SOME POTENTIAL CHEMOTHERAPEUTIC AGENTS
DERIVED FROM ARALKYL KETONES

by

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INTRODUCTION*

The objective of this present study is the synthesis of certain chemical compounds each of which represents a variation from the basic structure of a chemical substance of known antibacterial activity. Also, an indication of their activity as determined by experienced bacteriologists is desirable. The three fundamental types of substances, to which all of the compounds described herein are related, are shown on page 3. All the subsequent compounds may be regarded as being derived wholly, or in part, from the general structure IV (page 4). The first group consists of compounds related to the antibiotic, chloramphenicol (I), and may be more specifically indicated by structure V. Structure VI represents, in a

*By definition, a chemotherapeutic agent is a chemical substance which incapacitates a pathogenic invading organism with a minimum detrimental effect on the host. Ehrlich (2), who originated the term chemotherapy, regarded it as the specific treatment of parasitic diseases by direct chemical attack on the causative organism.

In recent years questions have been raised concerning the validity of this term. Many have felt that a drug cannot be classified a priori as a chemotherapeutic agent, since uniqueness of action cannot be closely correlated with any given structure. Obviously, the line of demarcation between a chemotherapeutic or pharmacodynamic agent, a drug which acts on various functions of the body, often becomes thin indeed. Yet, since such a distinction has existed in the literature for nearly half a century, it appears that little would be gained by abolishing these broad traditional boundaries. When the term chemotherapy appears in the following pages, it will do so in adherence to Ehrlich's classical definition.
general way, the variations applied to the antitubercular drug, amithiozone (II). Lastly, structure VII depicts the various modifications of the structure of III, 5-dimethylamino-1-phenyl-2-penten-3-one. Previous studies in this laboratory (1) had indicated a relatively high order of antibacterial activity for III, and an extension of the work was desirable.
FUNDAMENTAL TYPES OF COMPOUNDS

Part two

Part one

I Chloramphenicol (Chloromycetin)

II Amithiozone (Tibione)

III
REPRESENTATIVE TYPES OF COMPOUNDS PROPOSED FOR SYNTHESIS

IV

\[ \text{where } n = 0 \text{ or } 1 \]

V

\[ \text{where } n = 0 \text{ or } 1 \]

VI

\[ \text{where } n = 0 \text{ or } 1 \]

VII

\[ \text{where } n = 0 \text{ or } 1 \]
HISTORICAL

TYPE V COMPOUNDS - STRUCTURES RELATED TO CHLORAMPHENICOL

Chloramphenicol (I), also called Chloromycetin, has been isolated from strains of streptomycetes occurring in soil and compost (3). The initial species of streptomycetes was isolated from a soil sample obtained from a mulched field in Venezuela. The antibiotic substance isolated by Parke, Davis and Company workers from this hitherto unknown species of streptomycetes was later obtained independently from another soil culture at the University of Illinois (4). The name *Streptomyces venezuela* was logically proposed for the newly discovered organism.

The broad antibiotic spectrum of chloramphenicol specifically embraces many diseases caused by bacteria, rickettsiae and possibly viruses. Of particular significance is its effectiveness in certain diseases, possibly of viral etiology, including primary atypical pneumonia, psittacosis and lymphogranuloma venereum; in those of rickettsial origin including Q fever, typhus and Rocky Mountain spotted fever. Chloramphenicol has revolutionized the therapeutic outlook in typhus and many other such allied diseases.

Bartz (5) first isolated in pure crystalline form the active compound found in the earlier crude culture
broth. Its structure (I), determined by Rebstock, Crooks, Controulis and Bartz (6) was found to contain features not ordinarily encountered in a natural product. Not only does it contain an aromatic nitro group but it is a substituted amide of dichloroacetic acid. The nitro group, ordinarily considered to be harmful to animal life, elicits no unfavorable effects when this antibiotic is administered in therapeutic doses. Likewise, dichloroacetic acid is a keratolytic; customarily employed for the removal of corns, warts, etc. Properly combined in the chemical structure of chloramphenicol, however, it exerts no such action.

The characterization and synthesis of chloramphenicol (7), which constituted the first practical synthesis of a clinically important antibiotic, make this compound the first antibiotic in which the relation between structure and activity could be thoroughly studied. For purposes of discussion, the skeleton of chloramphenicol may be divided into two parts (I): first, the stereochemically specific 2-acylamido propanediol side chain, which can be regarded as a grouping native to physiological systems in the same sense that penicillin is peptide-like and streptomycin is carbohydrate-like, and, secondly, the nitrobenzene grouping which is more in the nature of the classical chemotherapeutic structure.

The concept of a spatial correlation between physiolo-
cally active molecules and the substrate upon which they act was first enunciated by Pasteur, and used by him to explain the stereospecificity of enzymes. Its value in the study of drug action is now widely accepted. Both van der Waals forces and hydrogen bonding are assumed to hold the drug molecules in intimate contact with the biological structure at specific receptor sites. Any variations which disturb (a) the spatial relationship and (b) the bonding relationship between drug and receptor will consequently lead to changes in the activity of the compound.

The importance of spatial relationship is well established. Thus, L-epinephrine is 10 to 20 times more active than the D-isomer in increasing arterial blood pressure. Chloramphenicol apparently forms no exception to this rule. All four of its isomers are known. The D-threo isomer alone possesses significant activity.

One might conclude that the chloramphenicol molecule can undergo bonding with fixed receptors in the effector cells through the nitro group, the hydroxy groupings and the dichloroacetyl residue. The molar volumes of these four groupings would then assume critical importance; any variation adversely affecting the intimate contact between the drug molecule and the biological structure on which it acts would thus negate the activity of the compound. These assumptions would then lead to the obvious:
D-threo represents the optimal spatial and structural requirements for antibiotic activity in compounds of this type.

Despite the manifest inference of these conclusions, subsequent to the isolation and synthesis of chloramphenicol, interest has been shown in the preparation of various analogs. Variation of the position of the nitro group (8) as well as its actual replacement by other substituents (9) has been carried out in an effort to ascertain the particular structural features responsible for its pharmacological activity. Studies have also been reported (10) on the effect produced by the replacement of the benzene ring by another ring system. From these studies it has become evident that such high structural specificity, especially in the aromatic nucleus, is not essential for activity. Various workers (8, 9) have reported that the m- and p-nitro isomers of I and other analogs containing a halogen atom in place of the p-nitro group exhibit some activity.

In consideration of these facts, since the similarity in chemical reactivity of a compound and its vinylog is well known, it seemed of interest to prepare a vinylog of chloramphenicol. The compound of particular interest in this regard, V, possesses a vinyl group between the aromatic nucleus and the propanediol side chain.
Considering the chemotherapy of tuberculosis, these are indeed stirring times, because there is a widespread and intensive search for compounds that may prove more useful than drugs used at present in combatting this disease. Historically, tuberculosis has plagued mankind since remote antiquity, and has persisted till the present. Always, it has stood high on the list of man-killing and diseases. Today, with our modern concepts of health and sanitation, balanced diets, and "one-a-day" vitamins, tuberculosis ranks seventh among the causes of death and stands in first place as the killer of persons between the ages of 15 and 45.

It is difficult to understand and perhaps easy to underestimate the intractable nature of a tuberculosis infection, particularly in this age when almost all other forms of bacterial infection are amenable to chemotherapy. Yet, in many ways, infection by Mycobacterium tuberculosis is quite unparalleled by that of any other disease of bacterial origin. There is no short and easy cure; to be strikingly frank, there is no sure cure.

The chemotherapeutic agents now in use do not kill

*The causative agent, first isolated by Koch in 1882, is a fungus-like bacterium designated according to scientific nomenclature as Mycobacterium tuberculosis.
and eradicate the bacillus. At best, they are tuberculostats and merely arrest the progress of the disease. The influence of a drug on the course of a tuberculosis infection is a function of its intrinsic antibacterial action and accessibility to the microorganism, modified by any secondary response to the infected host. The question of the permeability of the bacterial cell is one with which all serious students of drug mechanisms must continue to be concerned. The tuberculosis organism is sensitive to a wide range of organic substances in vitro, but only a few compounds influence the organism in vivo. This suggests that perhaps accessibility is the limiting factor. It must be realized, however, that permeability of the invading bacillus tubercle does not necessarily imply permeability of the invading bacillus. Indeed, there is no direct evidence to show that the penetration of the tubercle is an essential prerequisite for tuberculostatic activity (11).

The most active group of synthetic tuberculostats known today are the thiosemicarbazones (12). The investigation into the field of thiosemicarbazones began with Domagk's (13) observation that, of the many sulfa drugs known, sulfathiazole (VIII) and sulfadiazine (IX) showed in vivo tuberculostatic activity. In an attempt to establish a relationship between structure and activity, a series of sulfathia Diazoles were prepared by Behnish
(14) through cyclization of the appropriate thiosemicarbazones to the aminothiadiazole and condensation of the heterocyclic amine with the substituted benzenesulfonyl chloride, as shown on the following page. The end-products of this series proved uninteresting; but, impressed by the similarity in structure between the aminothiadiazoles and their thiosemicarbazone precursors, Behnisch and his fellow workers tested the latter and found them to be strongly tuberculostatic.

Domagk and his coworkers (15) next reported the tuberculostatic activity of certain thiosemicarbazones in 1946, after some twenty years of searching for an effective chemotherapeutic agent to be used in the treatment of tuberculosis. Early reports of the most active agent at that time, p-acetylaminobenzaldehyde thiosemicarbazone (II) - also known as amithiozone and Tibione, indicated that it was superior to para-aminosalicylic acid in experimental animals (16), but inferior to streptomycin (17). Reports of large-scale clinical trials, which support these earlier claims of activity, are now available. Though Tibione and similar agents have not been enthusiastically received in the United States, such drugs are being widely used in other parts of the world, particularly in Europe and Africa. Some workers (18) now claim that Tibione and other related compounds, especially p-ethylsulphonylbenezaldehyde
Synthesis of Sulfathiadiazoles

\[
\begin{align*}
\text{II} & \quad \text{I} \\
\text{Sulfa thiazole} & \quad \text{Sulfadiathiazole}
\end{align*}
\]

\[
\begin{align*}
\text{Synthesis of Sulfathiadiazoles} & \\
\text{NH}_2 & \\
\text{FeCl}_3 & \\
\text{NH}_2 & \\
\end{align*}
\]

\[
\begin{align*}
\text{X} & \quad \rho - \text{Acetylbenzylthiosemicarbazide}
\end{align*}
\]

\[
\begin{align*}
\text{XI} & \quad \text{Parasorbic Acid}
\end{align*}
\]

\[
\begin{align*}
\text{XII} & \quad \text{Benzoquinone}
\end{align*}
\]
thiosemicarbazone, are more effective in treating experimental animals for tuberculosis than is streptomycin except in the most advanced stages. Mertens and Bunge (19) substantiate these claims with a review of over ten thousand cases in which Tibione has been used.

It is said (20) that Tibione possesses a non-specific inflammation retarding action with effect on the plasma colloids and normalization of the vegetative organism. The best effect is gained in intestinal, skin and bone tuberculosis. In pulmonary tuberculosis complete healing is not to be achieved, but favorable results are noted in the lesions.

Dehnisch (14) has shown that the aldehydes are inactive themselves and that thiosemicarbazide is only slightly active and highly toxic. The inference that Tibione is not split in the body and owes its activity to the intact molecule is partially confirmed by the properties of p-acetylbenzylthiosemicarbazide (X). Hydrolytic cleavage is impossible, yet some workers (14) claim the same order of activity for this compound as for Tibione itself.

Scores of variations have been made in the structure of Tibione in an effort to obtain compounds with increased activity and decreased toxicity. Most of the changes have involved the character and position of the subordinate grouping, since it was soon discovered that substitution
of the thiosemicarbazone moiety by semicarbazones, oximes, hydrazones, azines, and anils abolished activity. This, perhaps indicates the importance of the sulfur atom in this type of compound. Donovick (21) pointed out that the activity is increased by the presence of substituents in the aromatic ring, particularly those containing nitrogen, sulfur or oxygen. Positional isomerism is also important, the general order of decreasing activity being: para > meta > ortho. Of the para substituted compounds, substituents rank in the following order of activity: ethylsulphonyl = isopropyl > amino = acetylamo = dimethy lamino > nitro = sulphonyl = methoxy.

Behnisch (14) has made five general statements to sum up the work in this area.

1. The sulfur atom plays an essential role.

2. Thiosemicarbazones of aldehydes are more favorable than the corresponding ketones.

3. The aldehyde should be aromatic in character.

4. Substitution at the nitrogen atom of the thiosemicarbazide residue decreases activity.

5. Action increases with suitable ring substitution.

Hurt and Hurni (22) contradict Behnisch's earlier statement concerning the activity of p-acetylaminobenzylthiosemicarbazide (X); they state that the thiosemicarbazide residue must be conjugated with carbon-to-carbon double bonds in the ring in order for the compound to
possess significant activity. Frahm and Lembke (23) have also shown that certain \( \alpha, \beta \)-unsaturated compounds such as parasorbic acid (XI) and benzoquinone (XII) inhibit the respiration of the tuberculosis organism.

Perhaps the most striking results are yet to be seen. Girard (24) and Fox (25) have independently reported the preparation of 3-pyridinecarboxaldehyde thiosemicarbazone. Girard (26) reported that as judged by the percentage of mice, which, after initial injection with the tuberculosis organism and a following sixty-day treatment, are found free of the organism, the active drugs may be classified as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Para-aminosalicylic acid</td>
<td>0%</td>
</tr>
<tr>
<td>Sulfones</td>
<td>0%</td>
</tr>
<tr>
<td>Tibione</td>
<td>0%</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15%</td>
</tr>
<tr>
<td>Pyridine-3-aldehyde Thiosemicarbazone</td>
<td>45%</td>
</tr>
</tbody>
</table>

The last two gave reciprocal potentiation, when coadministered, of the highest order yet realized in treating tuberculosis in experimental animals.

Even more recent has been the announcement from the laboratories of E. R. Squibb and Sons and Hoffmann-LaRoche of perhaps a truly "wonder" drug for the treatment of tuberculosis. On the basis of limited clinical trials, much hope is held for the success of these drugs, which are hydrazides of isonicotinic acid, in combatting tuberculosis.

Despite these hopes, much remains to be done before
tuberculosis can be treated as casually as some of the more completely "tamed" diseases which once took a heavy toll of human life.
TYPE VII COMPOUNDS - KETONIC MANNICH BASES

Shortly after Mannich (27) first described the general application of the reaction which now bears his name, he mentioned the fact that some of the compounds prepared possessed local anesthetic action. In the intervening thirty years spasmodic interest has been taken in the pharmacological evaluation of various Mannich bases. Most recently, Denton and associates (28) have cited the preparation and some pharmacological properties of a rather extensive series of Mannich bases. To many of their compounds was credited a rather marked anti-spasmodic activity. A later publication by other workers(1) in this laboratory lists another series of Mannich bases which were screened as analgetics, for it is of general knowledge (e. g., morphine and methadone) that spasmolytic and analgetic activities are frequently present in the same molecule. Despite this fact none of these compounds demonstrated appreciable analgetic activity. However, since Schraufstatter and Deutsch (29) and other workers have attributed marked antibacterial properties to certain \( \alpha, \beta \) -unsaturated ketones, these same compounds were tested for antibacterial activity. Type IV and related compounds showed unexpected activity against a wide variety of pathogenic bacteria. In addition, it was observed that certain Mannich bases which possessed no \( \alpha, \beta \)
-unsaturated carbonyl groups still exhibited activity against many strains of pathogens.

