SYNTHETIC RELATIVES OF AMIDONE AND MORPHINE

by

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October, 1952

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INTRODUCTION

The goal of the research described in this thesis is the synthesis of certain analogues of Amidone (I) and morphine (II).* Structures of the proposed types of compounds are shown on page 3. It may be noted that types IV, V and VI, and compound VII, all possess a substituted γ-arylpropylamine structure, and that they are spatially similar to Amidone and morphine. Together with these structural facts, the possible similarity in physicochemical characteristics, owing to the presence of a basic nitrogen, indicates potential analgetic activity. Structures IV and V represent spatial variations in the structure of morphine, while structure VI suggests more nearly those in the Amidone molecule. Compound VII, whose synthesis thus far has been unsuccessful, is a saturated analogue of Amidone. Finally, III depicts a group of substituted 2-tetralones, which are proposed intermediates to be used in a scheme directed toward a possible synthesis of the morphine alkaloids.

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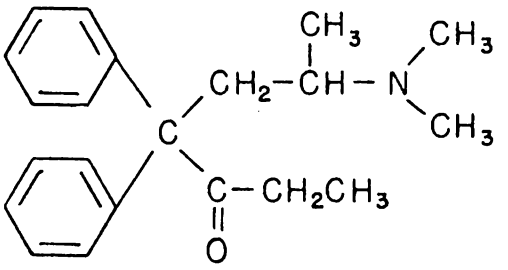
* The structure of Amidone may be written to show a similarity to that of morphine (1).

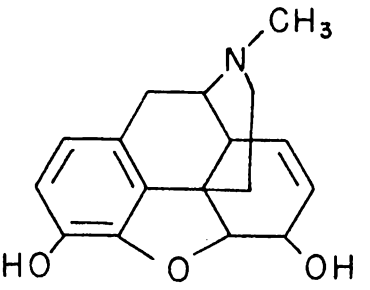
HISTORICAL

Analgetics are considered pharmacologically as belonging to the class of symptomatic drugs, having mainly a depressant action on the central nervous system, thereby raising the pain threshold of the body. There is some evidence to show that analgetics enhance parasympathetic activity in addition to the alleviation of pain. They also possess a spasmolytic action which is probably due to a direct papaverine-like depression of the muscle fibers. One advantage of this group over anesthetics, hypnotics and sedatives is the fact that they diminish or abolish the sensation of pain without stupefaction or loss of consciousness.

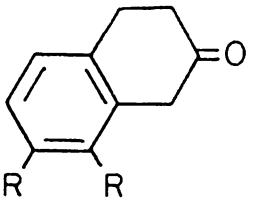
Opium is one of the oldest drugs used by man; its primary use being to produce analgesia against pain. Although the opium alkaloids possess violent addicting properties, morphine still retains distinction as the chief weapon against excruciating, sharp and intense pain. Serturner (2) first isolated morphine from opium in 1805, and it was soon shown that most of the narcotic activity of opium resided in this crystalline base. Since that time, many chemists have been trying to find the ideal analgetic - one with equal or greater potency than morphine without the undesirable side effects. Chemical work in this field of morphine alkaloids



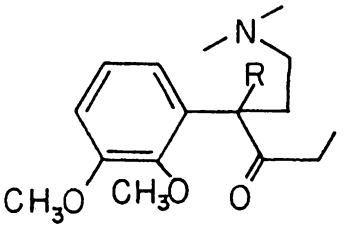
1 Amidone



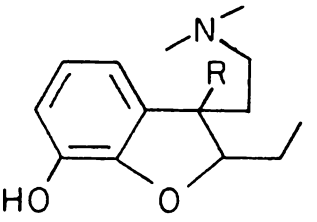
II Morphine



III



IV



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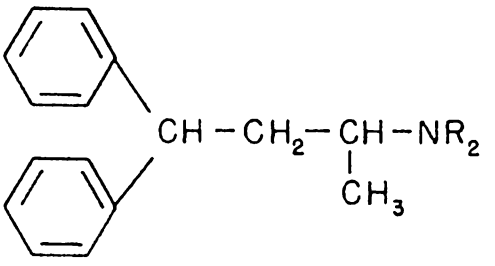
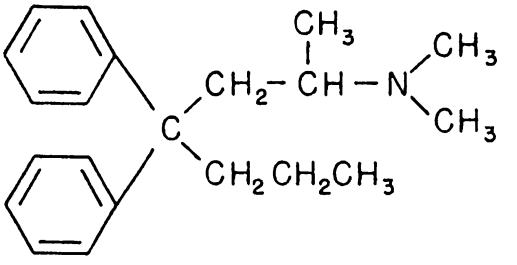


VI



VII

has taken several forms:

(a) the elucidation of the chemical structure of morphine;

(b) the preparation of more active derivatives;

(c) the formation of new compounds from moieties of the morphine molecule;

(d) the synthesis of compounds possessing true analgetic activity; and, finally,

(e) the total synthesis of morphine.

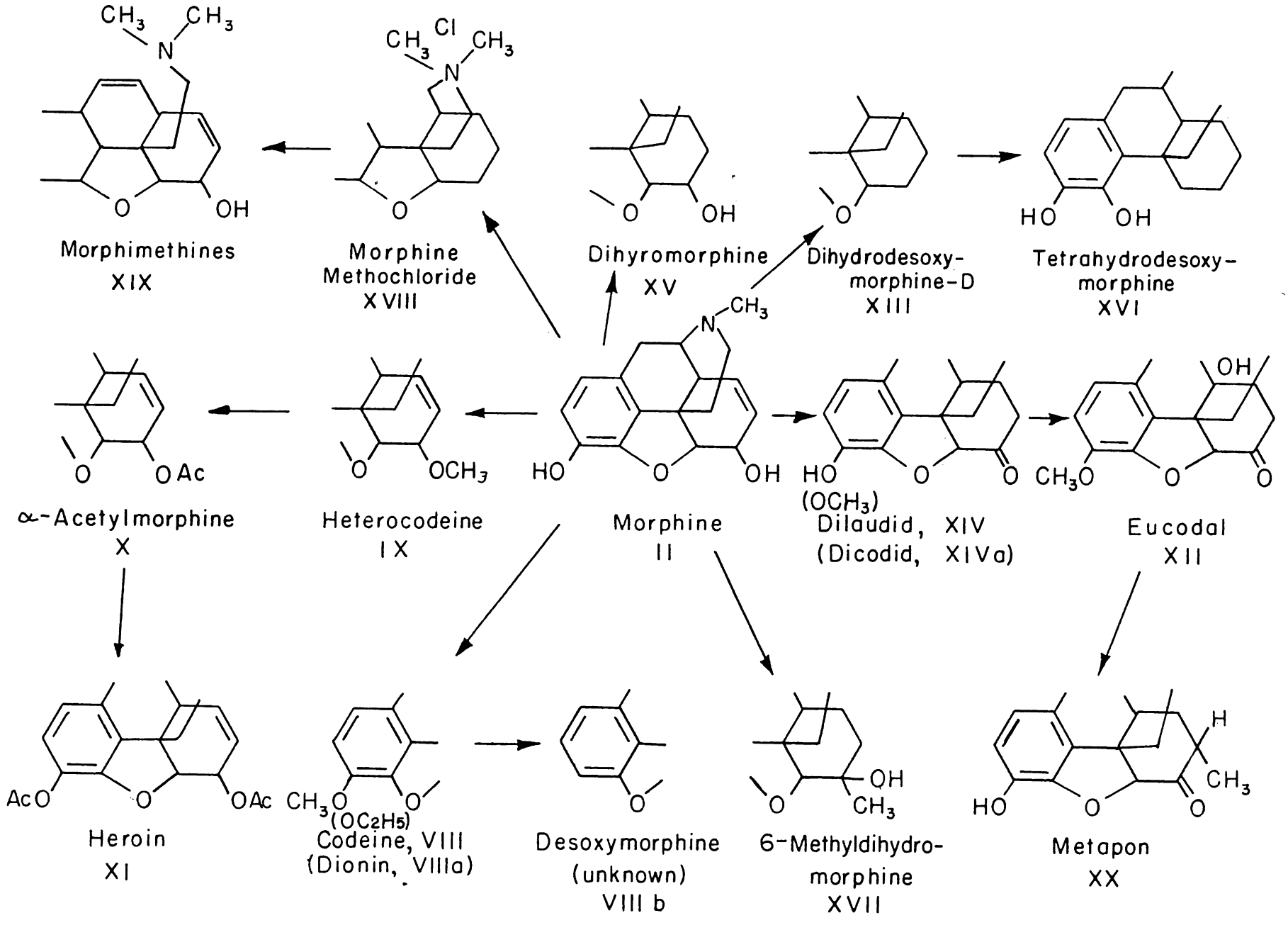
The structure of the morphine molecule (II), based upon the chemistry of codeine and thebaine, was established by Gulland and Robinson(3) who were supported by Schopf (4). This accepted structure was definitely proved by the recent synthesis of morphine by Gates and Tschudi (5).

