustrative purposes

the preparation of 2-N-piperidinoethyl 4,4'-dimethoxybenzilate hydrochloride will be described. Other esters prepared by Method B are listed in Table X.

2-N-Piperidinoethyl 4,4'-dimethoxybenzilate hydrochloride. A mixture of 2.3 g. (0.015 m.) of β -N-piperidinoethyl chloride, 4.3 g. (0.015 m.) of 4,4'-dimethoxybenzilic acid and 75 ml. of dried isopropyl alcohol was refluxed for twelve hours. When allowed to cool to room temperature, the contents of the flask solidified. This solid was filtered, washed with anhydrous ether and dried to give 6 g. (92 per cent) of the crude ester hydrochloride, m.p. 174-179°. After recrystallization from an ethanol-ether mixture (as described in A.7.a.), the small white needles melted at 181-182°.

Anal. Calcd. for $C_{23}H_{30}NO_5Cl$: C, 63.37; H, 6.94

Found: C, 63.08; H, 6.94.

c. Preparation of dicyclohexylglycolates. These esters were prepared by the complete hydrogenation of the analogous benzilate hydrochloride in acetic acid using platinum oxide as catalyst at room temperature. A known amount of the ester hydrochloride was dissolved in a minimum amount of redistilled glacial acetic acid. Initially 0.4 g. of platinum oxide was added. Further addition was made when needed. Initial hydrogen pressures were approximately 64 psi. Hydrogenation was continued until no further drop in pressure was observed.

At the end of the hydrogenation the solution was filtered through a sintered glass funnel to remove the catalyst. The acetic acid was distilled from the filtrate under reduced pressure. The

residue was crystallized by dissolving it in hot ethanol, adding sufficient anhydrous ether to produce cloudiness, and chilling. Recrystallization in the same manner was carried out until a sharp melting point was obtained. The compounds were then dried and analyzed. They are listed in Table X.

d. Preparation of quaternary ammonium salts. The method employed for 2-N-piperidinoethyl 4,4'-dimethoxybenzilate methyl bromide, which is typical, follows. The hydrochloride, 11.6 g. (0.0266 m.), was converted into the free base with dilute sodium hydroxide. The amino-ester was extracted with ether; the solution dried; and the ether removed. To a methanolic solution of the residue was added 20.5 g. (0.0533 m.) of methyl bromide in methanol (25 per cent). The stoppered flask was allowed to stand at room temperature for five days. Evaporation yielded a gummy residue which was crystallized from a hot acetonitrile solution by adding sufficient ether to produce slight cloudiness and chilling the solution. There was obtained 7.8 g. (53 per cent) of a white solid, m.p. 110-115°. Further recrystallization from the same solvent mixture and from ethanol containing a trace of ether raised the melting point to 147-148°.

Anal. Calcd. for $C_{24}H_{32}NO_5Br$: C, 58.30; H, 6.52

Found: C, 58.10; H, 6.62.

B. Amides

1. 2-N,N-Dialkylaminoethylamines

These amines were obtained commercially with the exception of 2-N-piperidinoethyl amine.

2-N-Piperidinoethylamine. The method of van Alphen¹⁹² was employed. A solution of 100 g. (0.43 m.) of 1,5-dibromopentane in 200 ml. of absolute ethanol was added slowly to 150 g. (1.9 m.) of ethylene diamine hydrate. After a one-hour reflux period, an excess of solid powdered potassium hydroxide was added and heating was continued for another hour. The potassium bromide was removed by filtration. The filtrate was distilled at atmospheric pressure until the ethanol and excess amine were removed. The pressure was reduced and the product was collected below 100°/20 mm. This distillate was fractionated at atmospheric pressure. The amine, a colorless liquid boiling at 187-189°, was obtained in 58 per cent yield (32 g.). (von Alphen¹⁹² gives 187°.)

2. Preparation of 2-N,N-Dialkylaminoethylamides of Substituted Glycolic Acids.

a. Method A. It was proposed to prepare these amides by the reaction of the methyl ester of the appropriate acid and the substituted ethylene diamine according to the procedure of Phillips.¹⁷¹ A solution of 7.4 g. (0.03 m.) of methyl phenylcyclohexylglycolate and 4.4 g. (0.05 m.) of N,N-dimethylethylene diamine in 100 ml. of absolute methanol was refluxed for twenty-four hours. The methanol was removed by distilla-

tion and the residue was allowed to cool to room temperature. The glassy mass which resulted was dissolved in ether with some difficulty. After drying over anhydrous magnesium sulfate, the ether solution was cooled in an ice bath and saturated with hydrogen chloride gas. No amine hydrochloride was obtained.

When the procedure was repeated using methyl benzilate instead of the phenylcyclohexyl ester, a 24 per cent yield of the amide was obtained, compared to the yields of 90-95 per cent reported by Phillips. Apparently methyl phenylcyclohexylglycolate is less reactive in this procedure than the benzilic ester. In view of the absence of reaction with the former ester and the low yield with methyl benzilate, this method of preparation of the amides was abandoned.

b. Method B. The method of Miescher, Meisel, and Hoffmann⁶⁷ was used to obtain these amides. The preparation of 2-N-piperidinoethyl dicyclohexylglycolamide hydrochloride is typical of the procedure. Other amides prepared by this method are listed in Table XI.

2-N-Piperidinoethyl dicyclohexylglycolamide hydrochloride. A mixture of 11.0 g. (0.045 m.) of methyl benzilate and 10.1 g. (0.08 m.) of 2-N-piperidinoethylamine was refluxed for two hours. The reaction mixture was dissolved in ether, the solution extracted three times with dilute hydrochloric acid and the combined extracts made strongly basic. An oil which quickly solidified separated to give 6.2 g. (41 per cent) of a yellow orange solid. After recrystallization from ethanol, a white solid, m.p. 115-116°, was obtained. The hydrochloride, prepared by saturating an ethereal solution of the amine with hydrogen

TABLE XI

2-N,N-DIALKYLAMINOETHYLAMIDE HYDROCHLORIDES OF DISUBSTITUTED GLYCOLIC ACIDS

R R' C OH $CONHCH_2CH_2N$ R'' R''' $\cdot HCl$										
					Per Cent Yield	Melting Point °C	Analyses			
R	R'	R''	R'''	Calculated C			H	Found C	H	
8.	C ₆ H ₅	C ₆ H ₁₁	CH ₃	CH ₃	12	215 - 216	63.42	8.56	63.70	8.27
9.	C ₆ H ₅	C ₆ H ₁₁	C ₅ H ₁₀ ^a		18	222 - 223	66.21	8.73	66.18	8.63
10.	C ₆ H ₁₁	C ₆ H ₁₁	CH ₃	CH ₃	29	233 - 234	62.31	10.17	62.27	10.39
11.	C ₆ H ₁₁	C ₆ H ₁₁	C ₂ H ₅	C ₂ H ₅	50	231 - 232	64.06	10.48	63.80	10.43
12.	C ₆ H ₁₁	C ₆ H ₁₁	C ₅ H ₁₀ ^a		35	260 - 261	65.17	10.16	65.05	9.96

^aPiperidino

chloride as previously described (A.7.a), melted at 203-204°.

This hydrochloride was hydrogenated as described previously (A.7.c). The completely hydrogenated amide was a white solid, m.p. 260-261°. Six grams (35 per cent) was obtained.

Anal. Calcd. for $C_{21}H_{39}N_2O_2Cl$: C, 65.17; H, 10.16

Found: C, 65.05; H, 9.96.