A considerable portion of this thesis is devoted to an extension of this earlier work. The toxic groups, nitro, chloro, bromo, and methoxy have been substituted in the benzene ring, and various amines have been inserted in the side chain in an effort to increase the biological effect.
DISCUSSION OF RESULTS

TYPE V COMPOUND - STRUCTURES RELATED TO CHLORAMPHENICOL

A synthetic scheme by which compound V might possibly be obtained is indicated on the following page. It should be pointed out, however, that this scheme does not take into consideration a separation of the diastereoisomers which would be necessary before obtaining a true vinylog of chloramphenicol. This preparation of V is patterned after previous work by Robinson (30) and Long (7). Robinson and associates prepared styryl benzoylaminomethyl ketone to be used in the subsequent preparation of 2-phenyl-5-styryloxazole. As intermediates in this synthesis they prepared styryl oximinomethyl ketone (XIV) and then reduced the oximino grouping with stannous chloride and hydrochloric acid. These are both essential intermediates in the method outlined for the synthesis of the proposed vinylog of chloramphenicol. Whereas Robinson's studies had dealt with these compounds in five-to fifteen-gram quantities, the present undertaking required their preparation in much larger amounts. It was found that the previously developed procedures were not satisfactory for larger runs.

The preparation of styryl oximinomethyl ketone from benzalacetone, isomyl nitrite and hydrochloric acid,
presented a problem in that the reaction required a relatively low temperature (20°); yet, near that temperature, benzalacetone tended to crystallize readily from the solution. The forces of nature combined to play a large part in the solution of this particular problem. Fortunately, during the period of time in which much of this work was done, the temperature in the laboratory during the night and early morning would range from 16-20°. Thus, if the solution of benzalacetone in Skelly B were prepared by melting the ketone and adding it to the solvent on the night prior to the day in which the reaction was to be run, the solution would cool slowly to room temperature without depositing crystals of benzalacetone in the flask. Then, the heat of the reaction could be controlled by the addition of small amounts of ice to the surrounding water bath. Otherwise, if the solution were cooled rapidly to 18-20° by ice and water, inevitably, crystals of benzalacetone separated before it was possible to begin the reaction.

The original workers (30) stated that, after the reaction had been run, they set aside the mixture for three hours and then collected the precipitated oximino ketone on a filter. It was our experience that such procedure led to the decomposition of the desired product. A better procedure seemed to be to continue stirring the mixture, which was surrounded by an ice-salt bath, for
Proposed Synthesis of V and Relatives

\[
\begin{align*}
\text{CHO} & \quad \xrightarrow{\text{NaOH}} \quad \text{XII} \\
\text{CH}=\text{CH}-\text{C}-\text{CH}_3 & \quad \xrightarrow{\text{HCl}} \quad \text{XIII} \\
\text{CH}=\text{CH}-\text{C}-\text{CH} = \text{NOH} & \quad \xrightarrow{\text{SnCl}_2} \quad \text{CH}=\text{CH}-\text{C}-\text{CH}_2-\text{NH}_2-\text{SnCl}_4 \\
\text{XIV} & \quad \xrightarrow{\text{HCl}} \quad \text{XV} \\
\text{CH}=\text{CH}-\text{C}-\text{CH}_2-\text{NH}-\text{C}-\text{CH}_3 & \quad \xrightarrow{\text{HNO}_3, \text{H}_2\text{SO}_4} \quad \text{XX} \\
\text{XVI} & \quad \xrightarrow{\text{HCl}} \quad \text{CH}=\text{CH}-\text{C}-\text{CH}_2-\text{NH}_2-\text{HCl} \\
\text{Cl}_2\text{CH}-\text{C}-\text{Cl} & \quad \xrightarrow{\{\text{C}_2\text{H}_5\}_3\text{N}} \quad \text{XVIII} \\
\text{XVII} & \quad \xrightarrow{\text{HCHO}, \text{NaHCO}_3} \quad \text{XIX}
\end{align*}
\]
Proposed Synthesis of V and Relatives (Continued)

XX \[ \text{HCl} \rightarrow \]

XXI

XXIV \[ \text{(C}_2\text{H}_5\text{)}_3\text{N} \rightarrow \]

XXV

XXII \[ \text{HCl} \rightarrow \]

XXIII

V
about two hours after the addition of all the reagents. The solid was then removed by filtration and washed alternately with water and benzene until the washings were colorless.

The stannous chloride reduction of this oxime also presented certain difficulties. In the original preparation the solid oxime was added directly to a stirred solution of stannous chloride in hydrochloric acid; the mixture stirred overnight and then the tin complex salt was obtained by filtration. In our hands this procedure led to the evolution of considerable amount of heat and resulted in the formation of large, dark lumps of solid which were difficult to purify. A solution to this problem was suggested by Johnson (31). The oxime was first dissolved in 95% ethyl alcohol and then this solution was added to the acid solution of stannous chloride.

The next step involved the acetylation of this tin complex salt. Foulds and Robinson (30) had prepared the benzoyl derivative in acetic acid, using sodium acetate as the buffering agent. The use of sodium acetate as the buffer, together with acetyl chloride, acetic anhydride or mixtures of the two, did not yield the desired acetyl compound in any appreciable quantity. Consequently, an alternate procedure (7) using sodium hydroxide was employed. This gave the desired compound consistently in good yield.
A procedure, similar to that used in the nitration of benzalacetone (XIII), was used to nitrate the α-acetamido-benzalacetone (XVI). It, however, unlike benzalacetone, apparently yields only the para isomer, since this was the only product isolated.

All attempts to hydroxymethyleate p-nitro-α-acetamido-benzalacetone (XX) resulted only in the recovery of starting material. This might be attributed to the lack of solubility of this compound in the solvents employed in the hydroxymethylation reaction. Although this compound is soluble in boiling ethyl alcohol, Long and Troutman (7) had indicated that the temperature should be kept between 35–40° in this reaction. Consequently, attempts were then made to hydroxymethyleate α-acetamidobenzalacetone (XVI), since it was more soluble than the corresponding p-nitro derivative in the solvents required for this reaction. It was thought that the diacetyl derivative could then be nitratated in the para-position. The ease with which solution of α-acetamidobenzalacetone occurs in the alcoholic solvent, with only slight warming, is only a forewarning of the many difficulties to be encountered later. No less than thirty attempts were made to monohydroxymethyleate α-acetamidobenzalacetone. In no case was there any apparent degree of success. Although a wide variety of conditions have been examined, we have been unable to stop these reactions at the monomethylol
stage. Pain and Slack (32) investigated the reactivity towards formaldehyde of the methylene group in compounds such as $\text{p-NO}_2\text{-C}_6\text{H}_4\text{-CO-CH}_2\text{N-RR'}$ (where $R = \text{acyl}$ and $R' = \text{aryl}$) and concluded that hydroxymethylation might well be uncontrollable. They point out that, using potassium carbonate as catalyst, Long and Troutman (7) found that $\alpha$-benzamidoacetophenone and formaldehyde gave 2,4-dibenzamido-1,5-diphenylpentane-1,5-dione but that $\alpha$-acetamido-p-nitroacetophenone, formaldehyde and sodium bicarbonate gave the required hydroxymethyl compound. Then, they concluded that the single alteration from $R = \text{H}$ to $R = \text{aryl}$ in the preceding formula would so increase the reactivity about the methylene group that substituted methanes would invariably be formed. The apparent fallacy in this argument is borne out by the incompleteness of their reference to Long and Troutman's work. Indeed, using potassium carbonate with $\alpha$-benzamidoacetophenone they did get the corresponding bis-methane; however, using sodium bicarbonate as catalyst they obtained the desired monohydroxymethyl compound in 77% yield. The fact remains nonetheless that our experience corroborates the results of Pain and Slack. They obtained bis-methane compounds or recovered the starting material. It was our experience that the use of sodium or potassium carbonate as catalyst at room temperature led to no reaction. When the temperature was raised to 50-60°; the bis-methane structure was
apparently formed. The product of the reaction using sodium bicarbonate as catalyst and warming to 35-40° was apparently a compound in which two hydroxymethyl groups had entered the molecule. The use of one, two or four equivalents of formaldehyde still resulted in the formation of the same compound. Concerning the condensation of formaldehyde with compounds containing activated hydrogens, Hays and associates (33) conclude that although the reaction may give the monomethylolol derivative, such is not the general rule. Obviously, our results are in complete accord with this conclusion.

Consequently, it appeared that some alteration in the procedure must be made if the desired compound was to be obtained. Thus, another approach, patterned after more recent work of Long and Troutman (34), was followed. 

\(\alpha\)-Acetamidobenzalacetone (XVI) and the corresponding \(p\)-nitro compound (XX) were hydrolyzed in dilute hydrochloric acid to the analogous amino compounds. The yields in this hydrolysis were neither good nor consistent. Inevitably, a considerable amount of decomposition took place. Both of these amine hydrochlorides were treated with dichloroacetyl chloride in the presence of triethylamine to yield the corresponding dichloroacetamido compounds (XVIII and XXV). Though a satisfactory analysis for \(p\)-nitro-\(\alpha\)-dichloroacetamidobenzalacetone was never obtained, infrared studies of the compound, conducted by
Mr. Bruce Scott and Dr. George Hoersch, Parke, Davis & Co., indicated this to be the correct structure for the compound. (For further information concerning these infra-red studies, see the next page.) The analytical data, being consistently high in the carbon and hydrogen values and low in the chlorine content, suggests that a starting material, dichloroacetyl chloride, was contaminated with some of the analogous monochloroacetyl chloride.

Next, an attempt was made to condense formaldehyde with \( \alpha \)-dichloroacetamidobenzalacetone to yield the monomethylol derivative (XIX). Here, unlike the previous experiments, apparently the desired compound was obtained. Nevertheless, because of the poor yields obtained in this sequence of reactions, it was deemed feasible to discontinue the synthesis at this point.

As a consequence of these poor yields and in view of the strong interest of others (35) in preparing analogues of chloramphenicol by condensing the appropriate aromatic aldehyde with glycine or its alkyl ester, work has been undertaken toward the possibility of obtaining the desired vinylog, V, in this manner. The scheme by which this might be accomplished is illustrated on the following page.

Erlenmeyer and Fruestueck (36) first condensed benzaldehyde with glycine in the presence of aqueous alkali to obtain \( \beta \)-phenylserine. This procedure however, does
Table I

<table>
<thead>
<tr>
<th>Wave-length, in microns</th>
<th>Wave-length ranges, in microns,**</th>
<th>of the absorption peaks</th>
<th>ordinarily observed in study of compounds containing similar functional groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-H</td>
<td>3.01</td>
<td>2.88 - 3.00</td>
<td></td>
</tr>
<tr>
<td>=O, keto</td>
<td>5.91</td>
<td>5.81 - 5.99</td>
<td></td>
</tr>
<tr>
<td>C=C, amide I*</td>
<td>6.00</td>
<td>5.99 - 6.25</td>
<td></td>
</tr>
<tr>
<td>C=C</td>
<td>6.18</td>
<td>6.02 - 6.11</td>
<td></td>
</tr>
<tr>
<td>C=H5C=C</td>
<td>6.28</td>
<td>6.30 - 6.35</td>
<td></td>
</tr>
<tr>
<td>Amide II*</td>
<td>6.45</td>
<td>6.39 - 6.67</td>
<td></td>
</tr>
<tr>
<td>Nitro I*</td>
<td>6.64</td>
<td>6.23 - 6.56</td>
<td></td>
</tr>
<tr>
<td>Nitro II*</td>
<td>7.45</td>
<td>7.20 - 7.60</td>
<td></td>
</tr>
</tbody>
</table>

*One of two characteristic bands in this region.

In addition to this information, Dr. Moersch stated that the ultra-violet examination of XXV gives an absorption very similar to p-nitrocinnamaldehyde, which would be expected for a structure of this type.
ALTERNATE SYNTHESIS OF V

CHO

\[ \text{KOH} \rightarrow \text{CH}_3\text{CHO} \]

\[ \text{CH}=\text{CH}-\text{CHO} \]

\[ \text{H}_2\text{N}-\text{CH}_2-\text{COOC}_2\text{H}_5 \]

\[ \text{CH}=\text{CH}-\text{CHOH}-\text{CH}_-\text{CH}_2\text{OH} \]

\[ \text{Cl}_2\text{CH}-\text{C}=\text{Cl} \]

\[ \text{NH}_2 \]

\[ \text{LiAlH}_4 \]

\[ \text{V} \]
not yield the corresponding vinyllog of $\beta$-phenylserine when cinnamaldehyde was treated with glycine, according to Ingersoll (37). However, he also reports no condensation with furfural under these conditions. Yet, other workers (38) have synthesized $\beta$-furylserine using a suitable modification of Erlenmeyer's method. Bergmann, Bendas, and Taub (35) condensed $\alpha$, $m$, and $p$-nitro-benzaldehyde with glycine ethyl ester to give the correspondingly substituted phenylserine ethyl ester. The fact that this terminal ester group can be reduced to the corresponding carbinol without affecting the nitro group was first noted by Felkin (39). This, coupled with the knowledge that unsaturated acids have been reduced to the corresponding unsaturated alcohol (40), makes this appear to be a particularly attractive method of synthesizing $\psi$.

Thus far, although the work of Bergmann and associates has been repeated and N-dichloracetylphenylserine obtained according to the method of Hübner and Scholz (41), cinnamaldehyde and $p$-nitrocinnamaldehyde have not been condensed with glycine or its ethyl ester to yield the desired compound.
A series of eighteen thiosemicarbazones were prepared (Table II). The object in preparing compounds of this type was to investigate the effect of substituting a ketonic carbonyl group for that of the aldehyde on the chemotherapeutic activity of a number of thiosemicarbazones. Earlier workers (14) had indicated that, in general, thiosemicarbazones of aldehydes were more effective than thiosemicarbazones of ketones. A rather extensive perusal of the existing literature indicates, however, that actually very few thiosemicarbazones of ketones have been studied in comparison with the large number of thiosemicarbazones of aldehydes which have been investigated as possible antitubercular agents. One group of workers (14), while indicating that ketones were less suitable than aldehydes, failed to list a single derivative using a ketone as the parent substance. Another research group (42) described the preparation of more than one hundred thiosemicarbazones from aldehydes, but listed only seven derived from ketones. Thus, an investigation into the possible antitubercular activity of a number of thiosemicarbazones derived from ketones was prompted. It seemed advisable to attempt to clarify the status of such compounds in relation to the compounds of known activity derived from aldehydes.
Shortly before this work was begun, the chemical structure of chloramphenicol was disclosed (6). This structure, which was proven by degradation and synthesis, contains two remarkable features which are new in naturally occurring substances, the p-nitrophenyl group and the dichloroacetyl radical. Because of the extremely high antibacterial activity of this compound, it was decided to model many of these compounds after this recently elucidated structure. Thus, it may be seen that compounds (XXVI - XXXIV) contain some features of the chloramphenicol structure.

Next, remembering the intrinsic antitubercular activity of certain \( \alpha, \beta \) -unsaturated carbonyl compounds, it was decided to prepare such compounds as XXXI, XXXIX, XL, and XLI, all of which contain the \( \alpha, \beta \) -unsaturated ketone grouping.