In addition to the postulation of Robinson (3) that a laudanosine type of compound was formed as an intermediate in morphine synthesis by the plant, most of the first chemical work dealt with modifications of morphine and related alkaloids. The naturally occurring methyl ether (codeine, VIII) exhibits about one-tenth the activity of morphine; this is also true for the synthetic ethyl ether, (VIIIa). Since desoxymorphine (VIIIb) is unknown, the contribution of the phenolic hydroxyl group to the activity of morphine must await further work. Methylation of the alcoholic group (IX) increases the

activity two to four times, but also increases the toxicity correspondingly. If morphine is acetylated (acetylmorphine, X, and heroin, XI), there is an increase in activity together with increases in both toxicity and euphorism. When the alcoholic group is oxidized to a keto group (XII) or converted into a methylene group (XIII), considerable increase in activity is noted (four to five and ten times, respectively). Dilaudid (XIV) and the corresponding codeine derivative, Dicodid (XIVa), have gained considerable recognition as therapeutics, although greater toxicity and a shorter duration of action appears. A slight increase of activity is noted in dihydromorphine (XV), which has the completely saturated aliphatic ring. Reductive processes easily open the ether bridge to give compounds of decreased activity and toxicity (XVI). The tertiary carbinol (XVII) exhibits a slight increase in activity together with a more prolonged effect.

Conversion of the tertiary nitrogen of morphine or codeine into a quaternary salt (XVIII) results in a certain curare-like effect with a marked decrease in activity. Improved pharmacological properties have been shown in only two cases (N-allylnorcodeine and N-allylnormorphine) where the N-methyl group was replaced by other alkyl or alkenyl groups. Rupture of the piperidine ring (XIX) leads to an almost complete loss of activity. Apomorphine, formed by a

Morphine and Its Derivatives



rearrangement of morphine by concentrated hydrochloric acid, is almost devoid of analgetic action, but is a potent emetic.

Metapon (XX) was prepared from dihydrothebaine through a complicated procedure by Small and co-workers (7).* One of the most important synthetic derivatives in the morphine series, Metapon is regarded highly as an analgetic in this country; however, it is only available under very restricted conditions, and the supply is limited. In comparison with morphine, Metapon is a more powerful analgetic with fewer undesirable side effects. It is not devoid of addiction properties, and tolerance toward its use develops slowly. Metapon, also, appears to be superior to morphine in the treatment of certain cancerous conditions.

Elucidation of the structure of naturally occurring morphine alkaloids by degradation and partial synthesis was an older field of endeavor. This field gave way to the search for synthetic analgetics embodying those portions of the morphine molecule which gave rise to its valuable properties and lacking others which are pharmacologically undesirable. A great number of compounds bearing more of a

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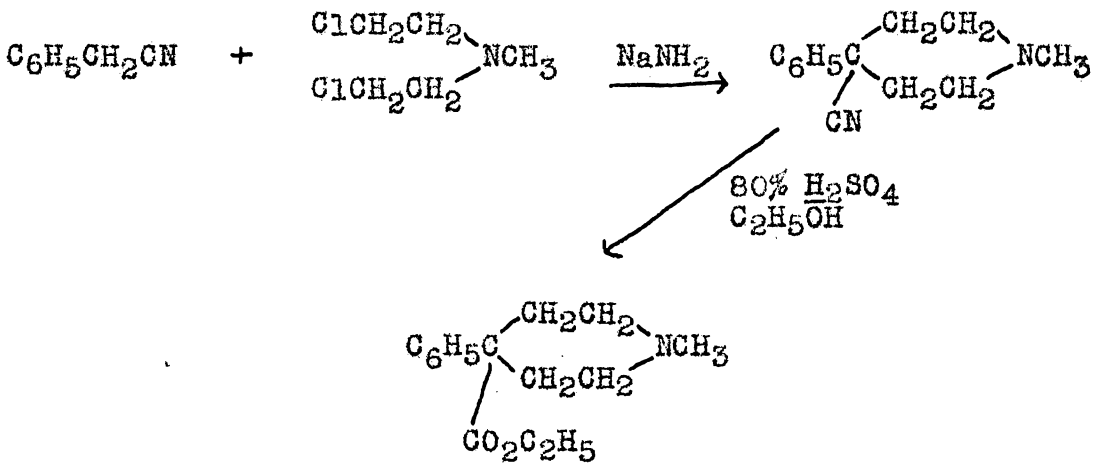
* There was inaugurated in 1929 a systematic program under the auspices of the Committee on Drug Addiction of the American National Research Council with the synthesis of the ideal analgetic as its objective. Metapon represents a practical result in this program.

steric than a chemical resemblance to morphine have been prepared. These more simple and accessible products generally did not require the development of synthetic methods directly applicable to the synthesis of morphine alkaloids; in fact, as far as can be ascertained, the two most prominent synthetic analgetics were discovered in a search for spasmolytic agents. Although, in recent years, there has been a tendency to explain the activity of some of the newly developed synthetic analgetics in terms of certain structural features present in the morphine molecule, such hypotheses have usually arisen after the activity of the drugs was discovered. A specific positional relationship of a tertiary nitrogen to a quaternary carbon and an aromatic nucleus is the most prominent hypothesis. Only, if new drugs are found as a result of its application, will the value of such speculation become apparent.

The first synthetic analgetic with morphine-like activity was prepared in 1938 when Eisleb and Schaumann (8) observed that ethyl 4-phenyl-1-methyl-piperidine-4-carboxylate (Demerol, XXI), originally designed as a spasmolytic, possessed about one-tenth the analgetic activity of morphine. Its structural relationship to morphine (II) is revealed when morphine is shown as a 4-phenylpiperidine derivative (see page 11). Demerol was first prepared by the condensation of phenylacetonitrile with bis-(2-chloroethyl)methylamine, and the resulting

nitrile hydrolyzed and esterified in a single step. However, because of the vesicant properties of the bis-(chloroethyl) amine, its use was avoided by the application of alternate syntheses.



XXI

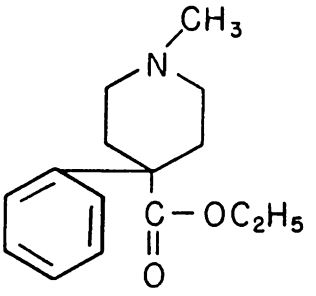
Like morphine, the Demerol molecule has been subjected to many modifications, both for the accumulation of data on the relation of structure to activity and for the production of a more active compound. Piperidine esters of a different type, studied independently by Jensen (9) and Lee (10), and their co-workers, appeared to be more active than Demerol. The most active of these were the 4-propionoxy (XXII) and the 3-methyl-4-propionoxy (XXIII) derivatives, which were prepared by the action of Grignard reagents or organolithium compounds on 4-piperidones, followed by acylation of the organometallic

complex. Ketobemidone (XXIV), the most active compound of the whole series, is thirty times more effective than Demerol, but unfortunately leads to a rapid development of addiction. It is formed by the action of ethylmagnesium bromide on the 4-phenylpiperidylnitrile of the Demerol synthesis (11).

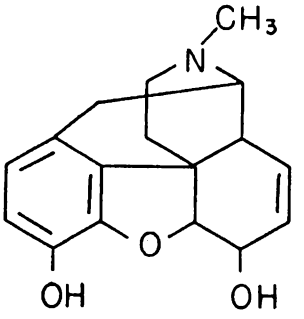
Further studies by American and English workers on modifications of the Demerol molecule yielded only products possessing less potency than the parent compound. Some of these changes involved replacement of the phenyl group, a shift in position of the phenyl group, removal of the acyloxy group, a shift in position of the acyloxy group, a change in the N-alkyl radical, addition of substituents to the piperidine ring, etc.

Since 1929, a large volume of work has been published on the preparation and activity of phenanthrenes and dibenzofurans as analgetic agents. Many workers studied other chemical types, such as isocoumarones (12), 2-benzylpiperidines (13), diphenylethylamines (14), bisphenylethylamines (13,15), benzylisoquinolines (16), 2-amino-1-tetralones (17), 1-dialkylaminoethyl-2-tetralones (18), phenylaminomethylcyclohexanes (13,19), phenyldecahydroquinolines (20), and tetrahydrofurans (21). Very few of these compounds possessed more than weak analgetic potency.