C. N-Methyl Amides

1. Preparation of 2-N,N-Dialkylaminoethyl Methylamines

a. Method A. The procedure of Kermack and Wight¹⁷³ was followed.

(1) 2-N-Piperidinoethyl methylamine. A mixture of 72 g. (0.39 m.) of β -N-piperidinoethyl chloride hydrochloride, 180 g. of a saturated solution of methylamine in absolute ethanol, and 48 g. of anhydrous potassium carbonate was refluxed with stirring for two hours. The reaction mixture was diluted with water, made strongly alkaline and extracted with ether. The dried extracts were distilled to give 16 g. (29 per cent) of colorless liquid, b.p. 185-190°. The dipicrate, prepared by the usual procedure, melted at 175-176° after recrystallization from ethanol. (Kermack and Wight¹⁷³ give the boiling range as 190-200°. They give 174° as the melting point of the dipicrate.)

(2) 2-N,N-Diethylaminoethyl methylamine. This compound was prepared by an analogous procedure from 66 g. (0.39 m.) of β -N,N-diethylaminoethyl chloride hydrochloride. The substituted ethylene diamine was a colorless liquid, b.p. 157-167°. There was obtained 8 g. (16 per cent). (Kermack and Wight¹⁷³ give the boiling range as 157-

160°.)

b. Method B. The method of Damiens¹⁷⁴ was used.

(1) 2-N,N-Diethylaminoethyl methylamine. In a pressure bottle equipped with a thermometer and a stopcock were placed 61 g. (0.45 m.) of β -N,N-diethylaminoethyl chloride and 270 ml. of 40 per cent aqueous methylamine solution. After the stopcock was closed, the bottle was shaken on a mechanical shaker. The temperature rose to 50°, at which point the stopcock was opened to release the pressure which had developed. The reaction was allowed to proceed with continued shaking until the temperature had returned to that of the room. When the solution had been made strongly basic, an organic layer separated. The alkaline mixture was extracted three times with ether and the dried extract was fractionated using a two-foot helix-packed column. The product was a colorless liquid, b.p. 152-154°/740 mm. (Kermack and Wight¹⁷³ give 157-160°.) There was obtained 18 g. (31 per cent).

(2) 2-N-Piperidinoethyl methylamine. This compound was prepared by an analogous procedure from β -N-piperidinoethyl chloride. The colorless liquid was collected from 187-192°/740 mm. (Kermack and Wight¹⁷³ give 190-200°.) The amine was obtained in 30 per cent yield.

(3) 2-N,N-Dimethylaminoethyl methylamine. This amine was prepared by an analogous procedure in 27 per cent yield. The material distilled at 115-117°. (Damien¹⁷⁴ gives the boiling range as 115-117°.)

2. Preparation of Acid Chlorides

The acid chlorides were prepared from the acid and phosphorus pentachloride by the method of King and Holmes.¹⁷²

a. α,α -Diphenyl- α -chloroacetyl chloride. In a flask which was immersed in an ice bath were placed 38 g. (0.18 m.) of phosphorus pentachloride and 20 g. (0.088 m.) of benzilic acid. The contents were mixed thoroughly. After two to three minutes a vigorous reaction began. When this reaction had ceased, the flask was heated to 100° for fifteen minutes. Phosphoryl chloride was distilled from the flask under reduced pressure produced by a water aspirator and the residue was poured into ice and water. This mixture was stirred vigorously until the organic material solidified. The cream colored solid was collected on a filter. It was dissolved in ligroin without heating. The ligroin solution was rapidly dried over anhydrous magnesium sulfate and then distilled under reduced pressure until about one-third of the original volume remained. This residue was chilled in an ice-water bath. There was obtained 11 g. (46 per cent) of the acid chloride, a white crystalline solid, m.p. 47-49°. (King and Holmes¹⁷² give 48.5-49.5°; Billman and Hidy¹⁰⁶, 50-51°.)

b. Attempted preparation of α -Phenyl- α -cyclohexyl- α -chloroacetyl chloride. The preparation of this substituted acetyl chloride was attempted by an analogous procedure starting with phenylcyclohexylglycolic acid. A brown liquid product, presumed to be the acid chloride, was obtained in 40 per cent yield. Distillation of this under reduced pressure gave a light yellow liquid, b.p. 136-139°/3 mm.

Because of difficulties which arose in obtaining correct analyses of the compounds prepared from this acid chloride, it was suspected that the compound was not α -phenyl- α -cyclohexyl- α -chloroacetyl chloride. A sample of the acid chloride was prepared by heating the acid with an excess of thionyl chloride. After removing the excess thionyl chloride by distillation under reduced pressure, the residue was divided into two portions, one of which was distilled. Both portions showed positive tests for unsaturation as evidenced by the decoloration of permanganate solutions and bromine solutions. A *p*-toluidide was prepared from the acid chloride by standard procedures. After four recrystallizations from ethanol-water, it still melted over a range, from 145-152°. Since it was apparent that the product was not the desired acid chloride, this method of preparation of the phenylcyclohexylglycolamides was abandoned.

c. Attempted preparation of α,α -dicyclohexyl- α -chloroacetyl chloride. The preparation of this compound was attempted by the procedure of (C.2.a) starting with dicyclohexylglycolic acid. The brown liquid product, presumed to be the acid chloride, was obtained in 68 per cent yield. Because of possible dehydrohalogenation, it was not distilled but was used in the crude state. Difficulty in obtaining pure compounds was also observed with this acid chloride. In view of the results with phenylcyclohexylglycolic acid, it seems probable that the material obtained in this reaction was not the desired acid chloride.

d. Attempted preparation of α,α -(*p,p'*-dimethoxyphenyl)- α -chloroacetyl chloride. All attempts to prepare this compound by the procedure of (C.2.a) were unsuccessful, a tarry material being obtained in each case. Several attempts to prepare the compound by treatment of

the acid with thionyl chloride or a benzene solution of thionyl chloride were also unsuccessful.

3. Preparation of 2-N,N-Dialkylaminoethyl Methyamides of Substituted Glycolic and Acetic Acids

a. Method A. These compounds were obtained by the method of Krapcho, Turk, and Pribyl.⁷¹ The preparation of 2-N-piperidinoethyl methylbenzylamide hydrochloride, which is typical, will be described. Other amides which were obtained by this procedure are listed in Table XII.