Behnisch, et al. (14) had earlier prepared the thiosemicarbazones of certain aldehydes, which were solubilized by placing functional groups for this purpose in the molecule. They did not comment on the efficacy of this type. Independent of this work, three of these compounds, XXXIII, XXXIV, and XLII were prepared in an attempt to retain the thiosemicarbazone residue in the molecule and, yet, to solubilize it. In this effort only partial success was achieved, since only the sodium salt of XLII was freely soluble in water.
The remaining compounds listed in Table II were prepared in an effort to extend this study in the general direction of thiosemicarbazones derived from aromatic ketones, since no aliphatic aldehyde or ketone has thus far demonstrated appreciable activity.

All the thiosemicarbazones were prepared by the interaction of the ketone with thiosemicarbazide in ethyl alcohol-water in the presence of a few drops of mineral acid. Usually fifteen to twenty minutes of heating at steam-bath temperature was sufficient. This is in marked contrast to the six or eight hours reported by Anderson, Duca and Scudi (43). In general, the yields using this short reaction time were quite good. Clearly, such a long period of heating is not necessary in most cases to obtain satisfactory yields.

The crude product obtained from the reaction was generally freed of unreacted thiosemicarbazide by heating with water and filtering while hot. This was possible since most of the thiosemicarbazones were insoluble in warm water.

In many cases the product precipitated spontaneously when the solutions containing the reagents were mixed. In other cases, it was necessary to heat the required time and then cool the flask to induce crystallization. In the case of the thiosemicarbazone of p-chloropropiophenone, the initial precipitate appeared even while warm,
<table>
<thead>
<tr>
<th>No.</th>
<th>Substituents</th>
<th>Procedure</th>
<th>Yield</th>
<th>M.p.</th>
<th>Formula</th>
<th>Analyses</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXVI</td>
<td>4-Nitro</td>
<td>A</td>
<td>90</td>
<td>243-244</td>
<td>C_{9}H_{10}N_{4}O_{4}S</td>
<td>Carbon: Calcd. 45.36, Found 45.87, Hydrogen: Calcd. 4.23, Found 4.03</td>
</tr>
<tr>
<td>XXVII</td>
<td>0,Acetyl</td>
<td>A</td>
<td>89</td>
<td>211-212</td>
<td>C_{11}H_{12}N_{4}O_{4}S</td>
<td>Carbon: Calcd. 44.60, Found 44.80, Hydrogen: Calcd. 4.09, Found 4.20</td>
</tr>
<tr>
<td>XXVIII</td>
<td>Acetamido</td>
<td>A</td>
<td>84</td>
<td>239-240</td>
<td>C_{11}H_{13}N_{5}O_{3}S</td>
<td>Carbon: Calcd. 44.73, Found 45.24, Hydrogen: Calcd. 4.44, Found 4.77</td>
</tr>
<tr>
<td>XXIX</td>
<td>3,5-Dinitro</td>
<td>A</td>
<td>88</td>
<td>195-196</td>
<td>C_{11}H_{11}O_{2}N_{5}O_{3}S</td>
<td>Carbon: Calcd. 36.27, Found 36.36, Hydrogen: Calcd. 3.06, Found 3.08</td>
</tr>
<tr>
<td>XXX</td>
<td>4-Nitro</td>
<td>A</td>
<td>90</td>
<td>257-258</td>
<td>C_{9}H_{9}N_{5}O_{4}S</td>
<td>Carbon: Calcd. 38.17, Found 38.17, Hydrogen: Calcd. 3.21, Found 3.10</td>
</tr>
<tr>
<td>XXXI</td>
<td>4-Nitro</td>
<td>A</td>
<td>92</td>
<td>249-250</td>
<td>C_{11}H_{12}N_{4}O_{2}S</td>
<td>Carbon: Calcd. 49.98, Found 50.06, Hydrogen: Calcd. 4.57, Found 4.67</td>
</tr>
<tr>
<td>XXXII</td>
<td>A-(p-Nitrophenyl)</td>
<td>A</td>
<td>77</td>
<td>264-265</td>
<td>C_{15}H_{14}N_{2}O_{3}S</td>
<td>Carbon: Calcd. 57.30, Found 57.77, Hydrogen: Calcd. 4.48, Found 4.45</td>
</tr>
<tr>
<td>XXXIII</td>
<td>Amino Hydro-Chloride</td>
<td>B</td>
<td>80</td>
<td>220-222</td>
<td>C_{12}H_{17}N_{5}O_{2}S•HCl</td>
<td>Carbon: Calcd. 49.67, Found 47.46, Hydrogen: Calcd. 47.14, Found 47.14</td>
</tr>
<tr>
<td>XXXIV</td>
<td>A-Dimethylaminomethyl</td>
<td>B</td>
<td>86</td>
<td>152-153</td>
<td>C_{12}H_{17}N_{5}O_{2}S•HCl</td>
<td>Carbon: Calcd. 49.67, Found 49.61, Hydrogen: Calcd. 50.01, Found 49.59</td>
</tr>
<tr>
<td>XXXV</td>
<td>4-Chloro</td>
<td>A</td>
<td>96</td>
<td>200-201</td>
<td>C_{9}H_{10}ClN_{3}S</td>
<td>Carbon: Calcd. 49.67, Found 49.67, Hydrogen: Calcd. 5.00, Found 5.00</td>
</tr>
<tr>
<td>XXXVI</td>
<td>4-Chloro</td>
<td>A</td>
<td>85</td>
<td>175-176</td>
<td>C_{10}H_{12}ClN_{3}S</td>
<td>Carbon: Calcd. 49.67, Found 49.61, Hydrogen: Calcd. 5.00, Found 5.00</td>
</tr>
<tr>
<td>XXXVII</td>
<td>4-Methoxy</td>
<td>A</td>
<td>94</td>
<td>150</td>
<td>C_{10}H_{13}N_{3}O_{3}S•H_{2}O</td>
<td>Carbon: Calcd. 49.61, Found 49.59, Hydrogen: Calcd. 6.14, Found 6.25</td>
</tr>
<tr>
<td>XXXVIII</td>
<td>4-Phenyl</td>
<td>A</td>
<td>90</td>
<td>263-264</td>
<td>C_{15}H_{15}N_{3}S</td>
<td>Carbon: Calcd. 66.88, Found 66.80, Hydrogen: Calcd. 5.61, Found 5.77</td>
</tr>
<tr>
<td>XXXIX</td>
<td>0, Methyl</td>
<td>A</td>
<td>95</td>
<td>146-147</td>
<td>C_{11}H_{13}N_{3}S</td>
<td>Carbon: Calcd. 52.57, Found 52.47, Hydrogen: Calcd. 5.21, Found 5.54</td>
</tr>
<tr>
<td>XL</td>
<td>2-Chloro</td>
<td>A</td>
<td>86</td>
<td>185</td>
<td>C_{11}H_{12}ClN_{3}S</td>
<td>Carbon: Calcd. 52.06, Found 52.50, Hydrogen: Calcd. 4.77, Found 4.71</td>
</tr>
<tr>
<td>XLI</td>
<td>2,3-Dimethoxy</td>
<td>A</td>
<td>91</td>
<td>188</td>
<td>C_{13}H_{17}N_{3}O_{2}S</td>
<td>Carbon: Calcd. 55.89, Found 56.00, Hydrogen: Calcd. 6.13, Found 6.16</td>
</tr>
<tr>
<td>XLII</td>
<td>0,Carboxymethyl</td>
<td>C</td>
<td>82</td>
<td>171</td>
<td>C_{11}H_{12}N_{3}O_{2}S</td>
<td>Carbon: Calcd. 52.57, Found 52.47, Hydrogen: Calcd. 5.21, Found 5.54</td>
</tr>
<tr>
<td>XLIII</td>
<td>None</td>
<td>A</td>
<td>89</td>
<td>136</td>
<td>C_{7}H_{9}N_{3}S_{2}</td>
<td>Carbon: Calcd. 42.18, Found 42.20, Hydrogen: Calcd. 4.55, Found 4.63</td>
</tr>
</tbody>
</table>
Footnotes to Table II

(a) Made available through the courtesy of Parke, Davis and Co. (b) 2-Acetylthiophene, the starting ketone, was obtained through the cooperation of Socony-Vacuum. (c) Calcd. Cl- 12.24. Found: 12.46. (d) Calcd. 10.68. Found: 10.82. (e) Purified only by alternate treatment with hot benzene, water, and ethyl alcohol. (f) S. Gheorghiu, Bull. Soc. Chem., 1, 97 (1934) reports 146°. (g) Supplied through the courtesy of Dr. S. H. Johnson. (h) By Mr. J. R. Campbell. (i) F. E. Anderson, D. J. Duca and J. V. Scude, J. Am. Chem. Soc., 72, 4967 (1951) report 143-149°. (j) All melting points are uncorrected.
but in the form of a yellow oil. On vigorous agitation of the flask, it quickly solidified.

The intermediate ketones were in general obtained by the well established methods of the literature. 

*p*-Nitrophenacyl alcohol acetate was readily prepared by the reaction of *p*-nitrophenacyl bromide with sodium acetate, which procedure was described by Engler and Zielke (44). *α*-Dichloroacetamido-*p*-nitroacetophenone was prepared according to the procedure of Long and Troutman (34). This synthesis is outlined on the following page.

3,5-Dinitroacetophenone was prepared by the method of Walker and Hauser (45) with certain modifications. Because of the difficulty of obtaining *p*-nitrobenzaldehyde and because of the oxidizing effect of alkali and air on it, the best procedure for obtaining *p*-nitrobenzalacetone involved the nitration of benzalacetone. The nitration was best performed at -20°C, using a mole for mole ratio of nitric acid.

*p*-(*p*-Nitrophenyl) acetophenone was synthesized by means of the Friedel-Craft reaction on *p*-nitrobibiphenyl according to the procedure of Grieve (46). *β*-Dimethylamino-*p*-nitropropiophenone was prepared in satisfactory yield by the customary procedure for the Mannich reaction as outlined by Maxwell (47). *β*-Benzoylpropionic acid was prepared according to the method of Knott (48) starting with acetophenone.
Synthesis of α-Dichloracetamido-ρ-nitroacetophenone

\[
\text{O} \quad \text{C-CH}_2\text{Br} \quad \text{O} \quad \text{C-CH}_2\text{Br} \cdot (\text{CH}_2)_4\text{N}_4
\]

\[
\text{NO}_2 \quad \xrightarrow{(\text{CH}_2)_6\text{N}_4 \text{ xylene}} \quad \text{NO}_2
\]

\[
\text{O} \quad \text{C-CH}_2\text{NH}_2\text{HCl} \quad \text{O} \quad \text{C-CH}_2\text{NH} \cdot \text{C-CHCl}_2
\]

\[
\text{NO}_2 \quad \xrightarrow{\text{Cl}_2\text{CH-C-Cl} \quad (\text{C}_2\text{H}_5)_3\text{N}} \quad \text{NO}_2
\]

Synthesis of β-Benzoylpropionic Acid

\[
\text{O} \quad \text{C-CH}_3 \quad \text{O} \quad \text{C-CH}_2\text{CH}_2\text{-N} \quad \text{CH}_3 \quad \text{N} \quad \text{CH}_3
\]

\[
\text{NO}_2 \quad \xrightarrow{(\text{C}_3\text{H}_3)_2\text{NH-HCl} \quad \text{HCHO}} \quad \text{NO}_2
\]

\[
\text{O} \quad \text{C-CH}_2\text{CH}_2\text{-CN} \quad \text{O} \quad \text{C-CH}_2\text{CH}_2\text{-CO-CH}_3
\]

\[
\text{NO}_2 \quad \xrightarrow{\text{HCl}} \quad \text{NO}_2
\]
TYPE VII COMPOUNDS - KETONIC MANNICH BASES.

The preparation of compounds of this type requires the use of the Mannich reaction, which involves the interaction of a compound containing an active hydrogen with formaldehyde and a primary or secondary amine. The amine is generally used as its hydrochloride. Example:

\[
\text{C}_6\text{H}_5\text{COCH}_3 + \text{CH}_2\text{O} + \text{R}_2\text{NH} \cdot \text{HCL} \rightarrow \text{C}_6\text{H}_5\text{COCH}_2\text{CH}_2\text{NR}_2 \cdot \text{HCL} + \text{H}_2\text{O}
\]

A series of substituted propiophenones, prepared as indicated above, are listed in Table III. These compounds were, in general, prepared by refluxing the appropriate ketone, paraformaldehyde and amine hydrochloride in absolute ethyl alcohol. The hot solution was poured into acetone and, upon cooling, the product precipitated. This was then removed by filtration and purified by recrystallization from the appropriate solvent. In the case of piperidine, morpholine, dipropylamine and pyrrolidine, which are usually available as the free amine, it was found to be more convenient to use a slightly modified procedure. The amine was dissolved in absolute ethyl alcohol. This solution was made acidic to Congo Red with concentrated hydrochloric acid. The other reagents were subsequently added and the previous procedure followed thenceforth.