Because of the analgetic activity of the 4-phenyl-



XXI



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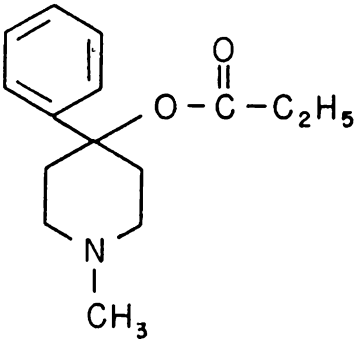
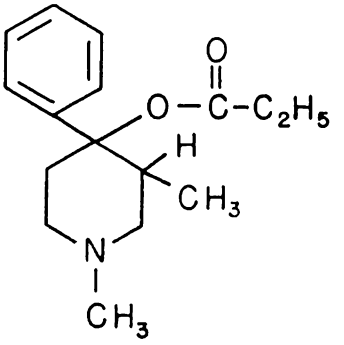
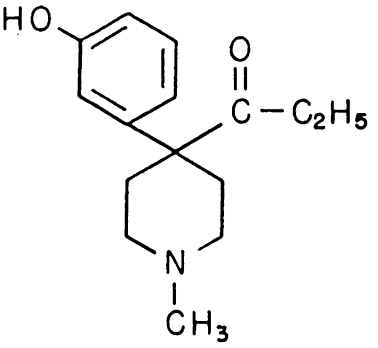


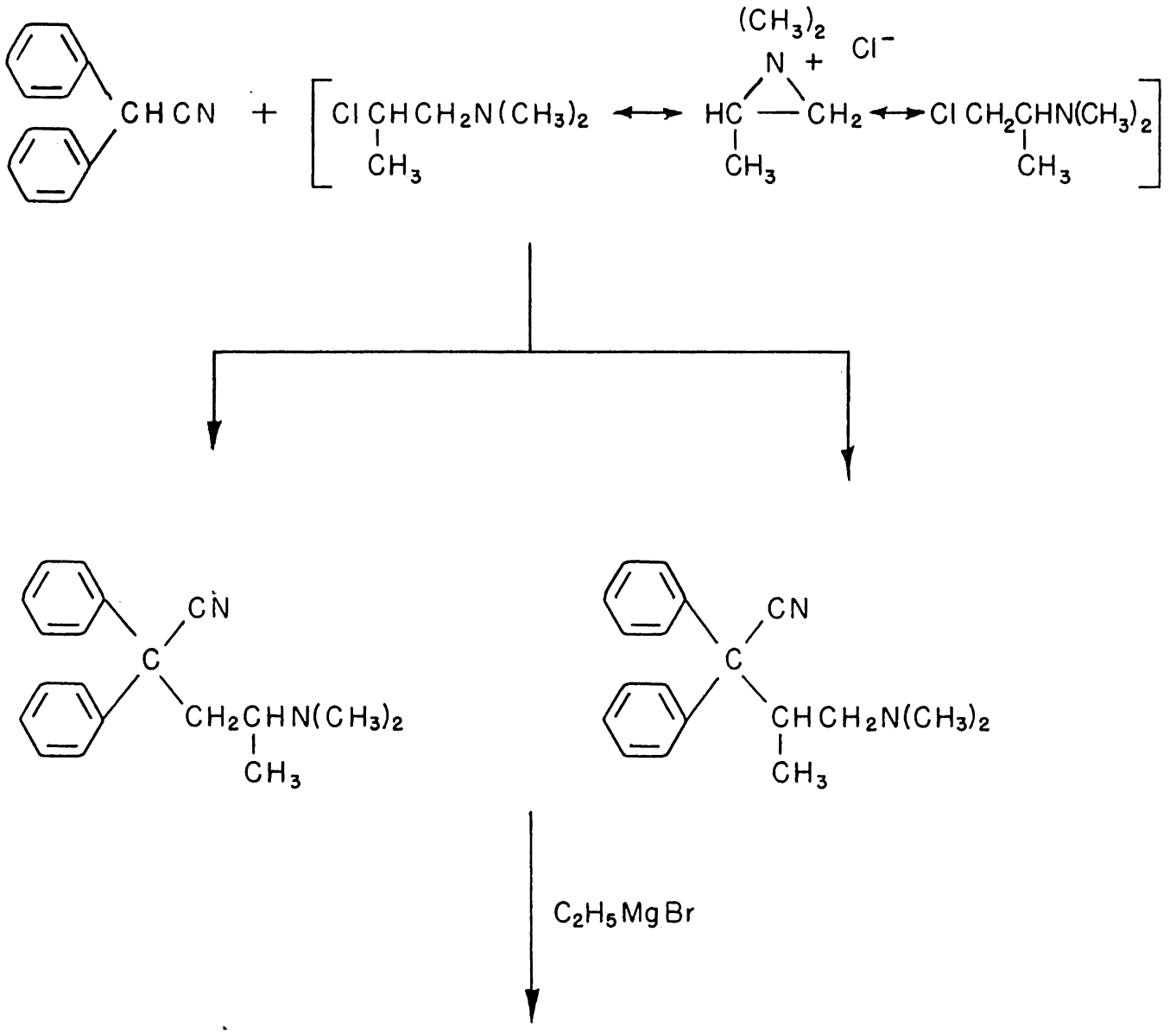
XXII



XXIII



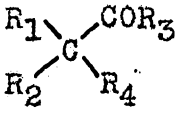
XXIV



Amidone XXV

Isoamidone XXVI

piperidine derivatives, and the known loss of activity brought about by rupture of the piperidine ring in morphine, it might have been concluded that this ring was an essential feature of an analgetic. However, a new class of potent analgetics which do not contain such a ring was discovered by I. G. Farbenindustrie workers at Hoechst. Bochmuhl and Ehrhardt (22) reported that esters of fluorenecarboxylic and diphenylacetic acids, carrying 2-dialkylaminoalkyl radicals in the alpha positions, possessed analgetic as well as spasmolytic properties. The Hoechst laboratories extended this work to the preparation of ketones corresponding to these esters. Of the twenty-three compounds prepared, the greatest activity was present when $R_1 = R_2$ = phenyl, R_3 = ethyl and R_4 = dimethylaminopropyl (XXV). This compound is



known as Amidone, and exhibits five to ten times the analgetic activity of Demerol.

In the United States Department of Commerce report (23) it was noted that the method given by the German chemists for the synthesis of Amidone (see page 11) would not be expected to lead to Amidone (XXV), but rather to Isoamidone (XXVI). The reaction of diphenylacetonitrile with 1-dimethyl-

amino-2-chloropropane either in the presence of sodamide or of potassium tertiary butoxide leads to a mixture of the isomeric nitriles, probably owing to a rearrangement of the chloramine into the ethylenimonium ion (24). The structures of these isomers have been established as follows: (a) Easton, Gardner and Stevens (25) proved the structure of Amidone by an unambiguous synthesis employing propylene oxide as an intermediate; (b) Bochmuhl (26) replaced the nitrile group with hydrogen by boiling in benzene with sodamide, and identified the resulting isomeric products by synthesis; (c) Schultz and co-workers (27) subjected the two nitriles to exhaustive methylation, reduced the nitrile and vinyl groups, and identified the products by synthesis. The final step in the preparation of Amidone consists in treating the nitrile with ethylmagnesium bromide.

Details of the resolution of Amidone with D-tartaric acid, and the formation of the dextro and levo isomers have been reported (28). Isoamidone has also been resolved, but the method has not been published. The levo forms of the optical isomers of Amidone and Isoamidone possess much more analgetic activity than the dextro forms.

The ketone group in Amidone and Isoamidone is remarkably inert, but can be reduced to the alcohol, which then can be easily dehydrated to the unsaturated compound. There is a

resultant decrease in analgetic activity in the alcohol, and the unsaturated product is completely inactive; however, acetylation of the alcohol brings about a profound increase in activity (29). Amidone is not reduced by the Clemmenson method, and loses the entire ketone chain in the modified Wolff-Kishner reaction.(30). According to Bochmuhl and Ehrhardt (31) the 2-morpholinyl-, 2-piperidyl and 2-pyrrolidyl-propyl analogues are equal to Amidone in analgetic potency, but exhibit less undesirable side effects.