2-N-Piperidinoethyl methylbenzylamide hydrochloride. A solution of 2.3 g. (0.0085 m.) of α , α -diphenyl- α -chloroacetyl chloride in 6 ml. of hexane and 4 ml. of benzene was maintained at 20-30° during the dropwise addition of a solution of 1.18 g. (0.0083 m.) of 2-N-piperidinoethyl methylamine in 2 ml. of benzene. A heavy white precipitate formed during this addition. After the amine had been added, the mixture was stirred for one hour at room temperature, refluxed for one hour, cooled and treated with water. After the mixture had been stirred for a few minutes, all of the solid had gone into solution. The layers were separated and the organic layer was extracted with dilute hydrochloric acid. The aqueous extracts were combined, washed with ether, and heated on a steam bath for ten minutes to hydrolyze the α -chloro group. The solution was made strongly basic and extracted with ether. The dried solution was saturated with hydrogen chloride gas as described previously (A.7.a).. There was obtained 1.5 g. (47 per cent) of a white solid, m.p. 215-217°. Recrystallization was performed by dissolving

TABLE XII

2-N,N-DIALKYLAMINOETHYLMETHYLAMIDE HYDROCHLORIDES OF SUBSTITUTED ACETIC ACIDS

$ \begin{array}{c} \text{R} \quad \text{X} \quad \text{CH}_3 \\ \diagdown \quad \quad / \\ \text{C} - \text{CON} - \text{CH}_2\text{CH}_2\text{N} \\ \diagup \quad \quad \quad \diagdown \quad \diagup \\ \text{R}' \quad \quad \quad \text{R}'' \quad \text{R}''' \end{array} \cdot \text{HCl} $											
	R	R'	R''	R'''	X	Per Cent Yield	Melting Point °C	Analyses			
								Calculated C	H	Found C	H
13.	C ₆ H ₅	C ₆ H ₅	CH ₃	CH ₃	OH	26	272-274 ^b	65.41	7.22	65.28	7.29
14.	C ₆ H ₅	C ₆ H ₅	C ₅ H ₁₀ ^a		OH	46	226-227 ^c	67.94	7.52	68.01	7.28
15.	C ₆ H ₅	C ₆ H ₁₁	CH ₃	CH ₃	H	89	206-207	67.34	9.22	67.23	9.38
16.	C ₆ H ₅	C ₆ H ₁₁	C ₅ H ₁₀ ^a		H	85	208-209	69.71	9.31	68.85	9.34

^aPiperidino^bKrapcho, Turk and Pribyl⁷¹ give 252-253°.^cKrapcho, Turk and Pribyl⁷¹ give 212-214°.

the compound in hot ethanol, adding sufficient anhydrous ether to produce cloudiness, and chilling. This gave fine white needles, m.p. 226-227°. (Krapcho, Turk and Pribyl⁷¹ give 212-214°.)

Anal. Calcd. for C₂₂H₂₉N₂O₂Cl: C, 67.94; N, 7.52

Found: C, 68.01; H, 7.28.

b. Method B. Since it was not possible to obtain pure α -phenyl- α -cyclohexyl- α -chloroacetyl chloride, the synthesis of the phenylcyclohexylglycolamides by the previously described ester interchange method (B.2.a) was attempted. Equimolar amounts of methyl phenylcyclohexylglycolate and the substituted ethylene diamine were refluxed in a variety of solvents but only trace amounts of the hydrochloride could be obtained. The solvents used were: isopropyl alcohol, excess amine, toluene, xylene, and cyclohexanone. In view of the extremely poor yields, the method of preparation was not pursued further.

c. Attempted preparation of phenylcyclohexylglycolamides.

Prior to the discovery that the compound presumed to be α -phenyl- α -cyclohexyl- α -chloroacetyl chloride was evidently not what it had been thought to be, two amides were prepared by the procedure described in Method A. The fact that it was not possible to obtain a correct analysis for these compounds helped to lead to the closer study of the purity of the intermediate acid chloride.

(1) 2-N-Piperidinoethyl methylphenylcyclohexylglycolamide.

The hydrochloride was obtained in 57 per cent yield as a white solid, m.p. 192-193°.

Anal. Calcd. for $C_{22}H_{35}N_2O_2Cl$: C, 66.89; H, 8.93

Found: C, 68.88; H, 8.78.

(2) 2-N,N-Dimethylaminoethyl methylphenylcyclohexylglycolamide. The hydrochloride was obtained in 27 per cent yield. It was a white solid, m.p. 156-158°.

Anal. Calcd. for $C_{19}H_{31}N_2O_2Cl$: C, 64.30; H, 8.81

Found: C, 60.42; H, 8.59.

d. Attempted reduction to dicyclohexylglycolamides. The reduction of the benzilamides was attempted using platinum oxide as previously described (A.7.c). The resulting products did not give the correct analyses although the theoretical amount of hydrogen appeared to have been consumed. Even after repeated exhaustive hydrogenations, the compounds gave analyses which were high in carbon and low in hydrogen.

(1) 2-N-Piperidinoethyl methyldicyclohexylglycolamide. The hydrochloride was a white solid, m.p. 241-242°.

Anal. Calcd. for $C_{22}H_{41}N_2O_2Cl$: C, 65.89; H, 10.31

Found: C, 66.41; H, 8.74.

(2) 2-N,N-Diethylaminoethyl methyldicyclohexylglycolamide. The hydrochloride was a white solid, m.p. 177-178°.

Anal. Calcd. for $C_{21}H_{41}N_2O_2Cl$: C, 64.83; H, 10.62

Found: C, 65.70, 65.91; H, 8.78, 8.92.

D. Thiol Esters

1. Preparation of 2-N,N-Dialkylaminoethyl Isothiouronium Chloride Hydrochlorides

The procedure of Albertson and Clinton⁷² was followed for the preparation of these compounds.

a. 2-N,N-Diethylaminoethyl isothiouronium chloride hydrochloride.

To a refluxing solution of 15.7 g. (0.207 m.) of thiourea in 50 ml. of absolute ethanol was added over a period of one and one-half hours a slurry of 35.2 g. (0.205 m.) of β -N,N-diethylaminoethyl chloride hydrochloride in 100 ml. of ethanol. The solution was refluxed for six hours, cooled and diluted with 200 ml. of ethyl acetate and 50 ml. of ligroin. There was obtained 46 g. (90 per cent) of a white solid, m.p. 183-185°. (Albertson and Clinton⁷² give 194-195°.)

b. 2-N,N-Dimethylaminoethyl isothiouronium chloride hydrochloride.

This compound was prepared by an analogous procedure in 60 per cent yield. It was a white solid, m.p. 184-186°. (Renshaw, Dreisbach, Ziff and Green¹⁹³ give 181-182°.)

c. 2-N-Piperidinoethyl isothiouronium chloride hydrochloride.

The reaction of thiourea and β -N-piperidinoethyl chloride hydrochloride gave a 60 per cent yield of white solid, m.p. 223-226°. (Clinton, Salvador, Laskowski, and Suter¹⁹⁴ give 225-225.5°.)

2. Preparation of 2-N,N-Dialkylaminoethanethiols

The substituted thiols were prepared by alkaline hydrolysis of the analogous isothiouronium compounds. A calculated amount of the

2-N,N-dialkylaminoethyl isothiuronium chloride hydrochloride was dissolved in a small amount of water and an excess of 40 per cent aqueous sodium hydroxide solution was added. The solution was extracted three to four times with ether and discarded. The dried ether extracts were used immediately in the preparation of the thiol esters.

3. Preparation of 2-N,N-Dialkylaminoethyl Thiolbenzilate Hydrochlorides

The procedure of Kolloff, Hunter, Woodruff, and Moffett⁷⁸ was followed. The preparation of 2-N,N-diethylaminoethyl thiolbenzilate hydrochloride is typical. Other thiol esters prepared by this method are listed in Table XIII.

2-N,N-Diethylaminoethyl thiolbenzilate hydrochloride. The ether extract from the decomposition of 25 g. (0.1 m.) of 2-N,N-diethylaminoethyl isothiuronium chloride hydrochloride was added dropwise to a cooled (ice-bath) solution of 22 g. (0.083 m.) of α, α -diphenyl- α -chloroacetyl chloride in 100 ml. of benzene. After the addition, the reaction mixture was refluxed for three hours. The white solid was filtered and dried. The crude 2-N,N-diethylaminoethyl 1,1-diphenyl-1-chlorothioglycolate hydrochloride weighed 12.9 g. and melted at 145-150°. The compound was recrystallized from hot methyl ethyl ketone by the addition of sufficient ether to produce cloudiness. The chilled solution gave white crystals, m.p. 153-155°. (Morrison and Königstein⁷⁹ give 160°.)