In general these reactions proceeded smoothly and
### TABLE III

3-Dialkylamino-1-(substituted phenyl)-1-propanones

| No. | Phenyl Substituents | Amino Group | M.p.°C | Yield % | Formula | Ionic Hologen %
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>XLIV</td>
<td>None</td>
<td>Dimethyl</td>
<td>144-147</td>
<td>66</td>
<td>C_{11}H_{15}NO•HCl&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>XLV</td>
<td>p-Nitro</td>
<td>Dimethyl</td>
<td>189-191</td>
<td>72</td>
<td>C_{11}H_{14}N_{2}O_{3}•HCl&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>XLVI</td>
<td>p-Nitro</td>
<td>Diethyl</td>
<td>149-150</td>
<td>66</td>
<td>C_{13}H_{18}N_{2}O_{3}•HCl 12.36 12.22</td>
<td></td>
</tr>
<tr>
<td>XLVII</td>
<td>p-Nitro</td>
<td>Dipropyl</td>
<td>139-140</td>
<td>26</td>
<td>C_{15}H_{22}N_{2}O_{3}•HCl 11.26 11.39</td>
<td></td>
</tr>
<tr>
<td>XLVIII</td>
<td>p-Nitro</td>
<td>Morpholyl</td>
<td>218</td>
<td>62</td>
<td>C_{13}H_{16}N_{2}O_{4}•HCl 11.79 11.82</td>
<td></td>
</tr>
<tr>
<td>XLIX</td>
<td>p-Nitro</td>
<td>Piperidyl</td>
<td>199-200</td>
<td>51</td>
<td>C_{14}H_{18}N_{2}O_{3}•HCl&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>p-Nitro</td>
<td>Diethanol</td>
<td>145-146</td>
<td>19</td>
<td>C_{13}H_{16}N_{2}O_{5}•HCl 11.12 11.31</td>
<td></td>
</tr>
<tr>
<td>L</td>
<td>p-Nitro</td>
<td>Pyrrolidyl</td>
<td>183-184</td>
<td>61</td>
<td>C_{13}H_{16}N_{2}O_{3}•HCl 12.45 12.60</td>
<td></td>
</tr>
<tr>
<td>LI</td>
<td>m-Nitro</td>
<td>Dimethyl</td>
<td>203-205</td>
<td>72</td>
<td>C_{11}H_{14}N_{2}O_{3}•HCl&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>LI</td>
<td>m-Nitro</td>
<td>Pyrrolidyl</td>
<td>181-182</td>
<td>63</td>
<td>C_{13}H_{16}N_{2}O_{3}•HCl 12.45 12.54</td>
<td></td>
</tr>
<tr>
<td>LIV</td>
<td>p-Chloro</td>
<td>Dimethyl</td>
<td>176</td>
<td>71</td>
<td>C_{11}H_{14}ClNO•HCl&lt;sup&gt;f&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>LV</td>
<td>p-Chloro</td>
<td>Diethyl</td>
<td>145</td>
<td>60</td>
<td>C_{13}H_{16}ClNO•HCl 12.84 12.83</td>
<td></td>
</tr>
<tr>
<td>LVI</td>
<td>p-Chloro</td>
<td>Piperidyl</td>
<td>183-190</td>
<td>56</td>
<td>C_{14}H_{18}ClNO•HCl 12.30 12.37</td>
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<tr>
<td>LVII</td>
<td>p-Bromo</td>
<td>Dimethyl</td>
<td>196</td>
<td>52</td>
<td>C_{11}H_{14}BrNO•HCl&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
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<tr>
<td>LVIII</td>
<td>p-Bromo</td>
<td>Diethyl</td>
<td>165-166</td>
<td>40</td>
<td>C_{13}H_{18}BrNO•HBr 21.88 22.01</td>
<td></td>
</tr>
<tr>
<td>LIX</td>
<td>p-Bromo</td>
<td>Piperidyl</td>
<td>188</td>
<td>42</td>
<td>C_{14}H_{18}BrNO•HBr 21.19 21.12</td>
<td></td>
</tr>
<tr>
<td>LX</td>
<td>p-Bromo</td>
<td>Pyrrolidyl</td>
<td>198-199</td>
<td>69</td>
<td>C_{13}H_{16}BrNO•HCl 11.13 11.29</td>
<td></td>
</tr>
<tr>
<td>LXI</td>
<td>p-Methoxy</td>
<td>Dimethyl</td>
<td>176-180</td>
<td>75</td>
<td>C_{12}H_{17}NO_{2}•HCl&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>LXII</td>
<td>p-Methoxy</td>
<td>Pyrrolidyl</td>
<td>183-184</td>
<td>38</td>
<td>C_{14}H_{19}NO_{2}•HCl 13.14 13.22</td>
<td></td>
</tr>
<tr>
<td>LXIII</td>
<td>p-Hydroxy</td>
<td>Dimethyl</td>
<td>192</td>
<td>56</td>
<td>C_{11}H_{15}NO_{2}•HCl&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>LXIV</td>
<td>o-Hydroxy</td>
<td>Dimethyl</td>
<td>155-156</td>
<td>33</td>
<td>C_{11}H_{15}NO_{2}•HCl 15.43 15.55</td>
<td></td>
</tr>
<tr>
<td>LXV</td>
<td>p-Phenyl</td>
<td>Dimethyl</td>
<td>191-192</td>
<td>69</td>
<td>C_{17}H_{19}NO•HCl 12.24 12.39</td>
<td></td>
</tr>
<tr>
<td>LXVI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Pyrrolidyl</td>
<td>169-170</td>
<td>48</td>
<td>14.43 14.60</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Footnotes to Table III

the yields were consistently good. There were exceptions to this however. In the preparation of LXV, consonant results were not achieved. In three separate runs, adhering closely to the same procedure, in two instances a near quantitative recovery of starting material resulted. Yet, on the third attempt, a yield of 69% was obtained. The only plausible explanation appears to involve the temperature at which the reactants were refluxed. When isoamyl alcohol was substituted as a solvent, uniformly good yields resulted.

Under the conditions employed it was not possible to effect the Mannich reaction with 3,5-dinitroacetophenone or with p-nitro-α-acetamidoacetophenone, though the latter will hydroxymethylate readily in good yield.

Furthermore, the earlier observation of Burger and Bryant (49) that dicyclohexylamine does not take part in this reaction was confirmed. It was not possible to cause the reaction to proceed between acetophenone, formaldehyde and dicyclohexylamine hydrochloride even with the use of acetophenone as solvent and with reflux being maintained for varying periods of time up to 36 hours.

The $\beta$-dialkylaminoketones obtained by the application of the Mannich reaction to p-nitroacetophenone are so unstable that they decompose readily in the presence of dilute alkaline solutions. However, they can be
prepared and stored for some time as the hydrochloride salt.

In addition to Mannich bases derived from simple aralkyl ketones, certain ones derived from \(\alpha,\beta\) -unsaturated ketones are listed in Table IV. The preparation of the starting ketones has previously been discussed under Type III compounds.

Subsequent to the discovery of the antibacterial activity of the Mannich bases derived from \(p\)-nitroacetophenones (50) and \(p\)-nitrobenzalacetone (1), interest was aroused in the reduction of these to the corresponding carbinols in order to study the effect of this variation in structure on the biological activity of these compounds. The majority of the \(\beta\) -substituted aminoketones prepared by the use of this reaction can be catalytically reduced to the corresponding \(\beta\) -substituted aminosalkanols, which are much more stable than the corresponding ketones. However, when such a procedure is applied to a \(\alpha\) -amino ketone containing a nitro group on the benzene ring, difficulties generally arise. The catalytic reduction of \(m\)-nitro-\(\beta\) -piperidylpropiophenone hydrochloride to the corresponding \(m\)-amino compound has been reported (51). The preparation has been repeated in this laboratory by Wei-Ling, who noted that the melting point and solubility of the product changed rapidly on standing (52). It has not been possible to isolate the analogous \(m\)-amino-
<table>
<thead>
<tr>
<th>No.</th>
<th>Phenyl Substituents</th>
<th>Amino Group</th>
<th>M. p\textsuperscript{a} ( ^\circ \text{C.} )</th>
<th>Yield</th>
<th>%</th>
<th>Formula</th>
<th>Chlorine % Calcd.</th>
<th>Found</th>
</tr>
</thead>
<tbody>
<tr>
<td>LXVII</td>
<td>None</td>
<td>Morpholinyl</td>
<td>177-178</td>
<td>66</td>
<td></td>
<td>C\textsubscript{15}H\textsubscript{19}NO\textsubscript{2}·HCl</td>
<td>12.58</td>
<td>12.46</td>
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<tr>
<td>LXVIII</td>
<td>None</td>
<td>Pyrrolidyl</td>
<td>177-178</td>
<td>42</td>
<td></td>
<td>C\textsubscript{15}H\textsubscript{19}NO·HCl</td>
<td>13.34</td>
<td>13.51</td>
</tr>
<tr>
<td>LXIX</td>
<td>2,3-Dimethoxy</td>
<td>Pyrrolidyl</td>
<td>155</td>
<td>65</td>
<td></td>
<td>C\textsubscript{17}H\textsubscript{23}NO\textsubscript{3}·HCl</td>
<td>10.88</td>
<td>11.01</td>
</tr>
<tr>
<td>LXX</td>
<td>p-Nitro</td>
<td>Dimethyl</td>
<td>182-185</td>
<td>53</td>
<td></td>
<td>C\textsubscript{13}H\textsubscript{16}N\textsubscript{2}O\textsubscript{3}·HCl\textsuperscript{b}</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LXXI</td>
<td>p-Nitro</td>
<td>Pyrrolidyl</td>
<td>195-196</td>
<td>57</td>
<td></td>
<td>C\textsubscript{15}H\textsubscript{18}N\textsubscript{2}O\textsubscript{3}·HCl</td>
<td>11.41</td>
<td>11.53</td>
</tr>
</tbody>
</table>

(a) All melting points are uncorrected.

\( \beta \)-dimethyl- and diethylaminopropiophenones through the catalytic hydrogenation of the nitro intermediates; instead, only water insoluble products were obtained. Evidently the free-amino group reacts very readily with the unreduced carbonyl function to give a Schiff's base; this could account for the unfavorable results.

It was evident from the outset that a procedure for the reduction of this type Mannich base, if it were to be successful, must be capable of being applied directly to the amine salt. This logically followed from the extreme instability of these compounds in alkaline solution, as noted above. The Meerwein-Ponndorf-Verley method of reduction, employing aluminum isopropoxide, seemed to fit the requirements. Since this reducing agent is such a specific one, other groups susceptible to reduction are not affected. For example, carbon-carbon double bonds, nitro groups and carboxylic esters are not reduced by this reagent, in contrast to other reductions involving metals in acid or alkaline media, or even to catalytic hydrogenation in certain of these cases. This procedure had previously been applied by Lutz and associates (53) to Mannich bases derived from \( p \)-chloro and \( p \)-bromoacetophenone, as well as to a number of \( \alpha \)-amino ketones. The reduction of the latter proceeded very smoothly; in only one case involving a Mannich base, however, were they able to isolate the
desired amino alcohol, and then in less than 10% yield. They attributed these poor results to reductive fission of the dialkylamino groups. In the early stages of our work, the same results were noted. In each case, the evolution of the lowboiling dialkylamines was noticeable, as the temperature of the reaction mixture was elevated. Meanwhile the contents of the flask became darker and resinous in appearance. Apparently the amine was being eliminated, and polymerization of the residual vinyl ketone occurred. Lutz (53) had successfully employed aluminum chloride to improve the yield in the reduction of the \( \alpha \)-amino ketones, although he had apparently not used it in connection with the reduction of Mannich bases, which are \( \beta \)-amino ketones. Consequently the use of anhydrous aluminum chloride in 50 mole% quantities in conjunction with aluminum isopropoxide was next attempted. Happily, this procedure worked very smoothly. No amine odor was noticeable at any stage of the reduction. The residue, after the removal of any residual isopropyl alcohol, was decomposed with ice-cold 10% hydrochloric acid. Ice was then added; the solution made strongly basic with 6N sodium hydroxide and subsequently ether extracted. After drying the ether solution over anhydrous sodium sulfate, the desired amino alcohol hydrochloride was obtained from it by bubbling in anhydrous hydrogen chloride.
In working up one of the reduction mixtures, an attempt was made to decompose the residue directly with concentrated sodium hydroxide. Though solution of the residue was effected, subsequent ether extraction failed to remove any of the desired amino alcohol. The exact significance of this is not clear. It may have been that the alkali did not properly decompose the complex; or the desired product, if formed, may have been decomposed. The latter seems very improbable since no appreciable amine odor was detected.

Generally, the previous workers employing this procedure have used a Vigreux column (54), a modified Widmer column (55), or Hahn condenser (56). In the present work ordinary ground glass equipment providing for the ready interchange of an upright condenser with one turned downward for distillation served very admirably.

A series of $\beta$-amino alcohols prepared in the manner described above are listed in Table V.

Previous studies (52) in this laboratory directed toward obtaining the type of compound indicated by LXXIX had failed due to the difficulty in isolating the desired $m$-amino-$\beta$-dialkylamino propiophenone from the catalytic reduction of the corresponding nitro derivative. It was apparent that catalytic reduction of the alcohols which contain nitro groups (Table V) should offer no difficulties through Schiff base formation, etc. Thus,
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<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>LXXII None</td>
<td>Dimethyl</td>
<td>133-134</td>
<td>65</td>
<td>C_{11}H_{17}NO·HCl</td>
<td>6.57</td>
<td>6.47</td>
<td>12.28</td>
<td>12.41</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LXXIII p-Nitro</td>
<td>Dimethyl</td>
<td>176</td>
<td>65</td>
<td>C_{11}H_{16}N_{2}O_{3}·HCl</td>
<td>50.67</td>
<td>50.89</td>
<td>6.57</td>
<td>6.47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LXXIV p-Nitro</td>
<td>Diethyl</td>
<td>139-140</td>
<td>54</td>
<td>C_{13}H_{20}N_{2}O_{3}·HCl</td>
<td>11.78</td>
<td>11.91</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LXXV p-Nitro</td>
<td>Piperidyl</td>
<td>176-177</td>
<td>55</td>
<td>C_{14}H_{20}N_{2}O_{3}·HCl</td>
<td>11.71</td>
<td>11.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LXXVI p-Nitro</td>
<td>Morpholinyl</td>
<td>184-185</td>
<td>67</td>
<td>C_{13}H_{18}N_{2}O_{4}·HCl</td>
<td>12.37</td>
<td>12.52</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LXXVII p-Nitro</td>
<td>Pyrrolidyl</td>
<td>167-168</td>
<td>61</td>
<td>C_{13}H_{18}N_{2}O_{4}·HCl</td>
<td>13.59</td>
<td>13.71</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LXXVIII m-Nitro</td>
<td>Dimethyl</td>
<td>187-188</td>
<td>42</td>
<td>C_{11}H_{16}N_{2}O_{3}·HCl</td>
<td>50.67</td>
<td>50.89</td>
<td>6.57</td>
<td>6.47</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(a) All melting points are uncorrected. (b) See C. Mannich and G. Heilner, *Ber.*, 55, 356 (1922).
if these compounds were reduced and then condensed with
the appropriate chloroheterocycle, a compound similar
to the above, differing only in the presence of a car-
binol rather than carbonyl grouping in the side chain,
should result (LXXX). Consequently, efforts were made
in this direction. Catalytic hydrogenation, using Adams'
catalyst and absolute ethyl alcohol as the medium, pro-
ceeded smoothly. The corresponding amino derivatives
were not actually isolated from the reduction mixture.
Rather the catalyst was removed by filtration and the
reduction product was next condensed with 4,7-dichloro-
quinoline to yield a compound resembling the antimalarial,
Camoquin (LXXXI).

In view of the recent discovery by Thompson of the
amebacidal activity of Atabrine (57), this work was
further extended by condensing the same amines with
2-methoxy-6,9-dichloroacridine to yield compounds similar
in structure to Atabrine (LXXXII).

Although not directly concerned with this thesis,
but as a matter of interest, the pyrrolidine analog of
Camoquin (LXXXIII) was prepared by the procedure outlined
by Burckhalter (58). In addition, the side chain com-
pound used in the above preparation was also condensed
with 2-methoxy-6,5-dichloroacridine to give an analogous
product.
LXXIX

\[
\begin{align*}
&\text{C-CH}_2\text{-CH}_2\text{-NR}_2 \\
&\text{NH}_2 \\
&\text{Cl} \\
&\text{Cl}
\end{align*}
\]

LXXX

\[
\begin{align*}
&\text{N}\text{-CH}_2\text{(CH}_2)_3\text{-N(C}_2\text{H}_5)_2 \\
&\text{Cl} \\
&\text{Cl}
\end{align*}
\]

LXXXI - Camoquin

\[
\begin{align*}
&\text{CH}_2\text{-N(C}_2\text{H}_5)_2 \\
&\text{Cl} \\
&\text{Cl}
\end{align*}
\]

LXXXII - Atabrine

\[
\begin{align*}
&\text{N}\text{-CH}_2\text{(CH}_2)_3\text{-N(C}_2\text{H}_5)_2 \\
&\text{OCH}_3 \\
&\text{Cl} \\
&\text{Cl}
\end{align*}
\]

LXXXIII

\[
\begin{align*}
&\text{CH}_2\text{-N} \\
&\text{Cl} \\
&\text{Cl}
\end{align*}
\]
DISCUSSION OF PHARMACOLOGICAL RESULTS

TYPE V COMPOUNDS. Unfortunately, none of the compounds of this type which seemed to have structures of sufficient interest to warrant pharmacological evaluation were produced in a quantity large enough to allow such tests to be carried out.

TYPE VI COMPOUNDS. It is perhaps worthy of note that the in vitro tests which have heretofore been widely used in screening techniques are now rapidly being discarded in many quarters because it has been shown that scores of compounds which possess relatively high in vitro activity were later found to be devoid of in vivo activity (12).