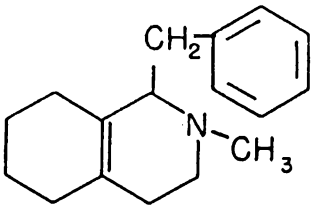
Many chemists have widely explored the possibilities of modifications of the Amidone molecule to effect further improvement (28,29,31,32); but none of the changes has developed greater analgetic activity than exists in Amidone itself, nor, probably, a better compound from the practical standpoint.

Recently, at least two attempts have been made to use the hypothesis of the quaternary carbon and tertiary nitrogen in beta relationship as an optimal and essential feature of potent analgetic agents. Rutenberg and Horning (33) have synthesized oxindoles; and Schwartzman (34) has begun work on spirocyclohexyl compounds, some of which show promise as true synthetic analgetics.

The nearest approach to a complete synthesis of the

morphine ring structure until the successful work of Gates and Tschudi was the preparation of N-methylmorphinan (XXVIII) by Grewe and co-workers (35, 36), who synthesized it by cyclization of N-methyl-1-benzyloctahydroisoquinoline (XXVII) with phosphoric acid. In the same way 3-hydroxy-N-methylmorphinan (XXIX) was obtained from the corresponding octahydroisoquinoline (37), and it obviously differs from desoxydihydromorphine (XIII) only through the lack of the ether-oxygen bridge. Both compounds possess considerable analgetic activity; however, XXIX is claimed to surpass morphine in the intensity and duration of the analgesia produced (38).

Other studies toward the synthesis of the morphine structure assumed varied forms; the phenanthrenes (39, 40), heterocyclics from phenanthrenes (41, 42), other heterocyclics (43, 44), and phenylcyclohexanones (44-48) being employed as intermediates. Ultimately, as predicted by Stern (49), one of the most interesting and difficult chapters in alkaloid chemistry came to a successful conclusion. Overcoming the difficulties of epimerization at C_{14}, Gates and Tschudi (5) synthesized morphine totally from 2,6-dihydroxynaphthalene in about twenty-seven ingenious steps. The synthetic morphine was unequivocally proved to be identical with the alkaloid derived from natural sources, thereby fulfilling the aim and dream of thousands of chemists throughout the world over the



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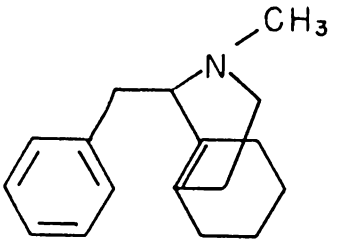
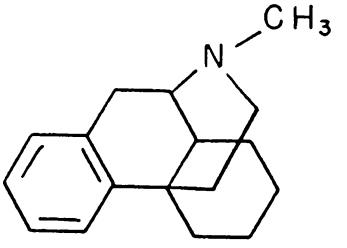


XXVII

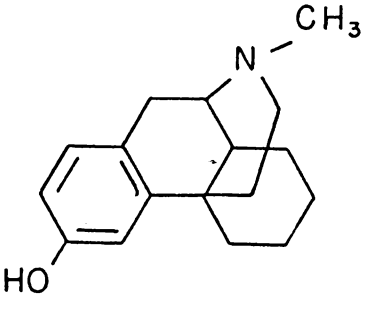
XXVII

H_3PO_4



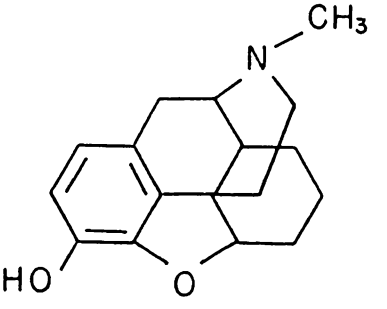
N-Methylmorphinan

XXVIII



3-Hydroxy-N-methyl-morphinan

XXIX



Dihydrodesoxy-morphine

XIII

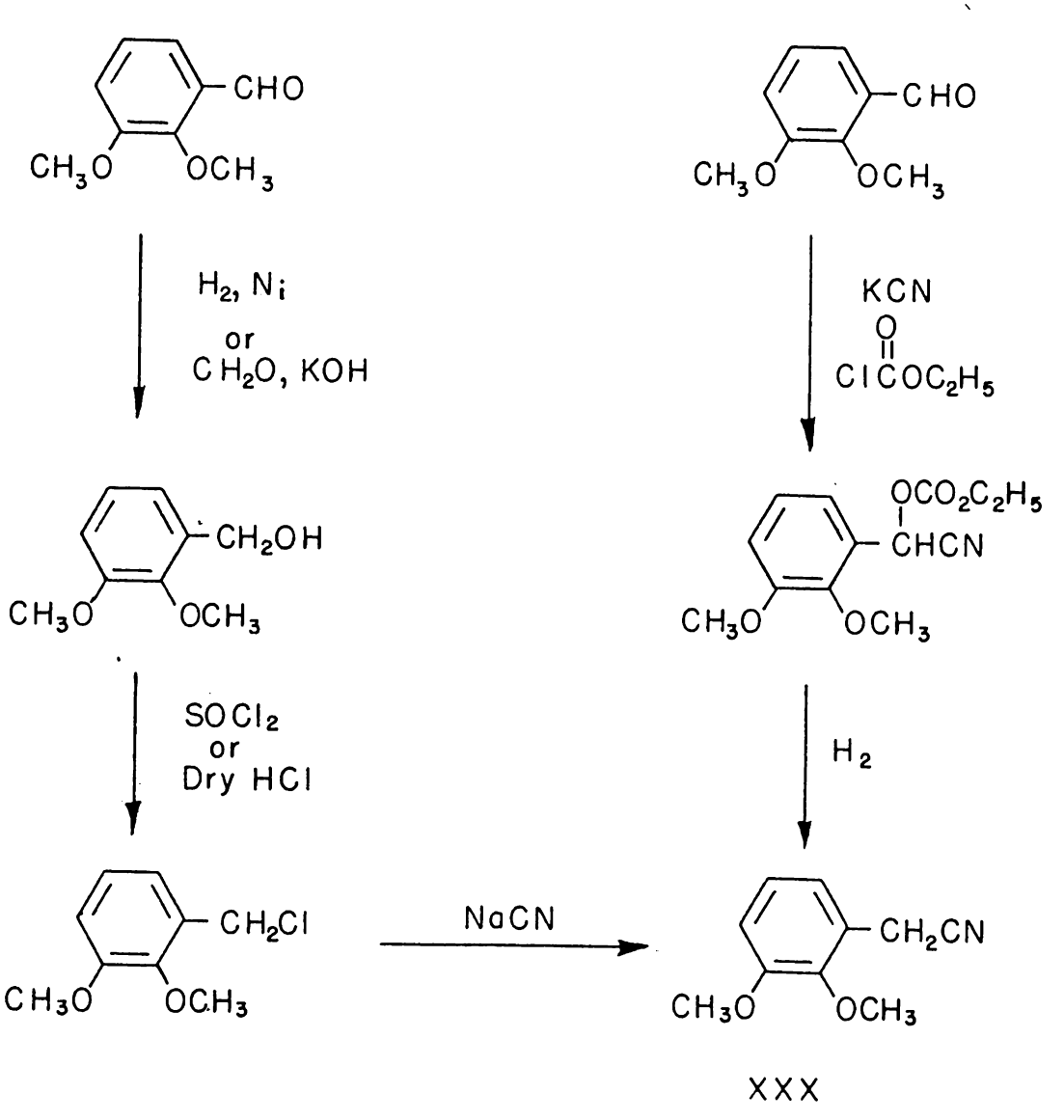
last century. However, the search must still progress unceasingly for the true synthetic analgetic, which will possess the analgetic activity of morphine without the undesirable side effects.

DISCUSSION OF RESULTS

TYPE III COMPOUNDS - STRUCTURES PROPOSED AS ALKALOID AND STEROID INTERMEDIATES

Synthetic schemes by which compounds of type III might possibly be obtained are presented on page 18a. The starting material, 2,3-dimethoxyphenylacetonitrile (XXX), was prepared from 2,3-dimethoxybenzaldehyde by two entirely different methods. In the first, the aldehyde was converted to the benzyl alcohol by low pressure hydrogenation using Raney nickel catalyst; the product was not isolated in its pure form. Also, upon applying the crossed Cannizzaro reaction to the aldehyde, the alcohol was obtained in quantitative yields, in contrast to those reported by Horning and co-workers (46). Although in the latter case the alcohol was purified by distillation, that obtained through both procedures was treated with either thionyl chloride or anhydrous hydrogen chloride to give 2,3-dimethoxybenzyl chloride. The hydrogen chloride method is preferred since no tars result nor side products form owing to impurities in the reagent, and fewer operations are required. The product must be thoroughly washed with base prior to distillation, or before applying the subsequent reaction, in order to remove all traces of acid. Any acid present lowers the yield of XXX, which is prepared from the above chloride by treatment with sodium cyanide. Either the

Preparation of XXX



XXX

pure, distilled chloride in ethyl alcohol, or the crude, washed benzene solution may be employed with good results. However, it must be handled with care because of its irritant and lachrymatory properties. One of the interesting facts developed in this work was that the nitrile (XXX) was obtained in better yields when the alcohol was prepared by hydrogenation. Evidently, some by-product is formed in the Cannizzaro reaction and distills with the alcohol.