Twelve grams of this compound was dissolved in very dilute hydrochloric acid and heated on a steam bath for five minutes to hydrolyze the alpha chloro group. Ice was added and the thoroughly cooled solu-

TABLE XIII

2-N,N-DIALKYLAMINOETHYL THIOLBENZILATE HYDROCHLORIDES

$ \begin{array}{c} \text{C}_6\text{H}_5 \quad \text{OH} \\ \diagdown \quad \diagup \\ \text{C} - \text{COSCH}_2\text{CH}_2\text{N} \begin{array}{l} \text{R} \\ \text{R}' \end{array} \cdot \text{HCl} \\ \diagup \quad \diagdown \\ \text{C}_6\text{H}_5 \end{array} $								
		Per Cent Yield	Melting Point °C	Analyses				
R	R'			Calculated		Found		
				C	H	C	H	
17.	CH ₃	CH ₃	7	153-154	61.46	6.30	61.22	6.45
18.	C ₂ H ₅	C ₂ H ₅	23	138-139	63.21	6.90	63.31	6.90
19.	C ₅ H ₁₀ ^a		17	185-187	64.34	6.69	64.06	6.47

^aPiperidino

tion was made basic with solid sodium carbonate. The free base was a white solid, m.p. 108-110°. (Morrison and Königstein⁷⁹ give 111-112°.) It weighed 9.5 g.

Without further purification this solid was dissolved in ether. The hydrochloride was prepared as described previously (A.7.a). It was an oil which crystallized after heating with ethyl acetate. Recrystallization was performed by dissolving the compound in hot acetonitrile, adding sufficient ethyl acetate to produce slight cloudiness, and chilling the solution. This operation was carried out three times. The thiol ester was then recrystallized from hot ethanol by adding anhydrous ether until the solution became cloudy, and chilling the solution. It was then recrystallized two more times from acetonitrile as described above. The thiol ester hydrochloride was obtained in the form of small, white needles, m.p. 138-139°.

Anal. Calcd. for $C_{20}H_{26}NO_2SCl$: C, 63.21; H, 6.90

Found: C, 63.31; H, 6.90.

E. Ketones

1. Preparation of 1,1-Diphenyl-1-hydroxypropanone-2

a. Method A. In a 1-l. three-necked flask containing 280 ml. of sodium-dried toluene was placed 6.9 g. (0.3 m.) of sodium cut into small pieces. The flask was heated with stirring until the sodium had melted and formed small globules. Then 17.6 ml. of absolute ethanol was added in small portions. When the reaction of the sodium was completed, 48.4 g. (0.2 m.) of methyl benzilate was added, followed by

35.2 g. (0.4 m.) of dried ethyl acetate. The mixture was refluxed with stirring for twenty-four hours. The toluene was then removed by distillation and the residue heated with an excess of sulfuric acid (1:2) for one hour to decompose the keto ester. This mixture was extracted with ether. The dried extracts were distilled. Two fractions were collected, one boiling at 147-167°/27 mm. and another at 177-185°/30 mm. The combined viscous, orange liquids were redistilled through a Vigreux column. The material which distilled at 110-120°/17 mm. was collected. This weighed 25.0 g. (55 per cent). An oxime was prepared from this liquid by standard procedures. The compound was recrystallized from hot ethanol by adding water until the solution became slightly cloudy. The oxime then precipitated from the cooled solution. After several recrystallizations in this manner, the white small needles melted at 145-146°. (Temnikova¹⁹⁵ gives 159-160°; Stevens and Sherr¹⁷⁶ give 161-162°.)*

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27

Found: C, 74.90; H, 6.08.

b. Method B. The procedure of Cason¹⁷⁷ was followed. A Grignard reagent was prepared from 2.4 g. (0.1 m.) of magnesium turnings and ex-

*When this material was used in the Mannich reaction, no amino-ketone was obtained. This prompted the search for an alternate method of preparation of the substituted propanone. This work was done in the early stages of the research when optimum conditions for the Mannich reaction had not been worked out. It is possible that, in spite of the differences in the melting points of the oximes, the compound prepared by this reaction was indeed, as the analysis indicates, 1,1-diphenyl-1-hydroxypropanone-2 and that failure of the Mannich reaction was due to the use of incorrect reaction conditions.

cess methyl iodide. To the cooled (ice-bath) solution was added 9.2 g. (0.05 m.) of anhydrous cadmium chloride during five minutes. The mixture was stirred under reflux for thirty minutes until a Gilman test¹⁹⁵ for the Grignard reagent was negative. The ether was distilled to near dryness, 65 ml. of benzene was added, and the solution was again distilled to near dryness. After the addition of 120 ml. of benzene, the solution was heated to boiling. Without external heating, 26.5 g. (0.1 m.) of α, α -diphenyl- α -chloroacetyl chloride in 30 ml. of benzene was added as rapidly as was consistent with control of the exothermic reaction. The solution was stirred under reflux for two hours, after which the complex was decomposed with ice and dilute sulfuric acid. The aqueous layer was separated and extracted with benzene. The combined organic solutions were washed with water, 5 per cent sodium carbonate solution, and water. The benzene was distilled from the dried solution. The residue was a dark viscous liquid which would not distil below 200°/20 mm. It did not form a 2,4-dinitrophenylhydrazone or oxime.

The reaction was repeated using the same procedure except that the dimethyl cadmium solution was cooled in an ice bath during the addition of the acid chloride. Again no ketonic material was obtained. This method of preparation was therefore abandoned.

c. Method C. The procedure of Stevens and Sherr¹⁷⁶ was employed to obtain the substituted acetone.

(1) Ethyl pyruvate. Two hundred grams (2.3 m.) of pyruvic acid was esterified with 165 g. (3.6 m.) of absolute ethanol without

the aid of the usual inorganic acid catalyst by adding 400 ml. of benzene to the reaction mixture and using a water separator to eliminate the water formed in the reaction. A reflux period of twenty hours was required to remove the major portion of the water. The benzene and excess ethanol were removed by distillation at atmospheric pressure. The residue was distilled under reduced pressure to give 161 g. (61 per cent) of ethyl pyruvate, b.p. 63-64°/35 mm.

(2) Ethyl α,α -Diethoxypropionate. In a 1-l. flask equipped with a reflux condenser and a calcium chloride drying tube were placed 333 g. (2.25 m.) of redistilled ethyl orthoformate, 276 g. (6 m.) of absolute ethanol, 156 g. (1.35 m.) of ethyl pyruvate and 15 drops of concentrated sulfuric acid. The mixture was allowed to stand at room temperature for twenty-four hours. It was then refluxed for eight hours. The organic material was removed from the acid catalyst by distillation, using a minimum of heat, at reduced pressure, first by the use of a water aspirator and finally a vacuum pump. The distillate was fractionated to give 215 g. (84 per cent) of a colorless liquid, b.p. 84-88°/18 mm. (Stevens and Sherr¹⁷⁶ give 93-94°/26 mm.)