The results of the in vitro testing, for many of the thiosemicarbazones, obtained by Dr. G. P. Youmans, of Northwestern University, are summarized in Table VI.

It may be seen that of the nine compounds tested thus far, only one has failed to show in vitro activity. From these results, it appears that p-chloroacetophenone thiosemicarbazone (XXXV) is the most active compound to date. As a consequence of these interesting in vitro activities, three of these compounds (XXVI, XXVIII, and XXX) have been submitted for testing in experimental animals.

TYPE VII COMPOUNDS. Although most of the Mannich
bases described in this paper were tested for their antibacterial activity, none were found to possess higher activity than III. No results have yet been obtained on the pharmacological evaluation of the carbinoles or of the acridine and quinoline derivatives described in this section.
TABLE VI

Least amounts of compounds which completely inhibit growth of M. H. 37 Rv

<table>
<thead>
<tr>
<th>No.</th>
<th>Activity mg.%</th>
<th>Plasma activity at 10 mg.%</th>
</tr>
</thead>
<tbody>
<tr>
<td>XXVI</td>
<td>5.0</td>
<td>no growth</td>
</tr>
<tr>
<td>XXVII</td>
<td>5.0</td>
<td>no growth</td>
</tr>
<tr>
<td>XXX</td>
<td>5.0</td>
<td>no growth</td>
</tr>
<tr>
<td>XXXV</td>
<td>0.625</td>
<td>no growth</td>
</tr>
<tr>
<td>XXXVII</td>
<td>2.5</td>
<td>no growth</td>
</tr>
<tr>
<td>XXXVIII</td>
<td>2.5</td>
<td>growth</td>
</tr>
<tr>
<td>XL</td>
<td>2.5</td>
<td>no growth</td>
</tr>
<tr>
<td>XLI</td>
<td>2.5</td>
<td>no growth</td>
</tr>
<tr>
<td>XLIII</td>
<td>1.25</td>
<td>no growth</td>
</tr>
</tbody>
</table>
EXPERIMENTAL*

TYPE V COMPOUNDS - STRUCTURES RELATED TO CHLORAMPHENICOL

Benzalacetone (XIII). - The procedure of Drake and Allen (59) was employed. A mixture of 424 g. (4.0 mole) of freshly distilled benzaldehyde, 400 ml. of water and 800 ml. of acetone was cooled to 10-15°. With stirring 100 ml. of 10% sodium hydroxide solution was added. Care was taken to insure that the temperature of the reaction did not rise above 30° during the addition. The mixture was then stirred at room temperature for two and one-fourth hours, then made acidic with dilute hydrochloric acid. The two layers which formed were separated by means of a separatory funnel. The lower aqueous layer was extracted with 100 ml. of benzene and this solution then combined with the original oily layer. After washing with 100 ml. of water, the benzene was removed on the steam bath and the residue distilled under reduced pressure yielding 432 g. (74%) of light yellow oil, b.p. 142-146° (16mm.). Drake and Allen obtained 78%, b.p. 123-128° (8mm.). The liquid solidified on standing.

Styryl Oximinomethyl Ketone (XIV). - Into a 3-l.,

*C and H analyses are by Mr. C. M. Beazley, Skokie, Illinois.
three-necked flask equipped with a mechanical stirrer was placed 1.5 l. of Skelly Solve B. One hundred grams (0.59 mole) of benzalacetone was melted on the steam bath and dissolved therein. The flask was allowed to come slowly to room temperature, surrounded by a water bath. To this solution was then added 225 ml. of isomethylnitrite (freshly prepared) and 40 ml. of concentrated hydrochloric acid in alternate portions. The temperature was maintained near 20° by the addition of small amounts of ice to the surrounding water bath. After the addition was complete, the flask was surrounded by an ice-salt bath and stirring continued for another two hours. The solid thus obtained was removed by filtration and washed alternately with benzene and water until the washings were colorless. The weight of air-dried material was 62 g. (65%). The product was recrystallized from methyl alcohol-water to yield a solid that melted at 143°. Robinson and Foulds (30) reported no melting point for this compound. In regard to yield they indicated only that it was "excellent". Recrystallization was not routinely employed, since experience indicated that the air-dried material was pure enough for the subsequent reaction.

**Styryl Aminomethyl Ketone Stannichloride (XV).**

Styryl oximino methyl ketone (40 g.; 0.23 mole) was dissolved in 95% ethyl alcohol. A solution of 110 g. of
stannous chloride in 300 ml. of concentrated hydrochloric acid was prepared, cooled and placed in 1-l. three-necked flask equipped with a mechanical stirrer. The flask was surrounded by an ice bath and the alcoholic solution of the oxime added slowly with stirring. Upon the completion of the addition, the ice bath was removed and the stirring continued for six hours. The solid was removed by filtration and washed thoroughly with alcoholic hydrogen chloride. A light tan solid was obtained upon air drying this material. Eighty-two grams (80%) of the tin complex was thus obtained.

1-Acetamido-4-phenyl-3-buten-2-one (XVI). - To a 3-l. flask equipped with an efficient stirrer, a thermometer and a dropping funnel was added the tin complex salt obtained from 35 g. (0.2 mole) of styryl oximinomethyl ketone and 250 ml. of hot water. The mixture was stirred until a clear solution was produced. The flask was then cooled to -5°. Twenty-five grams of acetic anhydride was added in one portion, and the resulting mixture stirred rapidly while a cold solution of 42 g. of sodium hydroxide in 100 ml. of water was added at such a rate as to keep the temperature below 10°. When about 75 ml. of the sodium hydroxide solution had been added and the mixture was almost alkaline, 7 g. of acetic anhydride was poured in. Addition of the hydroxide was completed and stirring maintained for thirty minutes at 0°.

The mixture was saturated with sodium chloride and
extracted five times with 500 ml. portions of ethyl acetate. The combined extracts were washed with saturated sodium chloride solution, dried over anhydrous sodium sulfate and concentrated to 200 ml. by removal of solvent. To the hot concentrate was added 180 ml. of Skelly B. The mixture was cooled to 5° and filtered. The yield was 34 g. (81%), m.p. 118-123°. An analytical sample was obtained by recrystallization from water. It melted at 127°.

**Anal.** Calcd. for C_{12}H_{13}NO_2: C, 71.90; H, 6.45.

Found: C, 71.74; H, 6.36.

**1-Acetamido-4-(p-nitrophenyl)-3-buten-2-one (XX).**

To a 200 ml. three-necked flask, equipped with a mechanical stirrer and thermometer, was added 60 ml. of sulfuric acid. The flask was surrounded by an acetone-dry ice bath and the temperature lowered to -20° by the addition of pieces of dry ice. To this was then slowly added 20.3 g. (0.11 mole) of 1-acetamido-4-phenyl-3-buten-2-one, care being taken to insure that the temperature did not rise above -10° during the addition. When all the solid had been added and the temperature again lowered to -20°, a nitrating solution of 6.4 ml. of concentrated nitric acid (S/G 1.42) and 10 ml. of concentrated sulfuric acid was added dropwise. The mixture in the flask became rather dark and very viscous. The mixture was stirred for fifteen minutes after the addition of the last portion of acid;
the cooling bath having been removed during this period of stirring. The mixture was then poured into one liter of cracked ice and water and stirred for two hours. A yellow, rather pasty solid formed at first, but this soon became more granular in appearance. The solid was removed by filtration and washed with water to remove the traces of acid present. It was then allowed to air-dry overnight, yield 12.2 g. (50%), m.p. 146-155°. A sample for analysis was purified by repeated recrystallization from ethyl acetate-Skelly B. The purified product is fluffy in appearance and light yellow in color. It melted at 171°.

Anal. Calcd. for C_{12}H_{12}N_{2}O_{4}: C, 53.05; H, 4.87.
Found: C, 53.32; H, 5.01.

1-Amino-4-phenyl-3-buten-2-one Hydrochloride (XVII). Eight and one-tenth grams (0.04 mole) of the corresponding acetamido derivative was heated for two hours on the steam bath with 100 ml. of 5% hydrochloric acid. The solid dissolved shortly after the heating began. The solution gradually became dark red in color and a dark oil formed on the bottom of the flask. The mixture was cooled slowly to room temperature and then the hydrolysate was twice extracted with ether to remove any neutral material. The aqueous solution of the hydrochloride was then taken to dryness in vacuo. The solid thus obtained was filtered and washed with acetone-ether; yield 3 g. (39%). The crude
solid was dissolved in an acetone-isopropyl alcohol solution, treated with charcoal, filtered and set aside in the refrigerator to cool. White crystals, m.p. 184-189°, were obtained. On further recrystallization from acetone-isopropyl alcohol, the melting point was raised to 193°.

**Anal.** Calcd. for C_{10}H_{11}NO·HCl: Cl, 17.94.

**Found:** Cl, 18.12.

1-Dichloroacetamido-4-phenyl-3-buten-2-one (XVIII).

Five and nine-tenths grams (0.03 mole) of the above amine and 5.1 g. (0.035 mole) of dichloroacetyl chloride were mixed together with 100 ml. of dry benzene in a 300 ml. flask equipped with a reflux condenser, mechanical stirrer and dropping funnel. The mixture was cooled and stirred while 6.67 g. (0.67 mole) of triethylamine was added over a period of fifteen minutes. Toward the end of the addition of the amine, the mixture thickened and the cooling bath was removed. Stirring was continued for another hour. The mixture was then heated to reflux and filtered while hot. As the filtrate cooled a quantity of solid product separated and this was removed by filtration. The filtrate was then evaporated to dryness by passing a current of air over it. The residue thus obtained was first washed with Skelly B and then with water. This residue was then combined with the solid previously obtained by filtration and both were recrystallized from 95% ethyl
alcohol-water; yield 3.8 g. (47%), m.p. 128-131°. An analytical sample was obtained by two additional recrystallizations from benzene; m.p. 133-134°.

Anal. Calcd. for C_{12}H_{11}Cl_{2}NO_{2}: C, 52.96; H, 4.07.
Found: C, 53.23; H, 4.13.

2-Dichloroacetamido-1-hydroxy-5-phenyl-4-penten-3-one (XIX). - A mixture of 1.35 g. (0.005 mole) of the above dichloroacetamidobenzalacetone, 10 ml. of 95% ethyl alcohol and 1.75 ml. (ca. 0.025 mole) of 37% aqueous formaldehyde was prepared in a 25 ml. round-bottomed flask equipped with a thermometer. The mixture was agitated by means of a magnetic stirrer. One-tenth gram of sodium bicarbonate was added and the mixture stirred and warmed to 35°. Soon a clear solution was formed. Stirring was continued for one and one-half hours, at the end of which time the solution was still clear. The solution was then poured into 25 ml. of ice and water. A gummy solid soon began to separate. The flask was then refrigerated for 48 hours, during which time the gummy mass solidified. The solid was removed by filtration, yield 0.9 g. (64%). This was recrystallized from benzene to yield a solid, m.p. 118-120°. On further recrystallization from benzene, the melting point was raised to 122°.

Anal. Calcd. for C_{13}H_{13}Cl_{2}NO_{3}: C, 51.67; H, 4.34.
Found: C, 51.96; H, 4.41.
1-Amino-4-(p-nitrophenyl)-3-buten-2-one Hydrochloride (XXIV). - Seven and five-tenths grams (0.03 mole) of 1-acetamido-4-(p-nitrophenyl)-3-buten-2-one was heated with 125 ml. of 5% hydrochloric acid on the steam bath for two and one-half hours. Slowly a red solution formed, but simultaneously a considerable amount of brown tar was deposited in the bottom of the flask. The mixture was filtered while warm and then set aside to cool. A yellow solid; 3 g. (41%), m.p. 262-266°, was thus obtained. This solid was then recrystallized from dilute ethyl alcohol to which a few drops of concentrated hydrochloric acid had been added. It melted at 276° (dec.). The compound begins to darken and shrink in the region of 210-215°, but true melting does not occur until the higher temperature is reached.

Anal. Calcd. for C₁₀H₁₀N₂O₃·HCl: Cl, 14.61.
Found: Cl, 14.74.

1-Dichloroacetamido-4-(p-nitrophenyl)-3-buten-2-one (XXV). - Seven and one-half grams (0.03 mole) of the corresponding amine hydrochloride and 5.1 g. (0.035 mole) of dichloroacetyl chloride were mixed together with 160 ml. of dry benzene in a 300 ml. flask equipped with a mechanical stirrer, dropping funnel and reflux condenser. The mixture was surrounded by an ice bath and cooled and stirred while 6.7 g. (0.065 mole) of triethylamine was added over
a period of twenty minutes. Stirring was continued for a total of two hours; the cooling bath having been removed toward the end of the addition of the triethylamine. The mixture was then heated to reflux and filtered hot. The filtrate was concentrated in vacuo. The residue was washed; first with Skelly B and then with water. It was dissolved in 95% ethyl alcohol by warming, treated with charcoal and filtered while hot. The filtrate was made slightly turbid by the addition of a few drops of water. This was again filtered and set aside to cool. The yellow solid which formed was removed by filtration; yield 3 g. (30%); m.p. 178-182°. An analytical sample was prepared by repeated recrystallization from benzene.

Three different samples were prepared by the above method and each was analyzed.

**Anal.** Calcd. for C$_{12}$H$_{10}$Cl$_2$N$_2$O$_4$: C, 45.44; H, 3.17; Cl, 22.36.

Found: C, 46.21; H, 3.61.

Found: C, 46.35; H, 3.65;

Cl, 20.15.

Found: C, 46.85; H, 3.59.

**Reactions of 1-Acetamido-4-phenyl-3-buten-2-one (XVI)** with Formaldehyde. - The general procedure in all cases was to dissolve or suspend the amide in methyl alcohol, ethyl alcohol or a mixture of the two, with or without the
addition of a few drops of water, and then to add the appropriate quantity of aqueous formaldehyde (37%) or paraformaldehyde. A trace of the desired catalyst was then added and the suspension heated and stirred for varying periods. Then the reaction mixtures were poured into ice water and the products collected and examined. The amide was recovered unchanged after many experiments, but the conditions tabulated led to either the formation of a compound A postulated as having the two active methylene hydrogens replaced by \(-\text{CH}_2\text{OH}\) groups or a compound B believed to be of the bis-methane structure.

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Solvent</th>
<th>Time</th>
<th>Equivalents of Formaldehyde</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaHCO₃</td>
<td>CH₃OH-HOH</td>
<td>2 hr.</td>
<td>1</td>
<td>A(40%)</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>HOH</td>
<td>2 hr.</td>
<td>2</td>
<td>A(75-85%)</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>HOH</td>
<td>2 hr.</td>
<td>4</td>
<td>A(75-85%)</td>
</tr>
<tr>
<td>Na₂CO₃</td>
<td>CH₃OH</td>
<td>2 hr.</td>
<td>2</td>
<td>B(poor)</td>
</tr>
<tr>
<td>NaHCO₃</td>
<td>CH₃OH</td>
<td>12 hr.</td>
<td>2(paraformaldehyde)B(poor)</td>
<td></td>
</tr>
<tr>
<td>K₂CO₃</td>
<td>C₂H₅OH</td>
<td>4 hr.</td>
<td>2</td>
<td>Undetermined</td>
</tr>
</tbody>
</table>

For Compound A: \(\text{C}_6\text{H}_5-\text{CH}==\text{CH}-\text{CO-C(\text{NHCOCH}_3)(CH}_2\text{OH})_2\):  

**Anal. Calcd. for \text{C}_{14}\text{H}_{17}\text{NO}_4:**  
\(\text{C}, 63.86; \text{H}, 6.51.\)

**Found:**  
\(\text{C}, 64.03; \text{H}, 6.52.\)

**Found:**  
\(\text{C}, 63.87; \text{H}, 6.61.\)

For Compound B: \((\text{C}_6\text{H}_5-\text{CH}==\text{CH}-\text{CO-CH(\text{NHCOCH}_3)})_2-\text{CH}_2\):
Anal. Calcd. for \( \text{C}_{25}\text{H}_{26}\text{N}_{2}\text{O}_{4}\cdot\frac{3}{2}\text{H}_{2}\text{O} \): C, 70.23; H, 6.40.