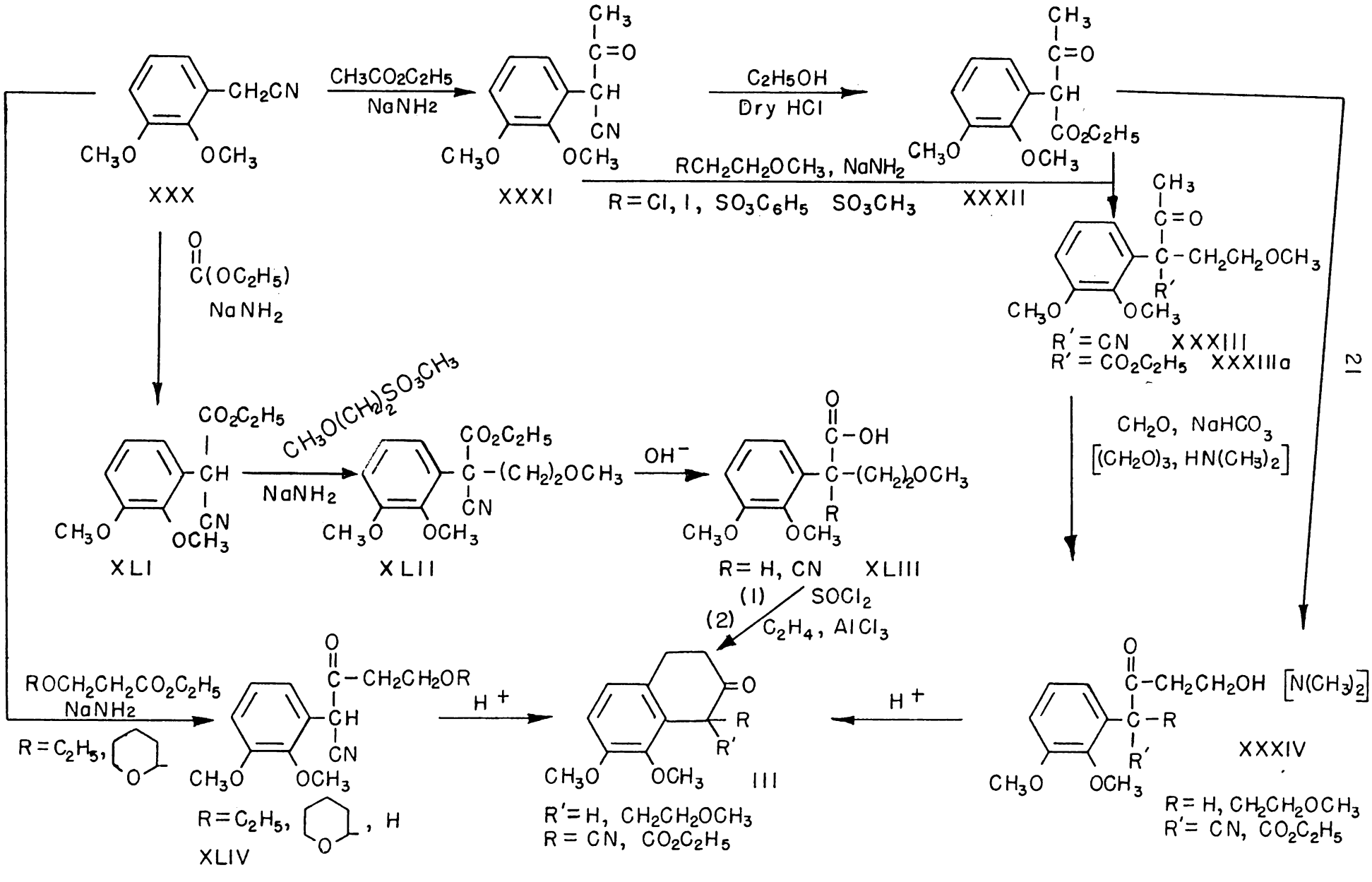
The other method by which 2,3-dimethoxyphenylacetonitrile (XXX) was prepared evolved from work on analogous compounds by Kindler and Schrader (50). Following their procedure, the intermediate esterified mandelonitrile was formed from 2,3-dimethoxybenzaldehyde, ethyl chlorocarbonate and potassium cyanide in the presence of magnesium sulfate heptahydrate. This intermediate was converted into XXX upon treatment with hydrogen and 5% palladium on charcoal; but the yield was very low, probably owing to the use of an insufficient amount of catalyst.

Compound XXXI was first prepared by Johnson (51) who utilized sodium ethoxide as the condensing agent. When sodamide was used instead, the more powerful amide ion caused condensation in much better yields than were usually obtained with the ethoxide ion. In fact, some reactions using the latter produced only starting material. Since XXXII was formed in poor yields upon applying Kimball's method (52), that of McElvain and co-workers (53) was used. Both procedures

are essentially the same, in that XXXII resulted from treatment of XXXI with both anhydrous ethyl alcohol and hydrogen chloride. However, the former describes a much more complicated isolation process, which probably accounts for the loss of product.

Difficulties were encountered in the condensation of XXXI or XXXII with $RCH_2CH_2OCH_3$ in the presence of sodamide to produce XXXIII and XXXIIIa; but, first, the side chain itself requires some discussion. β-Methoxyethyl chloride (R = Cl) was prepared from ethylene glycol monomethyl ether in two ways. When thionyl chloride was employed, the excess reagent was removed under reduced pressure. An azeotropic mixture forms if the thionyl chloride is decomposed with water, probably owing to a partial regeneration of the starting glycol. The chloride was also obtained by utilizing phosphorus trichloride in the presence of pyridine. β-Methoxyethyl iodide (R = I) resulted in only a 44% yield by the interaction of the above chloride with sodium iodide in acetone. When ethylene glycol monomethyl ether was allowed to react with benzenesulfonyl chloride in the presence of pyridine at 0°, β-methoxyethyl benzenesulfonate (R = $SO_3C_6H_5$) was formed in 83% yield, but in lower yields if the temperature was allowed to rise above 0° for any period of time. When the benzenesulfonyl chloride was replaced by methanesulfonyl chloride,

Proposed Synthesis of Type III Compounds



β-methoxyethyl methanesulfonate (R = SO_3CH_3) was formed in much lower yields, although Newman and Magerlein (42) reported 67%. The difficulties mentioned above, in preparing XXXIII and XXXIIIa, were encountered in the use of the β-methoxyethyl halides as alkylating agents, and only 6-17% yields of XXXIII were obtained. These results were partially overcome by performing the alkylation with β-methoxyethyl benzene- and methanesulfonates according to previous work (42, 54). Evidently, the halides are only weakly active as alkylating agents while the sulfonates exert a stronger effect on the sodium salt of XXXI. Even these sulfonates were inactive toward XXXII in the presence of sodamide, possibly because of steric factors and/or a decreased activity of the methylene hydrogen.

It was hoped that the methylcarbonyl chain of XXXIII and XXXIIIa could be lengthened by one carbon atom by application of hydroxymethylation or the Mannich reaction to give XXXIV. This would then be followed by ring closure to the 1,1-disubstituted-2-tetralone (III), which would be of great interest as an intermediate in syntheses directed toward morphine alkaloids. All attempts to hydroxymethylate XXXIII resulted only in the recovery of starting material, even though stronger catalysts, such as potassium carbonate, and temperatures of 60° were employed. Negative results were also

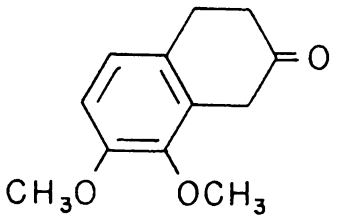
obtained with the Mannich reaction, using formaldehyde, dimethylamine hydrochloride and either ethyl or amyl alcohol. The failure of these reactions with XXXIII could be attributed to the great reactivity and electron density of the aromatic nucleus, where preferential attack would occur with such reagents.