(3) 1,1-Diphenyl-2,2-diethoxypropanol-1. In a 5-l., three-necked flask equipped with a reflux condenser, calcium chloride drying tube, stirrer, and dropping funnel were placed 83 g. (3 m.) of magnesium turnings and sufficient anhydrous ether to cover them. Through the dropping funnel was added 502 g. (3.2 m.) of bromobenzene in 550 ml. of ether. The solution was added at such a rate that gentle refluxing took place. This required two hours. After refluxing for three additional hours, the contents of the flask were cooled

in an ice bath and 240 g. (1.3 m.) of ethyl α,α -diethoxypropionate in 300 ml. of ether was added dropwise over two hours. After a two-hour reflux period, the flask was allowed to cool to room temperature. The complex was hydrolyzed by the slow addition of four 200-ml. portions of saturated aqueous ammonium chloride solution. The ether layer was separated and the aqueous layer was extracted twice with ether. The dried extracts were distilled. Two fractions were collected, one of 124 g., b.p. $70-140^{\circ}/2$ mm. and a second of 134 g. (35 per cent), b.p. $140-165^{\circ}/2$ mm. (Stevens and Sherr¹⁷⁵ give $130-160^{\circ}/1$ mm. as the boiling range.) Both fractions partially crystallized. Fraction two gave small crystals, m.p. $68-70^{\circ}$. (Stevens and Sherr¹⁷⁶ give $73-74^{\circ}$.)

(4) 1-1-Diphenyl-1-hydroxypropanone-2. Five grams (0.017 m.) of 1,1-diphenyl-2,2-diethoxypropanol-1 was refluxed for three hours with a mixture of 100 ml. of 95 per cent ethanol and 100 ml. of 1:1 hydrochloric acid. The solvent was removed by distillation under reduced pressure (2 mm.) at room temperature. The receiver was cooled in a "Dry Ice"-acetone bath. A brownish white solid residue was left, m.p. $47-50^{\circ}$. Recrystallization from ether and from acetone (with cooling in a "Dry Ice"-acetone bath) gave 2.0 g. (50 per cent) of a white solid, m.p. $60-61^{\circ}$. (Stevens and Sherr¹⁷⁶ give $66-67^{\circ}$; Temnikova¹⁹⁵, $65-66^{\circ}$.) Additional ketone could be obtained from the filtrate by further chilling. The oxime, prepared by standard procedures, melted at $157-158^{\circ}$ after recrystallization from ethanol-water as described in E.l.a. (Temnikova¹⁹⁵ gives $159-160^{\circ}$; Stevens and Sherr¹⁷⁶, $161-162^{\circ}$.)

d. Method D. The procedure of Tegner¹⁷⁸ for the preparation of methyl ketones was followed.

Finely cut lithium wire (6.9 g., 1.0 m.) in 300 ml. of anhydrous ether was treated during the introduction of a small flow of nitrogen gas with 5 ml. of methyl iodide. The mixture was heated gently until it began to reflux. The heating was stopped and the remainder of 71 g. (0.5 m.) of methyl iodide in 300 ml. of anhydrous ether was added dropwise at such a rate that gentle reflux was maintained. After this addition, the mixture was refluxed for one hour longer and allowed to cool to room temperature.

In a flask equipped with a stirrer, reflux condenser, dropping funnel, and nitrogen inlet tube was placed 25 g. (0.11 m.) of benzilic acid in 300 ml. of ether. The solution of methyl lithium was added to this at such a rate that reflux was maintained. Following the addition, the mixture was refluxed for thirty minutes longer and allowed to cool to room temperature. Fifty milliliters of water was added slowly to hydrolyze the complex. After the vigorous reaction had subsided, an additional 450 ml. of water was added and the layers were separated. The ether layer was washed with water, dried, and the ether removed by evaporation. No residue was found. After acidification of the aqueous extract, the original benzilic acid could be recovered quantitatively.

e. Method E. (1) Amyl nitrite. The method of Vogel¹⁹⁷ was used.

A 1-l., three-necked flask was equipped with a stirrer, a thermometer, and a separatory funnel with the stem extending to the bottom

of the flask. The flask was placed in a salt-ice bath and a solution of 117 g. of potassium nitrite in 375 ml. of water was added. When the temperature of the stirred solution had fallen to 0° , a mixture of 25 ml. of water, 62.5 g. of concentrated sulfuric acid, and 110 g. (1.25 m.) of n-amyl alcohol (cooled previously to 0°) was added slowly through the separatory funnel. The rate of addition was controlled so that the temperature was maintained at $0 \pm 1^{\circ}$. The reaction mixture was allowed to stand for one and one-half hours and then was filtered from the precipitated sodium sulfate. The upper yellow organic layer was separated, washed with a solution containing 1 g. of sodium bicarbonate and 12.5 g. of sodium chloride in 50 ml. of water, and dried. The crude n-amyl nitrite was distilled at atmospheric pressure to give 112 g. (59 per cent) of a clear yellow liquid, b.p. 104° . (Vogel¹⁹⁷ gives 104° .)

(2) Isonitrosopropiophenone. The procedure of Hartung and Crossley¹⁹⁸ was followed.

In a 3-l., three-necked flask equipped with a reflux condenser, a stirrer, a dropping funnel, and a gas delivery tube extending below the surface of the liquid was placed a solution of 258 g. (1.9 m.) of propiophenone in 1300 ml. of ether. The stirrer was started and hydrogen chloride gas was introduced at the rate of 6-10 bubbles per second. Amyl nitrite (224 g., 2.2 m.) was added slowly from the dropping funnel. The solution became a deep red-brown and began to reflux after about fifteen minutes. The rate of addition of the nitrite was adjusted so that the ether continued to reflux gently. It required about two hours to complete the addition. During this time the solu-

tion turned a clear yellow. After all the amyl nitrite had been added, stirring and addition of hydrogen chloride gas was continued for another thirty minutes. The reaction mixture was allowed to stand overnight. It was then extracted repeatedly with 250-ml. portions of 10 per cent aqueous sodium hydroxide until the extracting medium remained practically colorless. This required five portions of the base. The combined alkaline extracts were poured slowly with vigorous stirring into a mixture of 375 ml. of concentrated hydrochloric acid in 500 g. of ice. The crystals of isonitrosopropiophenone were filtered and dried. Recrystallization from toluene yielded white crystals, m.p. 108-109°. (Hartung and Crossley¹⁹⁸ give 112-113°.) These weighed 222 g. (72 per cent).

(3) 1,1-Diphenyl-1-hydroxy-2-propanone oxime. A Grignard reagent was prepared from 38 g. (1.6 m.) of magnesium turnings and 273 g. (1.7 m.) of bromobenzene by the procedure described previously (E.l.c(3)). To this was added an ethereal solution of 81.5 g. (0.5 m.) of isonitrosopropiophenone at such a rate that gentle reflux was maintained. This required one hour. The reaction mixture was refluxed for an additional hour and then poured into ice and dilute sulfuric acid. The ether layer was separated and extracted several times with 10 per cent aqueous sodium hydroxide. The combined alkaline extracts were added to a mixture of ice and hydrochloric acid. The white solid was filtered and dried to give 75 g. (62 per cent) of the oxime, m.p. 158-160°. (Temnikova¹⁹⁵ gives 159-160°; Stevens and Sherr¹⁷⁶, 161-162°.)

(4) Hydrolysis of the oxime. Several different attempts to hydrolyze the oxime to the corresponding ketone were made. These are summarized below.

(a) Ten grams of the oxime were heated on a steam bath for two hours with 8 ml. of concentrated hydrochloric acid and 8 ml. of 40 per cent formalin solution. A black solid which was insoluble in water or ether was obtained.