Found: C, 70.25; H, 6.66.

**Attempted Preparation of 2-Acetamido-1-hydroxy-5-(p-nitrophenyl)-4-penten-3-one (XXI).** - A mixture of 12.4 g. (0.05 mole) of 1-acetamido-4-(p-nitrophenyl)-4-buten-3-one, 50 ml. of 95% ethyl alcohol and 10 ml. (ca. 0.15 mole) of aqueous formaldehyde was prepared in a 200 ml. flask equipped with a stirrer and thermometer. Five-tenths gram of sodium bicarbonate was added and the mixture was warmed slowly to 35° where it was maintained, with stirring, for two hours. A clear solution was never formed. At the end of this period, the flask was cooled in the refrigerator overnight. The yellow solid was filtered and dried; yield 11.8 g. (85%), m.p. 156-159°. The product was recrystallized from absolute ethyl alcohol; m.p. 162-163°. Although there was some depression in the melting point of a mixture of this product and starting material, analysis indicated that this material was recovered starting material.
p-Nitrophenacyl Alcohol Acetate. - The procedure of Engler and Zielke (44) was used. A mixture of 24.4 g.
(0.1 mole) of p-nitrophenacyl bromide, 13.6 g. (0.1 mole)
of sodium acetate trihydrate, and 150 ml. of glacial acetic
acid was refluxed for 45 minutes. On cooling, a yellow
crystalline mass formed readily. The solid was collected
on a Buchner funnel yielding 14.5 g. (65%) of yellow
needles, m.p. 110-116°. The compound was purified by
repeated recrystallization from ethyl alcohol, m.p. 122-
123°. Engler and Zielke report 124°.

α-Dichloroacetamido-p-nitroacetophenone. - According
to the method of Long and Troutman (34), 21.8 g. (0.1 mole)
of α-amino-p-nitroacetophenone hydrochloride and 17.7 g.
(0.12 mole) of dichloroacetyl chloride were mixed together
with 250 ml. of dry benzene in a 500 ml. flask equipped
with a reflux condenser, a mechanical stirrer and a dropping
funnel. The mixture was cooled and stirred while 22.2 g.
(0.22 mole) of triethylamine was added over a period of
fifteen minutes. Stirring was continued for another one
and one-half hours, after the cooling bath had been re-
moved. The mixture was then heated to reflux and filtered
hot. As the filtrate cooled, a quantity of solid product
separated which was filtered off. The filtrate was con-
centrated in vacuo. The residue was washed with Skelly B
and then water. It was dissolved in hot alcohol and the resulting solution diluted to cloudiness with water. The mixture was cooled and filtered. The solid was combined with the material obtained originally and recrystallized from benzene; yield 9.3 g. (32%); m.p. 142-146°. A small sample was repeatedly recrystallized from benzene; m.p. 148-149°. Long and Troutman report a yield of 50%, m.p. 148-149°.

3,5-Dinitroacetophenone. - The following procedure is similar to that of Walker and Hauser (45), but differs in several important details.

Three and nine-tenths grams (0.11 mole) of magnesium turnings and a solution of 0.5 ml. of dry carbon tetrachloride in 2.5 ml. of absolute ethyl alcohol were placed in a 300 ml. flask equipped with a mechanical stirrer, a dropping funnel and a thermometer. As soon as the magnesium began to react with the ethyl alcohol, 25 ml. of dry chlorobenzene was added rapidly, the reaction between magnesium and the alcohol continuing. A solution of 17.6 g. (0.11 mole) of diethyl malonate, 12.5 ml. of chlorobenzene and 10 ml. of absolute ethyl alcohol was added with stirring and cooling at such a rate as to keep the temperature at about 65°. When the reaction had proceeded to the extent that the removal of the cooling bath did not result in a rise in temperature, the mixture was heated slowly to 85° and kept there until the amount of unreacted magnesium
was constant (about one and one-half hours).

The clear, dark solution was cooled to 25°, and a solution of 23.1 g. (0.1 mole) of 3,5-dinitrobenzoyl chloride in 75 ml. of chlorobenzene was added with stirring and moderate cooling so that the temperature did not exceed 35°. When about one-half of the acid chloride had been added, a brown, gelatinous mass precipitated and stirring became rather difficult. The mixture was stirred for thirty minutes at 35°. The flask was then cooled in an ice-bath and a solution of 7 ml. of concentrated sulfuric acid in 50 ml. of water was added immediately, slowly at first and then more rapidly.

The mixture was transferred to a separatory funnel and the lower layer, saturated with sodium sulfate, discarded. The chlorobenzene layer was concentrated in vacuo. The residue was refluxed with 30 ml. of glacial acetic acid, 4 ml. of concentrated sulfuric acid and 20 ml. of water for six hours. The cooled hydrolysis mixture was added slowly with stirring to 400 g. of cracked ice. The solid product was removed by filtration and washed with water. It was then melted under 100 ml. of water and stirred while 12 g. of sodium bicarbonate was added. The cooled mixture was filtered and the solid product was again treated with 4 g. of sodium bicarbonate. The solid was filtered from the cooled mixture and recrystallized from ethyl alcohol; the yield of off-white crystalline product
was 14.8 g. (67%), m.p. 82-83°.

p-Nitrobenzalacetone. - Four hundred grams of concentrated sulfuric acid was cooled to 0° and 170 g. (1.17 moles) of benzalacetone was slowly added. The temperature was then lowered to -20° by the use of an acetone-dry ice bath and a nitrating solution containing 90 g. (1.18 moles) of concentrated nitric acid (S.G. 1.42) in 200 g. of concentrated sulfuric acid was added as rapidly as possible without allowing the temperature to rise above -15°. (The nitrating mixture can be added quite rapidly, if large amounts of dry ice are placed in the surrounding bath). After an additional fifteen minutes stirring, the solution was poured onto 2000 g. of cracked ice. After stirring for three hours, the yellow solid was collected on a sintered glass funnel, thoroughly washed with water and then air dried. The solid was recrystallized from absolute ethyl alcohol yielding 155 g. (69%) of light yellow solid, m.p. 109-110° (60). The ortho isomer was not isolated, since no trace of it was visible in the original filtrate from the nitration, as had been previously experienced when the nitration had been performed at a higher temperature.

p-(p-Nitrophenyl)acetophenone. - The procedure of Grieve (46) was utilized for this preparation. To a mixture of 40 g. (0.2 mole) of p-nitrobiphenyl, 160 g. of anhydrous aluminum chloride and 600 ml. of carbon disulfide
contained in a 1-l., three-necked flask equipped with a mechanical stirrer, reflux condenser and dropping funnel was added dropwise 48 g. (0.60 mole) of acetyl chloride. Stirring was maintained throughout the period of the addition of the acetyl chloride. The mixture was then heated slowly to reflux, at which temperature it was maintained, with stirring, for ten hours. When it had refluxed for the designated time, the original orange-red color had changed to dark brown. The warm mixture was poured slowly onto 1500 g. of cracked ice. After standing for a short period, the red-brown solid which had formed was removed by filtration and then air dried. This solid was refluxed with 450 ml. of benzene for about ten minutes, and the resulting suspension was filtered hot. The filtrate was evaporated to dryness \textit{in vacuo}. The solid residue thus obtained was light brown to brown-yellow in color. The yield was 31 g. (64\%), m.p. 148-151°. After one recrystallization from benzene and decolorization with charcoal it melted at 150-152°.

\textit{β}-Benzoylpropionitrile. - Following Knott's procedure (78), 42.7 g. (0.2 mole) of \textit{β}-dimethylaminopropiophenone hydrochloride XLIV, 26 g. (0.4 mole) of potassium cyanide, and 520 ml. of water were placed in a one liter round-bottomed flask and refluxed for a period of thirty minutes. The mixture was then thoroughly cooled in an ice-bath. The reddish-oil solidified and greenish-white crystals
formed in the aqueous portion of the resulting liquid. The crude solid was removed by filtration and washed with cold water. The crude solid thus obtained was recrystallized from 95% ethyl alcohol, thence from benzene-Skelly B. The yield of recrystallized product was 19.1 g. (61%), m.p. 76°.

\(\beta\)-Benzoylpropionic Acid (XVIII). - Twelve grams (0.75 mole) of the above nitrile was refluxed for one hour with 125 ml. of 15% hydrochloric acid. The solution was then cooled and the resulting solid filtered off. This solid was purified by dissolving in 5% sodium bicarbonate solution, filtering, cooling and then carefully acidifying with concentrated hydrochloric acid. A light tan solid was thus obtained. Recrystallization from hot water yielded 12.6 g. (95%) of a white solid, m.p. 115-116°.

In general, the thiosemicarbazones listed in Table II were prepared by one of the three experimental procedures outlined below.

Procedure A. - Five-hundredths mole of the carbonyl compound was dissolved in the minimum amount of 95% ethyl alcohol. Concurrently, 4.5 g. (0.05 mole) of thiosemicarbazide was being dissolved in the requisite amount of warm water. The two solutions were poured together and 10 drops of concentrated hydrochloric acid were then added. This was followed by the addition of two grams of sodium acetate (trihydrate). The resulting mixture was
then heated on the steam bath for fifteen to twenty minutes, during which time a heavy precipitate generally formed. Then, the flask was cooled in an ice bath and its contents collected, washed with warm water and air-dried. In general, thiosemicarbazide is more water-soluble than the resulting thiosemicarbazones; consequently, trituration with boiling water or recrystallization of the excess thiosemicarbazide from water (to free the solid of unreacted thiosemicarbazide) may be profitably employed in the purification of these compounds. Analytical samples were routinely obtained by recrystallization from 95% ethyl alcohol or a mixture of this solvent and water.

Procedure B. - Five-hundredths mole of the amino ketone hydrochloride was dissolved by warming in dilute ethyl alcohol to which a few drops of concentrated hydrochloric acid had been added. Four and five-tenths grams (0.05 mole) of thiosemicarbazide was dissolved in a minimum amount of warm water. The two solutions were then poured together and allowed to heat on the steam bath for about 20 minutes. Next, the flask was allowed to cool slowly to room temperature. The flask was then refrigerated overnight, and the crop of yellow crystals, which had formed, collected. An analytical sample was obtained by repeated recrystallization from acidulated water - 95% ethyl alcohol solution.

Procedure C. - Eight and nine-tenths grams (0.05 mole)
of $\beta$-benzoylpropionic acid and 4.1 g. of sodium acetate were dissolved in 125 ml. of 95% ethyl alcohol. Four and five-tenths grams (0.05 mole) of thiosemicarbazide was dissolved with warming in 100 ml. of 95% ethyl alcohol to which 0.5 ml. of concentrated hydrochloric acid had been added. The two solutions were mixed and heated intermittently on the steam bath for 48 hours. The solution was then allowed to cool slowly to room temperature and finally refrigerated overnight. The white solid, thus formed, was filtered and the solid air-dried. An analytical sample was obtained by repeated recrystallization from 95% ethyl alcohol.
TYPE VII COMPOUNDS - KETONIC MANNICH BASES

\[ \beta \text{-Dimethylaminopropiophenone Hydrochloride (XLIV).} \]

According to the procedure of Maxwell (47), 120 g. (1.0 mole) of acetophenone, 81 g. (1.0 mole) of dimethylamine hydrochloride, 45 g. (1.5 mole) of paraformaldehyde and 120 ml. of 95% ethyl alcohol were placed in a round-bottomed flask. To this mixture was added 1 ml. of concentrated hydrochloric acid. It was then refluxed for two hours. The hot solution was poured into 400 ml. of acetone and the solution allowed to come slowly to room temperature, during which time a considerable portion of solid was collected on a Buchner funnel, washed with cold acetone and pressed dry. After drying in a vacuum desiccator overnight, 145 g. (66%) of white solid, m.p. 144-147°, was obtained. Maxwell obtained 68-72%, m.p. 138-141°.

\[ \text{p-Nitro-\(\beta\)-dimethylaminopropiophenone Hydrochloride (XLV).} \]

By the same method employed for the preparation of the above compound, 49.5 g. (0.3 mole) of \(p\)-nitroacetophenone, 24.3 g. (0.3 mole) of dimethylamine hydrochloride and 16 g. (0.37 mole) of paraformaldehyde yielded 55.8 g. (72%) of light yellow crystalline solid, m.p. 136-139° (61).

\[ \text{p-Nitro-\(\beta\)-diethylaminopropiophenone Hydrochloride (XLVI).} \]

By the above method, 16.5 g. (0.1 mole) of \(p\)-nitroacetophenone, 11 g. (0.1 mole) of diethylamine
hydrochloride and 4.5 g. (0.15 mole) of paraformaldehyde yielded 18.8 g. (66%) of light yellow crystalline solid, m.p. 133-142°. Recrystallization from 95% ethyl alcohol-acetone of a small sample raised the melting point to 149-150°.

**p-Nitro-β-dipropylaminopropiophenone Hydrochloride (XLVII).** - Ten and one-tenth grams (0.1 mole) of dipropylamine was dissolved in 25 ml. of absolute ethyl alcohol. This solution was made acid to Congo Red by the addition of concentrated hydrochloric acid slowly, with cooling. To this acid solution was added 16.5 g. (0.1 mole) of p-nitroacetophenone and 4.5 g. (0.15 mole) of paraformaldehyde. The mixture was refluxed for three hours and then poured into 200 ml. of acetone and allowed to cool to room temperature. The flask was then refrigerated overnight. The contents of the flask were removed by filtration to yield 8.2 g. (26%) of a white solid, m.p. 134-137°. A small sample, after recrystallization from 95% ethyl alcohol-acetone, melted at 139-140°.