As found by all workers investigating the possible extension of the ring system of the 2-tetralones to that of a 13-substituted hydrophenanthrene (XXXVI) typical of the morphine alkaloids, the major difficulty lay in the attainment of the proper 1-substituted-2-tetralone (III). Most of the studies until the present time have been concerned with the introduction of substituents into the 1-position of 2-tetralones, while our aim along with that of others has been the formation of 2-tetralones from intermediates already possessing the proper side chains. Although Soffer and coworkers (48) obtained disubstitution in the 1-position of 7,8-dimethoxy-2-tetralone (XXXV) with several alkylating agents in the presence of sodium hydride, ring closure to the 13-substituted hydrophenanthrene (XXXVI, R' = R' = OCH_3) would be difficult; and, assuming cyclization would occur, an undesired side chain would reside at C_{13}. As in our proposed intermediate (III), Soffer's 2-tetralone (XXXV) contained the two methoxy groups at appropriate positions where they could form the foundation of the hydroxy group and the ether linkage

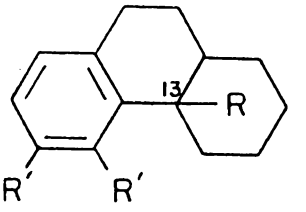
of the morphine molecule (II).

Barltrop and Saxton (44) succeeded in obtaining a 40% monosubstitution of 2-tetralone with 2-dialkylaminoethyl chloride and pure sodamide. The next step was treatment with bromine to form the piperidine ring of morphine (XXXVII). However, upon attempted formation of the phenanthrene nucleus, the keto group proved to be inert toward most reactions. They also obtained the 13-substituted phenanthrone (XXXVIII) on treating their 1-dialkylaminoethyl-2-tetralone with the methiodide of 1-dialkylamino-3-butanone, but were unable to effect cyclization to the 4-ring system of the morphine structure.

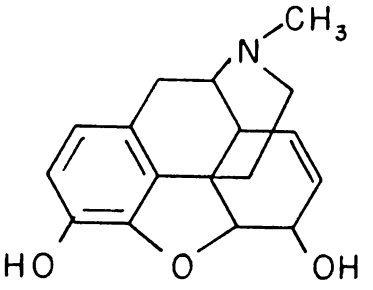
Others have attempted the synthesis of 1-substituted-2-tetralones through intermediates containing the appropriate side chain. Thus, Ghosh and Ribinson (40) prepared the 1-ethyl-2-tetralone (XXXIX) from 2-chloro-3,4-dimethoxyphenylbutyric acid through the following series of reactions: (a) cyclization of the acid to the 1-tetralone with sulfuric acid, (b) treatment of this with ethylmagnesium bromide, and (c) oxidation to the 2-tetralone (XXXIX) with hydrogen peroxide. Although it was converted into a 13-substituted hexahydrophenanthrene (XXXVI, R = C_2H_5, R' = R' = H) through reaction with the methiodide of 1-diethylamino-3-butanone over sodamide, followed by reduction, a relatively inactive



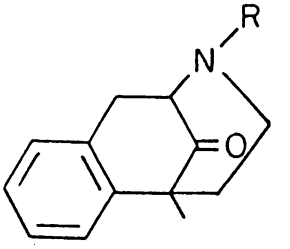
XXXV



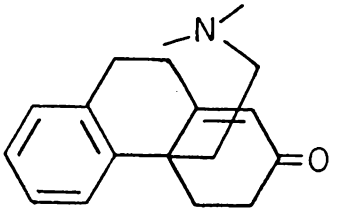
XXXVI



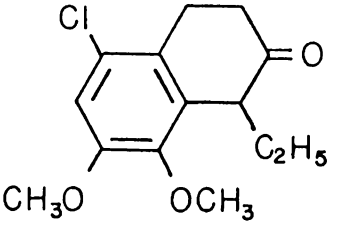
II



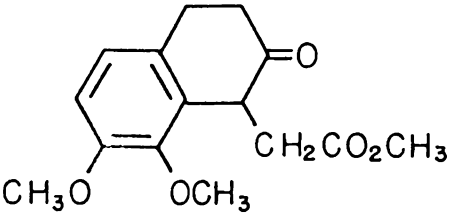
XXXVII



XXXVIII



XXXIX



XL

ethyl group remained at C_{13}; and difficulties in the way of introducing an angular group capable of suitable modification prevented further exploitation of this work. Another substituted 2-tetralone (XL) was synthesized through a very complex scheme from 2,3-dimethoxy-5-bromobenzaldehyde by Stork and Conroy (55). At the present time they are hoping to cause a reaction at the ketone group of XL and bring about ring closure to the 13-substituted hexahydrophenanthrene (XXVI, R = $CH_2CO_2CH_3$, R' = R' = OCH_3).

Concluding that the correct approach is through appropriately substituted intermediates which will generate III upon cyclization, our work, including that described previously, has followed this reasoning. A successful end to this work would be the attainment of two different side chains in the 1-position of 2-tetralone, one of which could form the phenanthrene nucleus, while the second could lead to the final ring of the morphine nucleus, the piperidyl ring.

Following this reasoning, other attempts were made to prepare III (see page 3). The sodium salt of 2,3-dimethoxyphenylacetonitrile (XXX) with diethylcarbonate gave XLI, whose sodic derivative with β-methoxyethyl methanesulfonate led to the ester nitrile (XLII) in good yield. Attempted hydrolysis of only the nitrile group in both XLI and XLII resulted in hydrolysis of both the ester and nitrile groups,

followed by decarboxylation, to yield 2,3-dimethoxyphenylacetic acid and XLIII (R = H), respectively. However, the acid chlorides were prepared and subjected to a reaction with anhydrous aluminum chloride and ethylene at 0°, in hoping for a simultaneous lengthening of the carbon chain by two carbons and ring closure to the 2-tetralone (III) (see page 21). The only discernible products were assumed to have resulted from the interaction of the acid chlorides with xylene, when it was employed as a solvent. Attempting to eliminate the selective hydrolysis step, another approach consisted in the treatment of ethyl 2,3-dimethoxyphenylacetate (whose physical properties have not previously been published) with carbon dioxide over sodamide in order to form the half ester-half acid, according to the method of Hauser and co-workers (56). This was followed by an attempted conversion into the half ester-half acid chloride with thionyl chloride, and, finally, into 1-carbethoxy-7,8-dimethoxy-2-tetralone (III, R = $CO_2C_2H_5$, R' = H) by the aluminum chloride-ethylene reaction. Instead of the desired 2-tetralone, a benzofuran resulted as described on page 34.

In an attempt to build up a carbon chain possessing suitable characteristics for ring closure into a 1-substituted-2-tetralone, XLIV was prepared from 2,3-dimethoxyphenylacetonitrile (XXX) with β-ethers of ethyl propionate ($ROCH_2CH_2CO_2$-

C_2H_5) in the presence of sodamide. The 2-tetrahydropyranyl ether of ethyl hydracrylate (R = 2-tetrahydropyranyl, formed from dihydropyran and ethyl hydracrylate) was used for two reasons: (a) for protection of the hydroxyl group of the ester in the reaction with sodamide, and (b) to give XLIV containing a terminal ether group which can be readily cleaved to the alcohol. A thorough literature survey showed that this constituted the first time dihydropyran had been utilized for the protection of the hydroxyl group of such an aliphatic hydroxy ester. Analogous to other cases where a 2-tetrahydropyranyl ether was subjected to alkaline reaction conditions, the ether linkage remained intact; however, it was hydrolyzed during the isolation procedure to give XLIV (R = H). A quantity of an oil, which exhibited the characteristics of the product, was obtained in addition to XLIV, but could neither be crystallized nor distilled. It was soluble in sodium hydroxide solution, a fact which may be attributed to the activity of the hydrogen on the central carbon between the activating carbonyl and nitrile groups. Of course, isolation could have been difficult owing to the presence of stereoisomers.