(b) An alcoholic solution of the oxime was heated with an excess of 40 per cent formalin. The starting material was recovered unchanged.

(c) A dilute acidic suspension containing 10 g. of the oxime was steam distilled. A black oily residue was obtained. No material could be recovered from the distillate.

(d) The oxime was heated with dilute hydrochloric acid for one-half hour. A black oil was obtained.

(e) The oxime was heated with an excess of 40 per cent formalin solution. The unchanged starting material was recovered.

f. Method F. The procedure of Stevens and Lenk¹⁷⁹ was employed.

(1) 1,1-Diphenylpropanone-2. This product was prepared by the method of Schultz and Mickey.¹⁹⁹ In a 3-l. flask equipped with stirrer, dropping funnel, and reflux condenser were placed 148 g. (1.1 m.) of phenylacetone and 800 ml. of dry, thiophene-free benzene. To the vigorously stirred solution was added dropwise over a period of one hour 180 g. (1.12 m.) of bromine. After the addition, a rapid stream of dry nitrogen was passed through the solution by means of an inlet tube which replaced the dropping funnel. This was continued un-

til no more hydrogen bromide fumes could be detected (three hours). The benzene solution of 1-phenyl-1-bromopropanone-2 was transferred to a 1-l. separatory funnel.

Into the original flask were placed 300 g. (2.24 m.) of anhydrous aluminum chloride and 600 ml. of dry, thiophene-free benzene. The stirred solution was heated to gentle reflux and the solution of 1-phenyl-1-bromopropanone-2 was added dropwise over a period of two hours. After the addition, the almost black reaction mixture was refluxed for an additional hour, cooled and poured with stirring onto 2 kg. of ice and 400 ml. of concentrated hydrochloric acid. After the ice had melted, the benzene layer was separated, the aqueous layer was extracted twice with ether, and the combined organic solutions washed with water and with a saturated aqueous solution of sodium bicarbonate. After drying for one hour over anhydrous magnesium sulfate, the solvents were distilled under reduced pressure produced by a water aspirator. The residue was distilled under reduced pressure to give 134 g. (58 per cent) of orange liquid, b.p. 132-136°/0.6 mm. This was triturated with low-boiling petroleum ether and chilled to give 117.5 g. of white solid, m.p. 58-60°. (Schultz and Mickey¹⁹⁹ give 60-61°.) Material of this purity was used in the subsequent reactions.

(2) 1,1-Diphenyl-1-bromopropanone-2. This was prepared by the direct bromination of 1,1-diphenylpropanone-2. A solution of 34 g. (0.162 m.) of 1,1-diphenylpropanone-2 in 250 ml. of dry carbon tetrachloride was cooled with vigorous stirring to -15° with a "Dry Ice"-acetone bath. To the solution was added dropwise 25.9 g. (0.162 m.)

of bromine. The resulting solution was stirred for an additional hour at this temperature. The solvent was removed by distillation under reduced pressure. The dark liquid residue was dissolved in low-boiling petroleum ether. With some difficulty, a solid product was obtained by cooling the solution in a "Dry Ice"-acetone bath and vigorously stirring the liquid which separated. The crude ketone (30 g., 64 per cent) was a light tan solid, m.p. 49-50°. (Stevens and Lenk¹⁷⁹ give 55-56° as the melting point of the pure product.) The bromo-compound was hydrolyzed without further purification.

(3) 1,1-Diphenyl-1-hydroxypropanone-2. This product was prepared by hydrolysis of the bromoketone. A solution of 30 g. (0.104 m.) of 1,1-diphenyl-1-bromopropanone-2 in 430 ml. of 1,4-dioxane and 100 ml. of water was refluxed for three hours. The solvents were removed by distillation under reduced pressure produced by a water aspirator. The residue was dissolved in low boiling petroleum ether. The crude ketone, 20 g., (84 per cent) was obtained by chilling the solution in a "Dry Ice" bath and vigorously stirring the liquid which separated. A portion of this was recrystallized from ligroin to give small white needles, m.p. 58-60°. A mixed melting point with an authentic sample of 1,1-diphenyl-1-hydroxypropanone-2 showed no depression. A similar mixed melting point with 1,1-diphenylpropanone-2 showed a marked depression.

2. Preparation of 1,1-Diphenyl-1-hydroxy-4-N,N-dialkylaminobutanone-2 Hydrochlorides

A modification of the procedure of Zaugg, Freifelder, and Horrom¹¹⁶ was used to prepare these ketones by a Mannich reaction. The preparation of 1,1-diphenyl-1-hydroxy-4-dimethylaminobutanone-2 hydrochloride is typical and will be described. Other aminoketones are listed in Table XIV.

(a) 1,1-Diphenyl-1-hydroxy-4-dimethylaminobutanone-2 hydrochloride.

A mixture of 5.3 g. (0.02 m.) of 1,1-diphenyl-1-hydroxypropanone-2, 2.4 g. (0.03 m.) of dimethylamine hydrochloride, and 1.6 g. of paraformaldehyde in 30 ml. of *n*-octyl alcohol was refluxed for ten minutes. Then a further 1.6 g. of paraformaldehyde was added in small portions over thirty minutes with continued refluxing. After the addition was complete, 0.3 ml. of concentrated hydrochloric acid was added and the mixture was refluxed for an additional five minutes. The mixture was extracted with water and with dilute hydrochloric acid. The combined extracts were made basic with sodium carbonate. The oil which separated was extracted with two portions of ether. These extracts were washed with water until the washings were neutral. The dried ethereal solution was saturated with hydrogen chloride gas while cooled in an ice bath. There was obtained 1.2 g. (19 per cent) of a white solid, m.p. 152-156°. Two recrystallizations were performed by dissolving the hydrochloride in hot ethanol, adding anhydrous ether until the solution became cloudy, and chilling. This gave white crystals, m.p. 163.5-165°.

Anal. Calcd. for C₁₈H₂₂NO₂Cl: C, 67.60; H, 6.94

Found: C, 67.74; H, 6.73.

TABLE XIV

SUBSTITUTED 4-N,N-DIALKYLAMINOBUTANONE-2 HYDROCHLORIDES

$\begin{array}{c} \text{R} \quad \text{X} \\ \diagdown \quad / \\ \text{C} \text{---} \text{COCH}_2\text{CH}_2\text{N} \begin{array}{l} \text{R}'' \\ \diagup \quad \diagdown \\ \text{R}''' \end{array} \cdot \text{HCl} \\ / \\ \text{R}' \end{array}$											
	R	R'	R''	R'''	X	Per Cent Yield	Melting Point °C	Analyses			
								Calculated		Found	
								C	H	C	H
20.	C ₆ H ₅	C ₆ H ₅	CH ₃	CH ₃	OH	19	163.5 - 165	67.60	6.94	67.75	6.75
21.	C ₆ H ₅	C ₆ H ₁₁	CH ₃	CH ₃	H	22	181.5 - 182	69.76	9.11	69.96	8.95
22.	C ₆ H ₅	C ₆ H ₁₁	C ₅ H ₁₀ ^a		H	25	214 - 215	72.06	9.22	71.85	9.09

^aPiperidino

(b) 1,1-Diphenyl-1-hydroxy-4-N-piperidinobutanone-2 hydrochloride.

Several attempts to prepare this compound were made. The products obtained did not possess the correct composition as indicated by elemental analyses.