**p-Nitro-β-morpholinylpropiophenone Hydrochloride (XLVIII).** - Sixteen and five-tenths grams (0.1 mole) of p-nitroacetophenone, 12.4 g. (0.1 mole) of morpholine hydrochloride and 4.5 g. (0.15 mole) of paraformaldehyde yielded 18.7 g. (62%) of a light yellow solid, m.p. 206-210°. A sample purified by recrystallization from ethyl alcohol-acetone melted at 218°.
p-Nitro-β-piperidylpropiophenone Hydrochloride (XLIX). - Following the general procedure outlined previously, 49.5 g. (0.3 mole) of p-nitroacetophenone, 25.5 g. (0.3 mole) of piperidine and 13.5 g. (0.45 mole) of paraformaldehyde yielded 45 g. (51%) of light yellow crystalline solid, m.p. 199-200°.

p-Nitro-β-diethanolaminopropiophenone Hydrochloride (I). - According to the general procedure of Maxwell (47), 33 g. (0.2 mole) of p-nitroacetophenone, 28.2 g. (0.2 mole) of diethanolamine hydrochloride (prepared according to the procedure of Levy and Nisbet (62), 13 g. (0.33 mole) of paraformaldehyde, 0.5 ml. of concentrated hydrochloric acid and 50 ml. of absolute ethyl alcohol were refluxed for two and one-half hours. The solution was then poured into 200 ml. of acetone and set aside to cool. The flask was then placed in the refrigerator overnight. When only a small amount of solid had formed on the following day, it was decided to allow the flask to remain under refrigeration for a longer period of time. When, after a period of two weeks, no appreciable amount of solid had formed, the volume of the solution was reduced materially by concentrating it in vacuo. Thus, 12 g. (19%) of white solid was obtained, m.p. 132-135°. An analytical sample, prepared by recrystallization from 95% ethyl alcohol, melted at 145-146°.

p-Nitro-β-pyrrolidylpropiophenone Hydrochloride (II).
By the procedure outlined for the preparation of the corresponding piperidine compound, 49.5 g. (0.3 mole) of p-nitroacetophenone, 21.3 g. (0.3 mole) of pyrrolidine, 13.5 g. (0.45 mole) of paraformaldehyde and 75 ml. of absolute ethyl alcohol yielded 51.2 g. (61%) of light yellow solid, m.p. 176-179°. A sample recrystallized from 95% ethyl alcohol-acetone melted at 183-184.5°.

m-Nitro-β-dimethylaminopropiophenone Hydrochloride (LII). - By the general procedure of Maxwell (47), 33 g. (0.2 mole) of m-nitroacetophenone, 16.2 g. (0.2 mole) of dimethylamine hydrochloride and 9 g. (0.3 mole) of paraformaldehyde yielded 37.1 g. (72%) of white solid. After recrystallization from ethyl alcohol-acetone, it melted at 203-205°. Mannich and Dannheil (63) report 209°.

m-Nitro-β-pyrrolidylpropiophenone Hydrochloride (LIII). - Forty-one and twenty five-hundredths grams (0.25 mole) of m-nitroacetophenone, 17.3 g. (0.25 mole) of pyrrolidine and 11.5 g. (0.38 mole) of paraformaldehyde yielded 45 g. (63%) of white solid, m.p. 174-178°. After recrystallization from ethyl alcohol-acetone, it melted at 181-182°.

p-Chloro-β-dimethylaminopropiophenone Hydrochloride (LIV). - Sixty-one and eight-tenth grams (0.4 mole) of p-chloroacetophenone, 32.5 g. (0.4 mole) of dimethylamine hydrochloride and 13 g. (0.6 mole) of paraformaldehyde yielded 70.4 g. (71%) of white solid, m.p. 169-170°.
After two recrystallizations from isopropyl alcohol, a sample melted at 176°. Dhont and Vibaut (64) report 170°, but subsequent to the present work, Adamson andBillinghurst (65) reported 174-175°.

**p-Chloro-β-diethylaminopropiophenone Hydrochloride (LV).** - By the general procedure outlined previously, 39.9 g. (0.2 mole) of p-chloroacetophenone, 22 g. (0.2 mole) of diethylamine hydrochloride and 9 g. (0.3 mole) of paraformaldehyde yielded 32 g. (60%) of a white crystalline solid, m.p. 133-141°. After a sample was recrystallized from isopropyl alcohol, it melted at 145°. Adamson andBillinghurst (65) reported 141-142°.

**p-Chloro-β-piperidylpropiophenone Hydrochloride (LVI).** - Fifteen and five-tenths grams (0.1 mole) of p-chloroacetophenone, 12.1 g. (0.1 mole) of piperidine hydrochloride and 4.5 g. (0.15 mole) of paraformaldehyde yielded 16.2 g. (56%) of white crystalline solid, m.p. 132-135°. On recrystallization from ethyl alcohol-acetone, a sample melted at 138-190° (dec.). Denton (28) reported 139-191°.

**p-Bromo-β-dimethylaminopropiophenone Hydrochloride (LVII).** - Ten grams (0.05 mole) of p-bromocetophenone, 4.1 g. (0.05 mole) of dimethylamine hydrochloride and 2.25 g. (0.075 mole) of paraformaldehyde yielded 7.4 g. (52%) of white crystalline solid, m.p. 183-190°. After two recrystallizations from 95% ethyl alcohol, a sample melted at 196°. Knott (43) obtained 49%, m.p. 196°.
p-Bromo-β-diethylaminopropiophenone Hydrobromide (LVIII). — After the procedure of Land, Ziegler and Sprague, 10 g. (0.05 mole) of p-bromoacetophenone, 7.7 g. (0.05 mole) of diethylamine hydrobromide and 2.25 g. (0.075 mole) of paraformaldehyde yielded 7.3 g. (40%) of crystalline solid, m.p. 157-160°. A sample, after recrystallization from 95% ethyl alcohol, melted at 165-166°.

p-Bromo-β-piperidylpropiophenone Hydrobromide (LIX). — Following the above procedure, 40 g. (0.2 mole) of p-bromoacetophenone, 23 g. (0.2 mole) of piperidine hydrobromide and 9 g. (0.3 mole) of paraformaldehyde gave 31.6 g. (42%) of white solid, m.p. 160-164°. After recrystallization from 95% ethyl alcohol, a sample melted at 183°.

p-Bromo-β-pyrrolidylpropiophenone Hydrochloride (LX). — Twenty grams (0.1 mole) of p-bromoacetophenone, 7.1 g. (0.1 mole) of pyrrolidine and 4.5 g. (0.15 mole) of paraformaldehyde yielded 22 g. (69%) of white crystalline solid, m.p. 192-196°. After recrystallization from 95% ethyl alcohol-acetone, a sample melted at 198-199°.

p-Methoxy-β-dimethylaminopropiophenone Hydrochloride (LXI). — Thirty grams (0.2 mole) of p-methoxyacetophenone, 16.2 g. (0.2 mole) of dimethylamine hydrochloride and 12 g. (0.4 mole) of paraformaldehyde yielded 54.8 g. (75%) of crystalline white material, m.p. 176-180°. Mannich and Lammering (66) report a melting point of 187-188° for the pure product.
p-Methoxy-β-pyrrolidylpropionophenone Hydrochloride (LXII). - Forty-five grams (0.3 mole) of p-methoxyacetophenone, 21.3 g. (0.3 mole) of pyrrolidine and 13.5 g. (0.45 mole) of paraformaldehyde gave 30.8 g. (38%) of white crystalline product, m.p. 177-180°. On being recrystallized from 95% ethyl alcohol-acetone, a sample melted at 183-184°.

p-Hydroxy-β-dimethylaminopropiophenone Hydrochloride (LXIII). - Adhering to the procedure described by Knott (48), 50 g. (0.3 mole) of p-hydroxyacetophenone, 40 g. (0.5 mole) of dimethylamine hydrochloride and 15 g. (0.5 mole) of paraformaldehyde yielded, after recrystallization from 95% ethyl alcohol, 46 g. (56%) of off-white crystalline product, m.p. 192°. Knott reports an 80% yield of the crude product.

o-Hydroxy-β-dimethylaminopropiophenone Hydrochloride (LXIV). - Twelve and five-tenths grams (0.091 mole) of o-hydroxyacetophenone, 10 g. (0.12 mole) of dimethylamine hydrochloride and 3.6 g. (0.12 mole) of paraformaldehyde gave 6.8 g. (33%) of crystalline white solid, m.p. 151-154°. An analytical sample, prepared by repeated recrystallization from 95% ethyl alcohol-acetone, melted in the range of 155-156°.

p-Phenyl-β-dimethylaminopropiophenone Hydrochloride (LXV). - Nineteen and six-tenths grams (0.1 mole) of p-phenylacetophenone, 3.1 g. (0.1 mole) of dimethylamine
hydrochloride and 4.5 g. (0.15 mole) of paraformaldehyde yielded 22 g. (69%) of white solid, m.p. 184-187°. A sample, after three recrystallizations from 95% ethyl alcohol, melted at 191-192°.

2-(β-Pyrrolidylpropionyl) thiophene Hydrochloride (LXVI). — By the previously described method, 37.8 g. (0.3 mole) of 2-acetylthiphene, 21.3 g. (0.3 mole) of pyrrolidine and 13.5 g. (0.45 mole) of paraformaldehyde yielded 36 g. (43%) of white crystalline solid, m.p. 157-162°. A sample, after having been recrystallized from absolute ethyl alcohol-acetone, melted at 169-170°.

1-Morpholinyl-5-penten-3-one Hydrochloride (LXVII). — A mixture of 29.2 g. (0.2 mole) of benzalacetone, 24.4 g. (0.2 mole) of morpholine hydrochloride, 9 g. (0.3 mole) of paraformaldehyde and 0.5 ml. of concentrated hydrochloric acid in 40 ml. of 95% ethyl alcohol was refluxed for three hours. The hot solution was then poured into 200 ml. of acetone and the flask set aside to cool to room temperature. The flask was then placed in the refrigerator and allowed to cool overnight. The solid was removed by filtration; yield 37 g. (66%), m.p. 171-174°. On recrystallization from 95% ethyl alcohol-acetone, a sample melted at 177-178°.

1-Dimethylamino-5-(p-nitrophenyl)-4-penten-3-one Hydrochloride (LXX). — Following the general procedure of Maxwell (47), 19.1 g. (0.1 mole) of p-nitrobenzalacetone,
3.1 g. (0.1 mole) of dimethylamine hydrochloride, 4.5 g. (0.15 mole) of paraformaldehyde, 0.5 ml. of concentrated hydrochloric acid and 30 ml. of absolute ethyl alcohol were refluxed for three hours. The solution was then poured into 150 ml. of acetone. The light yellow solid, thus formed, was removed by filtration; yield 16.5 g. (53%), m.p. 182-185°. Johnson (2) obtained 68%, m.p. 187°.

1-Pyrrolidyl-5-(p-nitrophenyl)-4-penten-3-one Hydrochloride (LXXI). - By the previously described procedure, 19.1 g. (0.1 mole) of p-nitrobenzalacetone, 7.1 g. (0.1 mole) of pyrrolidine and 4.5 g. (0.15 mole) of paraformaldehyde yielded 17.7 g. (57%) of light yellow solid, m.p. 188-190°. A sample, after recrystallization from 95% ethyl alcohol-acetone melted at 195-196°.

1-Pyrrolidyl-5-phenyl-4-penten-3-one Hydrochloride (LXVIII). - By the general procedure outlined above, 43.8 g. (0.3 mole) of benzalacetone, 21.3 g. (0.3 mole) of pyrrolidine and 13.5 g. (0.45 mole) of paraformaldehyde yielded 64 g. (65%) of light yellow solid, m.p. 149-151°. Recrystallization from 95% ethyl alcohol-acetone yielded a light yellow solid, m.p. 155°.

1-Dimethylamino-5-(p-nitrophenyl)-4-penten-3-ol Hydrochloride (LXXXIII). - To a hot slurry of 20 g. (0.1 mole) of aluminum isopropoxide and 3.3 g. (0.025 mole) of anhydrous aluminum chloride in 175 ml. of dry isopropyl alcohol contained in a 500 ml. three-necked flask equipped
with a mechanical stirrer and reflux condenser was added 14.3 g. (0.05 mole) of 1-dimethylamino-5-(p-nitrophenyl)-4-penten-3-one hydrochloride. The mixture was brought to full reflux and maintained at that temperature for fifteen minutes. Then, the upright condenser was replaced by one turned downward for distillation and stirring and removal of acetone continued until the distillate gave a negative acetone test (about two hours). The upright condenser was reinserted and full reflux maintained for about ten minutes. Once again, the upright condenser was replaced by one placed so as to allow distillation to proceed and a few drops of distillate were collected. Since the acetone test was still negative, it was concluded that reduction was complete. The residual isopropyl alcohol was removed in vacuo. The solid residue was cooled and then treated with 200 ml. of ice-cold 10% hydrochloric acid. This suspension was dissolved in about 375 ml. of water. With cooling and stirring the aqueous solution was made strongly basic (pH about 12) with 40% potassium hydroxide. The basic solution was thoroughly ether extracted. The ether extract was washed with saturated sodium chloride solution and then dried with anhydrous sodium sulfate overnight. The ether extract was then filtered free of the drying agent and treated with anhydrous hydrogen chloride. An orange oil was thus produced. On standing for 43 hours in the refrigerator, this oil solidified. The solid was removed
by filtration and washed with cold acetone; yield 10.4 g. 
(72%) of light yellow solid, m.p. 177-180°. After three 
recrystallizations from 95% ethyl alcohol-acetone, a sam-
ple melted at 180-181°.

The starting amino ketone hydrochloride melted at 
187°, and the melting point of a mixture of the above pro-
duct and starting material was 165-176°.

**Anal. Calcd.** for C_{13}H_{18}N_{2}O_{5}·HCl: C, 54.45; H, 6.68.

**Found:** C, 54.42; H, 6.75.

**3-Dimethylamino-1-(p-nitrophenyl)-1-propanol Hydro-
chloride (LXXII).** - Following the above described procedure, 
12.9 g. (0.5 mole) of p-nitro-β-dimethylaminopropiophenone 
hydrochloride, 20.0 g. (0.1 mole) of aluminum isopropoxide 
and 3.3 g. (0.025 mole) of anhydrous aluminum chloride 
yielded 815 g. (65%) of white crystalline solid, m.p. 
153-163°. A sample for analysis was recrystallized once 
from 95% ethyl alcohol, thence from acetone until a constant 
melting point of 176° was obtained.

The melting point of a mixture of this product and 
starting material was 155-168°.

**3-Piperidyl-1-(p-nitrophenyl)-1-propanol Hydrochloride 
(LXXV).** - Following the general procedure outlined above, 
45 g. (0.15 mole) of p-nitro-β-piperidylpropiophenone 
hydrochloride, 60 g. (0.3 mole) of aluminum isopropoxide 
and 9.95 g. (0.075 mole) of anhydrous aluminum chloride
yielded 25 g. (55%) of white crystalline solid, m.p. 163-172°. On recrystallization from 95% ethyl alcohol-acetone, a sample melted at 176-177°.

The melting point of a mixture of this product and starting material was 158-170°.

3-Morpholinyl-1-(p-nitrophenyl)-1-propanol Hydrochloride (LXXVI). - By the above procedure, 50 g. (0.1 mole) of p-nitro-β-morpholinylpropophenone hydrochloride, 40 g. (0.2 mole) of aluminum isopropoxide and 6.6 g. (0.05 mole) of anhydrous aluminum chloride yielded 20 g. (67%) of light yellow crystalline product, m.p. 178-182°. A sample, after recrystallization from 95% ethyl alcohol-acetone, melted at 184-185°.

The melting point of a mixture of this product and starting material was 173-182°.

3-Pyrrolidyl-1-(p-nitrophenyl)-1-propanol Hydrochloride (LXXVII). - By the method outlined previously, 22.7 g. (0.08 mole) of p-nitro-β-pyrrolidylpropophenone hydrochloride, 32 g. (0.16 mole) of aluminum isoprooxide and 5.3 g. (0.04 mole) of anhydrous aluminum chloride yielded 14 g. (61%) of a crystalline white solid, m.p. 159-164°. After being recrystallized from absolute ethyl alcohol-acetone, a sample melted at 167-168°.