The ethyl ether (XLIV R = C_2H_5), was formed from the sodium salt of 2,3-dimethoxyphenylacetonitrile (XXX) with ethyl β-ethoxypropionate, although analysis of the product indicated the presence of a higher carbon content. An attempt

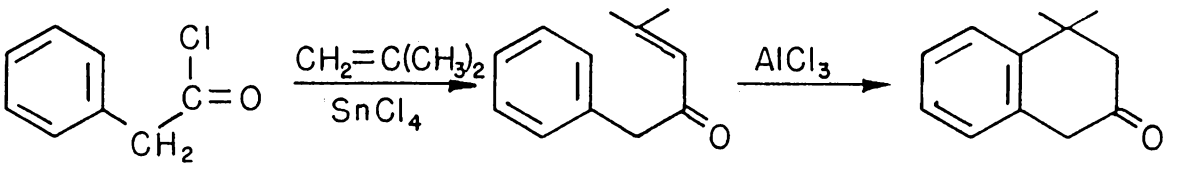
to convert XLIV (R = H) into the substituted 2-tetralone (III, R = CN, R' = H) by means of sulfuric acid failed to effect cyclization. This failure may have resulted because of the high electron density existing in the aromatic nucleus, which would be easily sulfonated in preference to any ring closure.

The conception of the idea of the ethylene-aluminum chloride reaction, mentioned above, whereby simultaneous chain enlargement and cyclization occur, arose as a result of work by McMahon and Bowden and their associates (57). While they desired only to form aliphatic β-chloroethyl and vinyl ketones through the reaction of aliphatic acid chlorides with ethylene and aluminum chloride at 0°, our proposal consisted in the conversion of arylacetyl chlorides into the intermediate β-chloroethyl or vinyl ketones in the same manner. However, in the presence of aluminum chloride the ketones should react further by ring closure to give polycyclic ketones. This prediction proved to be true as shown by the synthesis of certain 2-tetralones. A similar idea, which was not known to us at the time of the inception of our work, was advanced by Colonge and Chambion (58), who prepared 4,4-dimethyl-2-tetralone (XLVII) by the use of two Friedel-Crafts type reactions: phenylacetyl chloride (XLV) reacted with isobutylene in the presence of stannic chloride to yield the β,β-dimethylvinyl ketone (XLVI), which gave the 2-tetralone upon cycliza-

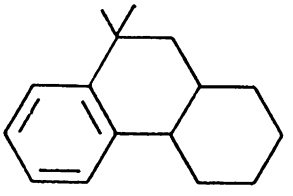
tion with aluminum chloride. Although it was obtained in 78% yield, this method requires two steps to the desired product, while our procedure uses but one. One definite drawback to the utilization of their intermediate 2-tetralones in the synthesis of the polycyclic nuclei of morphine and the steroids is the presence of the two methyl substituents in the 4-position. Upon applying the appropriate reactions, these could likely be converted into the morphine or steroid skeleton (XLVIII or XLIX), but undesired methyl groups in the 10- and 5-positions, respectively, would be present. Our process, however, employing the simple gas, ethylene, avoids this difficulty.

2-Tetralone (LIII) has been prepared by several different methods (59-61); however, the yields have been observed to be extremely low or the intermediates very difficult to obtain. The most feasible process until now has been by the reduction of 2-naphthols or 2-methoxynaphthalenes either catalytically or with sodium in a suitable medium (62,63). Very recently and after the inception of our studies, Barltrop and Saxton (44) obtained 2-tetralone in an 80% yield by reduction of 2-naphthol with sodium in liquid ammonia. Concurrently, our procedure using phenylacetyl chloride (XLV) with aluminum chloride and ethylene gave a 75% yield.

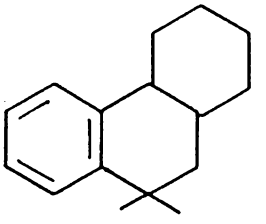
To serve as a model compound for the possible future



XLV XLVI XLVII



XLVIII



XLIX

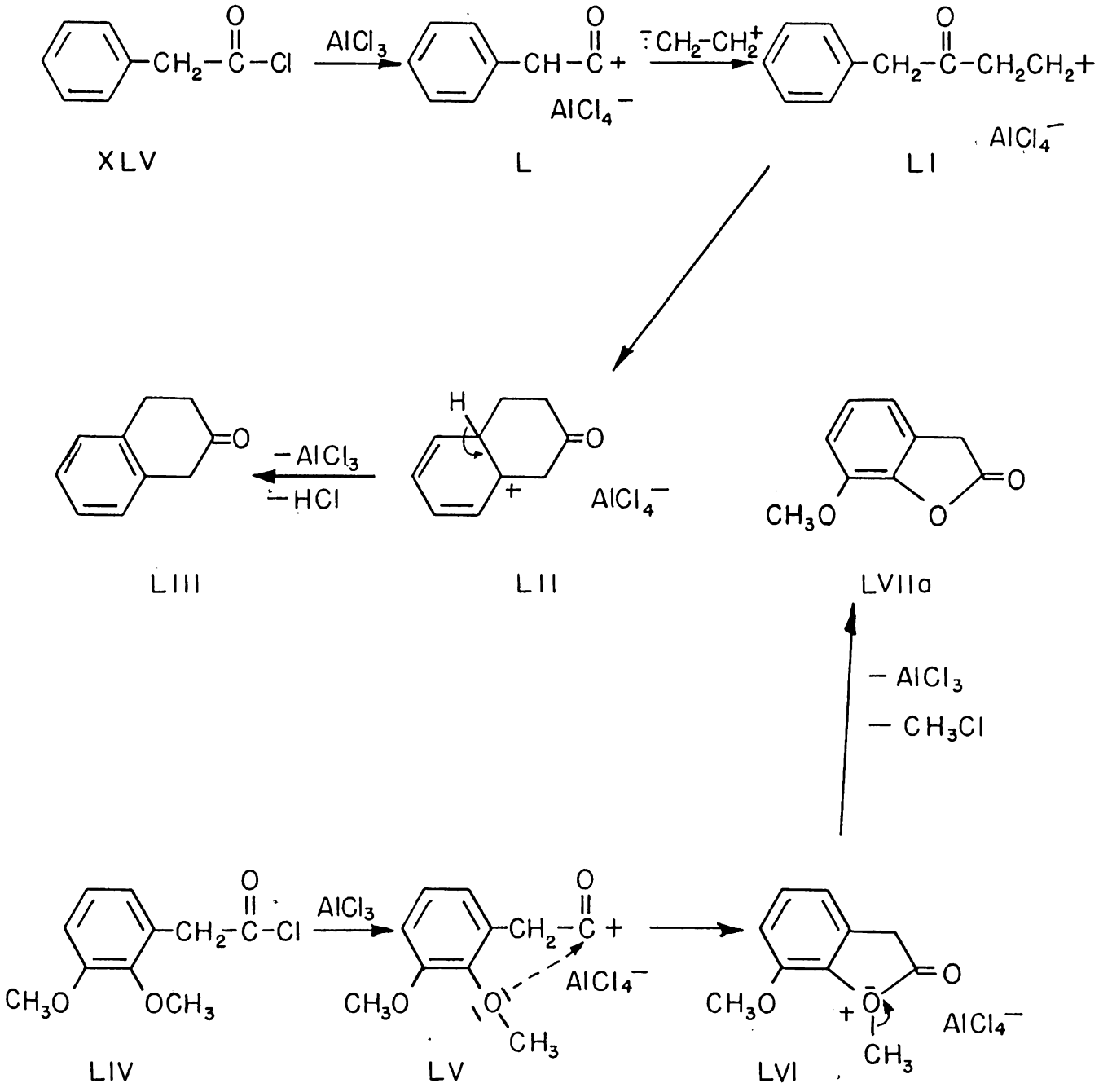
preparation of LVII, 2-tetralone (LIII) was prepared by the addition of ethylene to the aluminum chloride complex of phenylacetyl chloride in carbon disulfide at 0°. Difficulties became apparent in the first reactions attempted when the aluminum chloride was slowly added in portions to the acid chloride dissolved in carbon disulfide. Large aggregations of the complex and aluminum chloride formed; this made stirring impossible, preventing attack by the ethylene. The difficulties were largely overcome by the use of greater amounts of solvent, more vigorous stirring and a reversal of the addition process. Thus, when a solution of the acid chloride in carbon disulfide was slowly added to a cooled and vigorously stirred suspension of aluminum chloride in carbon disulfide, followed by the introduction of ethylene for four hours, the reaction proceeded smoothly to give a 30% yield of 2-tetralone. This yield was subsequently increased to 75% by employing two equivalents of aluminum chloride per equivalent of phenylacetyl chloride.

A mechanism consistent with the known facts is proposed on page 34. In the first place, phenylacetyl chloride (XLV) reacts with aluminum chloride to form the carbonium ion (L), which gives the new carbonium ion (LI) upon addition to the double bond of ethylene (shown in one of its possible resonance forms). LI could form the β-chloroethyl ketone upon reaction with the aluminum chloride ion, and thence the

vinyl ketone by elimination of hydrogen chloride. However, in the presence of aluminum chloride, LI and both ketones would add across one of the "double bonds" of the benzene nucleus to form the new ion (LII), which finally loses hydrogen chloride giving 2-tetralone (LIII) and aluminum chloride.