Anal. Calcd. for $C_{21}H_{26}NO_2Cl$: C, 70.08; H, 7.28

Found: C, 65.93, 61.08, 57.01, 59.21; H, 7.65, 8.32, 9.03, 9.58.

The melting points of the samples were 166-167°, 168-169°, 168-169°, and 199-200°, respectively. It is possible that piperidine hydrochloride was present as an impurity since mixed melting point determinations of the compound with this amine hydrochloride showed no depression.

(c) 1,1-Diphenyl-1-hydroxy-4-N,N-diethylaminobutanone-2 hydrochloride. The only product obtained from several attempts to prepare this ketone was recovered diethylamine hydrochloride.

3. Preparation of 1-Phenyl-1-cyclohexylpropanone-2

a. Method A. Sodium isopropoxide was prepared from 18.4 g. (0.8 m.) of finely cut sodium and 600 ml. of anhydrous isopropyl alcohol. After the solution had cooled to room temperature, 107 g. (0.8 m.) of phenylacetone was added followed by the dropwise addition over thirty minutes of 143 g. (0.88 m.) of bromocyclohexane. The mixture was refluxed for two hours, during which time a white solid separated. After the addition of 250 ml. of water, the isopropyl alcohol was removed by distillation. Additional water was added as the last of the alcohol was removed. The organic layer was separated and the aqueous layer

was extracted with ether. The dried organic solutions were fractionally distilled. There was obtained 30 g. of colorless liquid, b.p. 88-90°/4 mm. The 2,4-dinitrophenylhydrazone of this liquid melted at 136-138° and showed no depression of melting point when mixed with an authentic sample of the 2,4-dinitrophenylhydrazone of phenylacetone, m.p. 137-139°. A large amount of high boiling residue was left in the distilling flask.

Alkylation under similar conditions using sodamide as alkylating agent also did not give any of the desired ketone. Since no 1-phenyl-1-cyclohexylpropanone-2 was obtained by this direct alkylation of phenylacetone, the method was abandoned and other methods of synthesis were investigated.*

b. Method B. (1) Phenylcyclohexylacetone nitrile. This was prepared by the method of Hancock and Cope.²⁰³ In a 1-l. flask were placed 200 ml. of liquid ammonia and a small crystal of hydrated ferric nitrate. To the vigorously stirred solution was added a small cube of metallic sodium. When the deep blue color had disappeared, the remainder of 8.1 g. (0.35 m.) of dry sodium was added about as rapidly as it could be cut.

The flask was cooled in a "Dry Ice"-acetone bath during the addition over a period of ten minutes of 41 g. (0.35 m.) of phenylacetone nitrile. The cooling bath was removed, after which the solution was

*The failure of this method of preparation must be in some way associated with the nature of the cyclohexyl group. The alkylation of phenylacetone with a variety of alkyl halides has been described by a number of investigators, including Tiffeneau and Levy,²⁰⁰ Levy and Jullien,²⁰¹ and Suter and Weston.²⁰² However, no one has reported alkylation of the compound using a cyclohexyl halide.

stirred for fifteen minutes. Then 200 ml. of dry toluene and 25 ml. of ether were added dropwise while the ammonia evaporated. The flask was allowed to stand overnight to permit further evaporation of the ammonia. The last traces of ammonia were removed by warming the flask until the ether had distilled over.

To the warm solution was added 65.2 g. (0.4 m.) of bromocyclohexane during a twenty minute period. The reaction mixture was refluxed for two hours, cooled and washed with 300 ml. of water. The aqueous layer was extracted with two 50-ml. portions of benzene. The combined organic layers were washed with two 50-ml. portions of water and distilled. There was obtained 33 g. (50 per cent) of phenylcyclohexylacetonitrile, a colorless liquid, b.p. 127-129°/0.7 mm. This solidified to a white crystalline material, m.p. 55-56°. (Hancock and Cope²⁰³ give 56-58°.)

(2) 1-Phenyl-1-cyclohexylpropanone-2. A modification of the procedure of Hauser and Humphlett¹⁸⁰ was used to prepare the substituted propanone. A Grignard reagent was prepared from 17.5 g. (0.72 m.) of magnesium and excess methyl iodide. To the refluxing solution of this reagent was added during a twenty minute period an ethereal solution of 33 g. (0.18 m.) of phenylcyclohexylacetonitrile. The resulting solution was refluxed for five hours. The cooled mixture was decomposed by the addition of ice and hydrochloric acid. The solution was allowed to stand overnight to insure complete hydrolysis of the water soluble ketimine intermediate. The organic layer was separated and distilled to give 13.7 g. (35 per cent) of a clear orange liquid, b.p. 140-141°/1.5 mm. The oxime was prepared by the standard method. Recrystalli-

zation was performed by dissolving the compound in hot ethanol, adding sufficient water to produce slight cloudiness, and chilling the solution. After several recrystallizations, the white solid melted at 123-124°.

Anal. Calcd. for $C_{15}H_{21}NO$: C, 77.87; H, 9.15

Found: C, 78.27; H, 9.10.

The 2,4-dinitrophenylhydrazone was prepared by the standard procedure. After several recrystallizations from ethanol, long, silky, orange needles were obtained, m.p. 155-156°.

Anal. Calcd. for $C_{21}H_{24}N_4O_4$: C, 63.62; H, 6.10

Found: C, 63.52; H, 6.15.

c. Method C. (1) Phenylcyclohexylacetyl chloride. A solution of 43.6 g. (0.2 m.) of phenylcyclohexylacetic acid in 60 ml. (0.82 m.) of thionyl chloride was refluxed for two hours. The excess thionyl chloride was removed by distillation under reduced pressure. The last traces of the compound were removed by adding dry benzene to the residue and distilling the major portion of it under reduced pressure. The residue was distilled to give 40 g. (85 per cent) of a clear yellow liquid, b.p. 136-139°/3 mm.

(2) 1-Phenyl-1-cyclohexylpropanone-2. Dimethyl cadmium was prepared as previously described (E.1.b.) from 2.9 g. (0.12 m.) of magnesium turnings, excess methyl iodide and 11 g. (0.06 m.) of anhydrous cadmium chloride. To the hot benzene solution of this reagent was added, without external heating, 26 g. (0.11 m.) of phenylcyclohexylacetyl chloride in 30 ml. of benzene. The acid chloride was added as

rapidly as was consistent with control of the exothermic reaction (about two minutes). The solution was stirred and refluxed for five hours, after which procedure the complex was decomposed with ice and dilute sulfuric acid. The aqueous layer was separated and extracted with benzene. The combined benzene solutions were washed with water, 5 per cent aqueous sodium carbonate and water and dried over anhydrous magnesium sulfate. Distillation of the solution gave a clear yellow liquid, b.p. 124-150°/4 mm. This was redistilled through a modified Claisen head to give 11.7 g. (49 per cent) of a clear yellow liquid, b.p. 132-136°/2.5 mm. The 2,4-dinitrophenylhydrazone of this liquid melted at 152-153° after recrystallization from ethanol. It showed no depression of melting point when mixed with an authentic sample of the 2,4-dinitrophenylhydrazone of 1-phenyl-1-cyclohexylpropanone-2.