The melting point of a mixture of this compound and starting material was 149-158°.
3-Dimethylamino-1-(p-nitrophenyl)-1-propanol Hydrochloride (LXXIV). - Following the previously indicated procedure for the application of the Meerwein-Ponndorf-Verley reduction to this type of Mannich base, from 28.6 g. (0.1 mole) of \( p \)-nitro-\( \beta \)-dimethylaminopropiophenone hydrochloride, 40 g. (0.2 mole) of aluminum isopropoxide and 6.6 g. (0.05 mole) of anhydrous aluminum chloride was obtained 15.6 g. (54%) of white solid, m.p. 133-136\(^\circ\). After having been recrystallized from 95\% ethyl alcohol-acetone, a sample melted at 139-140\(^\circ\).

The melting point of a mixture of this compound and starting material was 124-133\(^\circ\).

3-Dimethylamino-1-(m-nitrophenyl)-1-propanol Hydrochloride (LXXVIII). - From 25.3 g. (0.1 mole) of \( m \)-nitro-\( \beta \)-dimethylaminopropiophenone hydrochloride (LII), 40 g. (0.2 mole) of aluminum isopropoxide and 6.6 g. (0.05 mole) of anhydrous aluminum chloride was obtained 11 g. (42\%) of a crystalline white solid, m.p. 179-184\(^\circ\). Recrystallized from 95\% ethyl alcohol-acetone, a sample of this compound melted at 187-188\(^\circ\).

The melting point of a mixture of this compound and starting material was 168-180\(^\circ\).

3-Dimethylamino-1-phenyl-1-propanol Hydrochloride (LXXII). - Two procedures, in addition to catalytic hydrogenation, have been employed in order to obtain this compound. By the method employed previously (aluminum
isopropoxide), 21.3 g. (0.1 mole) of \( \beta \)-dimethylaminopropiophenone hydrochloride, 60 g. (0.3 mole) of aluminum isopropoxide and 6 g. (0.045 mole) of anhydrous aluminum chloride yielded a crystalline white solid. After one recrystallization from 95% ethyl alcohol and three subsequent recrystallizations from acetone, 11.6 g. (65%) of white solid, m.p. 133-134°, was obtained. A mixed melting point of this compound and an authentic sample prepared by catalytic hydrogenation using Adams' catalyst showed no significant depression. Mannich (67) reports the melting point of this compound, prepared by reducing the corresponding amino ketone catalytically over palladium, as 134°.

Following the general procedure of Chaikin and Brown (63), a solution of 1.85 g. (0.05 mole) of sodium borohydride in 100 ml. of 50% methyl alcohol, cooled to 20°, was prepared and placed in a 300 ml. round-bottomed flask, equipped with a stirrer, reflux condenser and dropping funnel. Meanwhile, 10.6 g. (0.05 mole) of \( \beta \)-dimethylaminopropiophenone hydrochloride was dissolved in a minimum amount of water and made basic with ice-cold 20% sodium hydroxide. The basic mixture was then ether extracted. The ether was removed by gentle heating and the free base dissolved in about 75 ml. of methyl alcohol. The flask containing the sodium borohydride solution was surrounded by a cooling bath and the alcoholic solution of the amino ketone added
dropwise with stirring and cooling so as to maintain the temperature below 30°. After the addition was complete, the flask was removed from the cooling bath and warmed gently to 45-50° so as to decompose the excess sodium borohydride. The solution was then concentrated in vacuo to remove the alcohol. The residue was made basic with 6N sodium hydroxide and ether extracted. The ether extract was dried overnight with anhydrous sodium sulfate. The drying agent was removed by filtration and a stream of anhydrous hydrogen chloride was then passed through the ether solution to precipitate the hydrochloride of the amine. Soon, a fine white precipitate began to appear. The solution was cooled and the precipitate removed by filtration; yield 7.2 g. (67%), m.p. 128-132°. After recrystallization from acetone, a sample melted at 133-134°.

The melting point of a mixture of this compound and an authentic sample of the carbinol prepared by catalytic reduction of the corresponding amino ketone using Adams' catalyst showed no depression.

3-Dimethylamino-1-(p-(7-chloro-4-quinolylamino)phenyl)-I-propanol (LXXXIV). - Three grams (0.011 mole) of LXXIII was suspended in absolute ethyl alcohol and reduced catalytically using Adams' catalyst. The clear solution thus obtained was treated with a slight excess of alcoholic hydrogen chloride and filtered to remove the catalyst. An equivalent amount, 2.2 g. (0.011 mole), of 4,7-dichloroquinoline
was added to this filtrate and the resulting mixture refluxed for about two hours, during which time a clear solution was formed. The reaction mixture was made basic with 28% ammonium hydroxide and a light yellow solid precipitated; yield 4 g. (78%), m.p. 207-212°. The product was then recrystallized from 95% ethyl alcohol-water in order to obtain an analytical sample. It melted at 218-220°.

Anal. Calcd. for C_{26}H_{22}ClN_{3}O: C, 67.49; H, 6.23.

Found: C, 68.07; H, 6.77.

3-Pyrrolidyl-1-(p-(7-chloro-4-quinolylamino)phenyl)-1-propanol (LXXV). - Following the general procedure outlined previously, 12 g. (0.042 mole) of LXXVII was suspended in absolute ethyl alcohol and catalytically reduced using Adams' catalyst. The clear solution thus obtained was treated with a slight excess of alcoholic hydrogen chloride and filtered to remove the catalyst. The filtrate was then divided into two portions; one to be used in this preparation and the other to be used in the corresponding acridine derivative. Then, to one of these portions was added 4.2 g. (0.021 mole) of 4,7-dichloroquinoline and the resulting mixture refluxed for about two hours, during which time a clear solution formed. The solution was then made alkaline with 28% ammonium hydroxide and a light yellow precipitate resulted; yield 7.3 g. (82%), m.p. 182-191° (dec.). An
analytical sample was prepared by recrystallization from 95% ethyl alcohol-water; m.p. 195-196° (dec.).

Anal. Calcd. for C_{22}H_{24}Cl_{2}N_{3}O: C, 69.18; H, 6.33. Found: C, —; H, —.

3-Pyrroolidyl-1-(p-(2-methoxy-6-chloro-9-acridylamino)phenyl)-1-propanol Dihydrochloride Sesquihydrate (LXXXVI). - To the aliquot portion of the filtrate obtained in the reduction mentioned in the above reaction was added 5.8 g. (0.021 mole) of 2-methoxy-6,9-dichloroacridine. The resulting mixture was then refluxed for about two hours, during which time a clear solution did not form. A crystalline solid formed on cooling this reaction mixture and it was removed by filtration; yield 19 g. (76%), m.p. 190-193°. To obtain an analytical sample, a portion of the above solid was first precipitated from absolute ethyl alcohol-acetone with ether. The product thus obtained was recrystallized from absolute ethyl alcohol-acetone. It melted at 194-195°.

Anal. Calcd. for C_{27}H_{28}Cl_{2}N_{3}O_2·HCl·1.5H_2O: C, 57.70; H, 6.01. Found: C, 57.60; H, 6.38.

3-Piperidyl-1-(p-(7-chloro-4-quinolylamino)phenyl)-1-propanol Dihydrochloride (LXXXVII). - Following the general procedure outlined above, 5.9 g. (0.03 mole) of 4,7-dichloroquinoline was refluxed for about two hours with
the filtrate obtained from the catalytic reduction of 9.9 g. (0.03 mole) of LXXV. Since, on cooling the solution thus obtained, no solid was formed, the solution was made alkaline with 28% ammonium hydroxide, resulting in the deposition of a yellow oil, which slowly solidified. When two successive attempts to recrystallize the amorphous mass resulted in the formation of the same type of oily mass, which would slowly solidify; the solvent was decanted and the solid material dissolved in ether. The ether solution was dried overnight with anhydrous potassium carbonate. The ether solution was then removed from the drying agent by filtration and then a stream of anhydrous hydrogen chloride was passed through the solution. Soon, a yellow precipitate began to form. After the etheral solution was saturated with hydrogen chloride, it was cooled and the solid removed by filtration; yield 7.3 g. (46%), m.p. 278-281° (dec.). After two successive recrystallizations from 95% ethyl alcohol-acetone, the melting point was constant at 283-284° (dec.).

Anal. Calcd. for C_{23}H_{26}Cl_{13}N_{3}O·2HCl: C, 58.92; H, 6.02.
Found: C, 58.67; H, 6.12.

3-Diethylamino-1-(p-(7-chloro-4-quinolylamino)phenyl)-1-propanol (LXXXVIII). - In accord with the procedure previously outlined, 4.0 g. (0.02 mole) of 4,7-dichloroquinoline was added to one-half of the filtrate obtained from the
catalytic reduction of 11.5 g. (0.04 mole) of LXXIV and the resulting mixture refluxed for about two hours. On cooling, the product was worked up in the manner indicated previously; yield 5.2 g. (58%) of light yellow solid, m.p. 199-201° (dec.). Recrystallization from 95% ethyl alcohol-water raised the melting point to 203-204° (dec.).

**Anal. Calcd. for C_{22}H_{26}ClN_{3}O:** C, 68.82; H, 6.83.

**Found:** C, 68.48; H, 6.82.

3-Diethylamino-1-(p-(2-methoxy-6-chloro-9-acridylamino)phenyl)-1-propanol Dihydrochloride Monohydrate (LXXXIX). - Five and six-tenths grams (0.02 mole) of 2-methoxy-6,9-dichloroacridine was added to one-half of the filtrate obtained from the catalytic reduction of LXXIV and the resulting suspension refluxed for about two hours. On cooling, the solid which formed was removed by filtration; yield 7.6 g. (69%), m.p. 192-195° (dec.). A sample, after having been recrystallized from 95% ethyl alcohol-acetone melted at 195-197° (dec.).

**Anal. Calcd. for C_{27}H_{30}ClN_{3}O_{2}·2HCl·H_{2}O:** C, 58.43; H, 6.18.

**Found:** C, 58.30; H, 6.48.

3-Dimethylamino-1-(m-(7-chloro-4-quinolylamino)phenyl)-1-propanol (XC). - Following the customary procedure, 10 g. (0.039 mole) of LXXVIII was suspended in absolute ethyl alcohol and catalytically reduced, using Adams' catalyst.
The clear solution was then treated with a slight excess of alcoholic hydrogen chloride and filtered to remove the catalyst. To one-half of the filtrate thus obtained was added 4.0 g. (0.02 mole) of 4,7-dichloroquinoline and the mixture refluxed for about two hours, during which time a clear yellow solution formed. The solution, on cooling, was made basic with 28% ammonium hydroxide and a light yellow solid precipitated; yield 4.6 g. (66%), m.p. 196-201\degree. A sample, after recrystallization from 95% ethyl alcohol-water, melted at 203-205\degree (dec.).

Anal. Calcd. for C_{20}H_{22}ClN_{3}O: C, 67.49; H, 6.23.

Found: C, ...; H, ...

3-Dimethylamino-1-(m-(2-methoxy-6-chloro-9-acridylamino)phenyl)-1-propanol Dihydrochloride (XCl). - To one-half of the filtrate obtained above, 5.6 g. (0.02 mole) of 2-methoxy-6,9-dichloroacridine was added and the mixture refluxed for about two hours. On cooling, an orange solid precipitated, yield 6.7 g. (67%), m.p. 174-178\degree. A sample, after having been recrystallized from 95% ethyl alcohol-acetone, melted at 179-180\degree.

Anal. Calcd. for C_{25}H_{26}ClN_{3}O_{2}2HCl·2½H_{2}O: C, 54.30; H, 6.07.

Found: C, 54.20; H, 6.00.

4-(7-Chloro-4-quinolylamino)-α-pyrrolidyl-o-cresol (LXXXIII). - Following the procedure of Burckhalter (58),
45.3 g. (0.3 mole) of p-acetamidophenol, 25 ml. (ca. 0.3 mole) of 37% formaldehyde solution, 21.3 g. (0.3 mole) of pyrrolidine and 75 ml. of 95% ethyl alcohol were refluxed for two and one-half hours. When, on cooling, no solid separated, the solvent was removed in vacuo. A thick, syrupy residue resulted. One-third of this residue was then refluxed for one hour with 50 ml. of 20% hydrochloric acid. The solution was cooled and treated with 6N sodium hydroxide until just acid to Congo Red. Nineteen and eight-tenths grams (0.1 mole) of 4,7-dichloroquinoline was then added and the mixture refluxed for two hours. Since no solid appeared after this solution was cooled, it was then made basic with 28% ammonium hydroxide. This produced a light yellow solid; yield 27.5 g. (78%), m.p. 186-191°. A sample was prepared for analysis by repeated recrystallization from isopropyl alcohol-water. It melted at 196-198°.

**Anal. Calcd. for C_{20}H_{20}Cl_{13}N_{3}O:** C, 67.83; H, 5.69.

**Found:** C, 67.60; H, 5.76.

4-(2-Methoxy-6-chloro-9-acridylamino)-α-pyrrolidyl-o-cresol Dihydrochloride Sesquihydrate (XGII). - One-third of the residue obtained in the above described Mannich reaction on p-acetamidophenol was treated as described previously. Then 27.8 g. (0.1 mole) of 2-methoxy-6,9-dichloroacridine was added and the resulting mixture
refluxed for two hours. The hot solution was filtered through a pre-heated funnel to remove the insoluble material present, regarded as being 6-chloro-9-(4-hydroxyanilino)-2-methoxy-acridine. On cooling the filtrate, a thick orange precipitate appeared; yield 30 g. (56%), m.p. 245-249° (dec.). A sample for analysis was prepared by repeated recrystallization from 95% ethyl alcohol-acetone. It melted at 252-253° (dec.).

**Anal. Calcd. for C_{25}H_{24}ClN_{3}O_{2}\cdot2HCl\cdot1\frac{1}{2}H_{2}O:** C, 56.25; H, 5.47.

**Found:** C, 56.54; H, 5.37.
1. An approach, which could not be followed beyond the synthesis of XIX and XXV (p. 21), was made to the preparation of a vinyllog of chloramphenicol.

2. Eighteen thiosemicarbazones, derived from aralkyl ketones, were prepared to be tested for possible activity against *Mycobacterium tuberculosis*. In connection with this portion of the work, it was shown that a much shorter reaction time than that ordinarily employed will, in many cases, give very satisfactory yields.

3. A series of twenty-three Mannich bases was prepared from various substituted acetophenones. None of these compounds showed any higher antibacterial activity than III (p. 3).

4. A series of five Mannich bases was prepared from various benzalacetones. Likewise, none of these so far tested have shown any higher activity than III.

5. A series of eight 3-dialkylamino-1-(substituted phenyl)-1-propanols has been prepared by the Meerwein-Ponndorf-Verley reduction of the Mannich bases derived from \( m^- \) and \( p^- \) nitroacetophenone. The use of aluminum chloride in conjunction with the aluminum isopropoxide has thus allowed this type reduction to be successfully applied to the Mannich bases derived from \( m^- \) and
p-nitroacetophenone for the first time.

6. A series of eight compounds, analogues of Camoquin and Atabrine, has been prepared by the catalytic reduction of the aforementioned propanols and subsequent condensation with the appropriate chlorocheterocycle.

7. The pyrrolidine analogue of Camoquin has been prepared by the procedure originally used in the synthesis of Camoquin. Also, this pyrrolidine-substituted Camoquin side chain has been condensed with 2-methoxy-6,9-dichloroacridine.

8. Although the pharmacological evaluation of these compounds, which is being conducted by Parke, Davis & Co., is incomplete, data thus far received indicate that some of the compounds possess significant in vitro antitubercular activity.
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