4. Preparation of 1-Phenyl-1-cyclohexyl-4-N,N-dialkylaminobutanone-2 Hydrochlorides

The procedure of Wilson and Kyi¹¹⁵ for the Mannich reaction was followed. The preparation of 1-phenyl-1-cyclohexyl-4-N,N-dimethylaminobutanone-2 hydrochloride will be described. Other compounds prepared by this procedure are listed in Table XIV.

a. 1-Phenyl-1-cyclohexyl-4-N,N-dimethylaminobutanone-2 hydrochloride. A solution of 8.0 g. (0.037 m.) of 1-phenyl-1-cyclohexylpropanone-2, 4.9 g. (0.06 m.) of dimethylamine hydrochloride, 1.8 g. (0.06 m.) of paraformaldehyde, 8 drops of concentrated hydrochloric acid and 25 ml. of absolute ethanol was refluxed for sixteen hours. The solution was cooled and poured into anhydrous ether. There was

obtained 8.5 g. of white solid, m.p. 159-161°. Recrystallization from ethanol-ether gave 6.5 g. of white solid, m.p. 152-153°. This was converted to the free base by treatment with excess dilute base. The free aminoketone was extracted from the solution with ether. After drying over anhydrous magnesium sulfate, the hydrochloride was prepared in the usual way (A.7.a). This gave 2.5 g. (22 per cent) of white crystals, m.p. 177-178°. Two recrystallizations from ethanol-ether gave small, white crystals, m.p. 181.5-182°.

Anal. Calcd. for $C_{18}H_{28}NOCl$: C, 69.76; H, 9.11

Found: C, 69.96; H, 8.96.

b. 1-Phenyl-1-cyclohexyl-4-N,N-diethylaminobutanone-2 hydrochloride. The product obtained was not the desired ketone. It was a white solid, m.p. 231-232°. A mixed melting point determination with diethylamine hydrochloride showed no depression. The elemental analysis also indicated that the material was recovered diethylamine hydrochloride.

Anal. Calcd. for $C_{20}H_{32}NOCl$: C, 71.09; H, 9.55

Found: C, 46.11; H, 11.15.

5. Attempted Preparation of 1-Phenyl-1-cyclohexyl-1-hydroxypropanone-2

Five grams (0.023 m.) of 1-phenyl-1-cyclohexylpropanone-2 was dissolved in 35 ml. of carbon tetrachloride. After the solution had been cooled to -15°, 3.8 g. (0.023 m.) of bromine was added dropwise with vigorous stirring. The mixture was stirred for an additional hour. The solvent was removed by distillation under reduced pressure and the clear liquid residue (5.6 g.) was refluxed for three hours with 80 ml. of 1,4-dioxane and 20 ml. of water. This solvent mixture was also re-

moved by distillation under reduced pressure. The residue was distilled to give 3.5 g. of light orange liquid, b.p. 160-170°/5.5 mm. This was checked for unsaturation by the Baeyer and the bromine tests. Both were positive, thus indicating that at least a portion of the material was unsaturated. Since the desired ketone was not obtained or at least not in pure form, the method was abandoned.

CHAPTER IV

SUMMARY

Several compounds have been prepared in order to investigate their physiological activity. All of these are derivatives of benzilic, disubstituted glycolic and acetic acids or of the analogously substituted 2-butanones.

The following compounds were prepared in the course of this research.

- (1) 2-N,N-Dimethylaminoethyl phenylcyclohexylglycolate hydrochloride.
- (2) 2-N-Piperidinoethyl phenylcyclohexylglycolate hydrochloride.
- (3) 2-N-Piperidinoethyl phenylcyclohexylglycolate methyl bromide.
- (4) 2-N,N-Dimethylaminoethyl dicyclohexylglycolate hydrochloride.
- (5) 2-N-Piperidinoethyl dicyclohexylglycolate hydrochloride.
- (6) 2-N-Piperidinoethyl 4,4'-dimethoxybenzilate hydrochloride.
- (7) 2-N-Piperidinoethyl 4,4'-dimethoxybenzilate methyl bromide.
- (8) 2-N,N-Dimethylaminoethyl phenylcyclohexylglycolamide hydrochloride.
- (9) 2-N-Piperidinoethyl phenylcyclohexylglycolamide hydrochloride.
- (10) 2-N,N-Dimethylaminoethyl dicyclohexylglycolamide hydrochloride.
- (11) 2-N,N-Diethylaminoethyl dicyclohexylglycolamide hydrochloride.
- (12) 2-N-Piperidinoethyl dicyclohexylglycolamide hydrochloride.
- (13) 2-N,N-Dimethylaminoethylmethyl benzilamide hydrochloride.

- (14) 2-N-Piperidinoethylmethyl benzilamide hydrochloride.
- (15) 2-N,N-Dimethylaminoethylmethyl phenylcyclohexylacetamide hydrochloride.
- (16) 2-N-Piperidinoethylmethyl phenylcyclohexylacetamide hydrochloride.
- (17) 2-N,N-Dimethylaminoethyl thiolbenzilate hydrochloride.
- (18) 2-N,N-Diethylaminoethyl thiolbenzilate hydrochloride.
- (19) 2-N-Piperidinoethyl thiolbenzilate hydrochloride.
- (20) 1,1-Diphenyl-1-hydroxy-4-N,N-dimethylaminobutanone-2 hydrochloride.
- (21) 1-Phenyl-1-cyclohexyl-4-N,N-dimethylaminobutanone-2 hydrochloride.
- (22) 1-Phenyl-1-cyclohexyl-4-N-piperidinobutanone-2 hydrochloride.
- Krapcho, Turk, and Pribyl⁷¹ have reported the previous preparation of 13 and 14. However, the melting points listed by these authors differ from those found in the present work.
- The previously unreported ketone, 1-phenyl-1-cyclohexylpropanone-2, was prepared for use as an intermediate. Its oxime and 2,4-dinitrophenylhydrazone are also reported.

Incomplete preliminary pharmacological testing indicates that compound 14 is more active than atropine in preventing mortality from a standard dose of an anticholinesterase compound. Compound 2 appears to be the most active antispasmodic.

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APPENDIX

APPENDIX

2-N,N-DIETHYLAMINOETHYL METHYL PHENYLCYCLOHEXYLACETAMIDE HYDROCHLORIDE

The reaction of α -phenyl- α -cyclohexylacetyl chloride and 2-N,N-diethylaminoethyl methylamine was carried out as previously described (C.3.a). The white solid product was hygroscopic. This hydrochloride was recrystallized three times by dissolving it in ethanol, adding ether until the solution became cloudy, and chilling. Each time a white crystalline material was obtained which became gummy after it had been filtered. This material melted at 110-113°. It was recrystallized from hot acetonitrile by adding ether until cloudiness resulted and cooling. The product was again a white hygroscopic solid which melted at 110-113°. The hydrochloride was converted to the free base by treatment with aqueous base. The dried ether extract from this solution was saturated with hydrogen chloride gas while cooled in an ice bath. This material was recrystallized from hot ethanol as described above. The product was again a white crystalline material which became gummy after being exposed to the atmosphere. It melted at 110-113°. Since it was not possible to obtain a pure, non-hygroscopic material, attempts to prepare the compound were discontinued. This decision was reached too late to allow inclusion of these results in the body of the dissertation.

VITA

Thomas Alexander Magee was born on April 19, 1930 in Brookhaven, Mississippi where he attended the public schools. After his graduation from high school in May 1948, he entered Tulane University from which he received the B. S. degree in May 1952. From September 1952 until September 1954 he attended the Graduate School of Tulane University, during which time he held a graduate assistantship. The M. S. degree was awarded in May 1955. Since September 1954 he has been enrolled in the Graduate School of The University of Tennessee where he has held a research fellowship sponsored by The National Institutes of Health.

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