Since methoxy groups in the 7,8-positions of 2-tetralone would be ideal as the foundation of the 3-hydroxy and 4,5-ether bridge of the morphine alkaloids, the preparation of 7,8-dimethoxy-2-tetralone (LVII) was attempted. Indeed, the ethylene-aluminum chloride reaction with 2,3-dimethoxyphenylacetyl chloride (LIV) produced a 62% yield of colorless plates which melted at 79°. However, Soffer, et al., (48) reported a melting point of 76°, no ketonic derivatives could be formed, and the analysis indicated a different compound. When an ethyl alcohol solution of the solid was treated with a little dilute sodium hydroxide, a blue-green color developed This is indicative of a positive "tetralone-blue" test (63). Only one compound, 7-methoxy-2-oxo-2,3-dihydrobenzofuran (LVIIa), could explain these data. It melts at 80°, possesses no ketonic group, agrees with the analysis, and reacts with sodium hydroxide in the "tetralone-blue" test by cleavage of the lactone ring. In order to support these conclusions, the lactone ring was intentionally hydrolyzed to the known 2-hydroxy-3-methoxyphenylacetic acid, which melted at 124° and gave a green phenol test with ferric chloride. These properties are

Type III Compounds

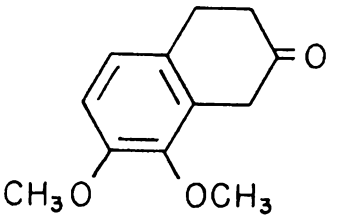


XLV L LI

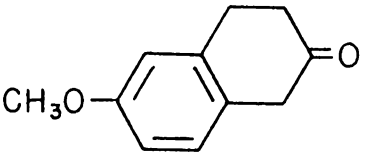
LIII LII LVIIa

LIV LV LVI

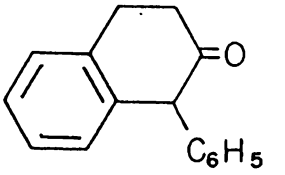
Type III Compounds Cont.



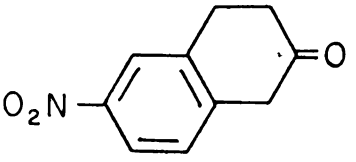
LVII



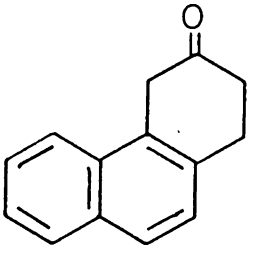
LVIII



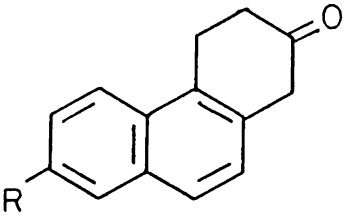
LIX



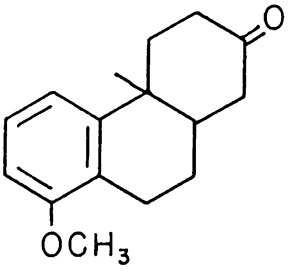
LX



LXI



LXII



LXIII

in complete agreement with those found by Mosimann and Tambor (64).

A mechanism by which the benzofuran is formed may be postulated. Thus, 2,3-dimethoxyphenylacetyl chloride (LIV) yields the carbonium ion (LV) upon treatment with aluminum chloride. One of the free pairs of electrons on the ortho-methoxy oxygen forms a new bond with the carbonyl carbon atom resulting in the new complex (LVI). Finally, a chlorine ion from the aluminum chloride radical displaces the methyl group to give methyl chloride, aluminum chloride and the neutral benzofuran (LVIIa). Evidently, the ethylene played no part in this reaction. By the same reasoning, LVIIa resulted from the aluminum chloride-ethylene reaction with the acid chloride corresponding to ethyl α-cyano-2,3-dimethoxyphenylacetate (XLI), as mentioned previously.

These results constitute a new synthesis of 7-methoxy-2-oxo-2,3-dihydrobenzofuran (LVIIa) in a 62% yield at 0°. Mosimann and Tambor obtained it from 2,3-dimethoxymandelonitrile with hydriodic acid. Certainly, our method employes more readily attainable starting materials, and eliminates any possibility of demethylation with the use of hydriodic acid at elevated temperatures. The method could probably be varied so as to increase the yield, and extended to the synthesis of a variety of substituted benzofurans. As far

as can be ascertained, the synthesis of benzofurans from ortho-substituted phenylacetyl derivatives usually requires that the ortho-substituent consist of a hydroxyl group or its acyl derivative. This appears to be the first time a benzofuran has been prepared from the methyl ether of the ortho-substituent.

One difficulty which arose in the studies just described was the preparation of 2,3-dimethoxyphenylacetyl chloride (LIV). Upon formation of this acid chloride from the corresponding acid (prepared by hydroysis of XXX) using thionyl chloride, the excess reagents must be removed under reduced pressure at room temperature. Heat causes the decomposition of LIV, even when subjected to high vacuum distillation. Consequently, it was utilized in its crude form after removal of the reagents.

Another approach which, it was hoped, would lead to the synthesis of 7,8-dimethoxy-2-tetralone (LVII) was attempted. While ethylene was introduced, a mixture of 2,3-dimethoxyphenylacetic acid and phosphoric acid or phosphoric acid-phosphorus pentoxide was heated to 150° for several hours. Only starting material was recovered.

In most of the synthetic schemes utilizing 1-substituted-2-tetralones as intermediates in the preparation of

morphine alkaloids, one of the important steps is the replacement of the keto group with a suitable side chain by means of the Reformatsky or some similar reaction. This substituent would then be modified so as to give the 13-substituted hexahydrophenanthrene (XXXVI) by cyclization. During the course of the last two years and after our studies had begun, two groups of chemists (44,65) have shown that the keto group of 1-substituted 2-tetralones is highly unreactive when substituents are present in the 1-position. Either the reactions did not proceed, or abnormal products resulted from the addition. In fact, in some cases the keto group failed to form even the standard ketone derivatives.

Although LVII could not be obtained by use of the ethylene reaction, which had been successfully applied to LIII, an extention to other 2-tetralones was desirable. Thus it was found that 6-methoxy-2-tetralone (LVIII) could be prepared from p-methoxyphenylacetyl chloride, which itself was obtained from p-methoxybenzyl alcohol (anisyl alcohol) via the benzyl chloride, nitrile and acid. This acid was formed in 85% yields without isolation of any of the intermediate compounds. The ethylene reaction with its acid chloride gave LVIII in a 56% yield. The latter has been prepared by other methods (61,63,66,67), but, again, most of them are not practical owing to difficulties in preparing intermediates or to

complex procedures which give low yields. Thus, the ethylene reaction with p-methoxyphenylacetyl chloride offers several distinct advantages. The yield could probably be increased by varying solvents and reaction conditions, and by eliminating the aggregations which always formed during the course of the preparation.

On attempting to prepare 1-phenyl-2-tetralone (LIX) from diphenylacetyl chloride by this method, only polymers resulted. These probably were formed by an interaction of the highly reactive carbonium ion with the acid chloride. Only starting material was recovered when the ethylene reaction was employed in the attempted preparation of 6-nitro-2-tetralone (LX) from p-nitrophenylacetyl chloride. This failure can probably be attributed to the positive character of the aromatic nucleus containing the highly electronegative nitro group, thereby hindering ring closure. In some instances the solvent, carbon disulfide, was replaced by nitrobenzene or benzene, and ethylene introduced simultaneously with the acid chloride to the reaction mixture. However, these varied conditions also failed to yield any of the desired 2-tetralones.

It might be pointed out that all the acid chlorides were prepared from their corresponding acids in yields ranging around 90%. In most cases a mixture of the acid, dry benzene

and an excess of thionyl chloride was allowed to stand at room temperature until the initial reaction subsided. Then, it was refluxed on a steam bath until the evolution of gases stopped, and, finally, allowed to stand at room temperature overnight. The excess reagents were removed under reduced pressure, and the products purified by distillation or recrystallization.

Some conclusions as to the generality of the ethylene reaction might be made. Evidently, an electron donating group in the benzene ring of the acid chloride allows the reaction to proceed, while an electron withdrawing group hinders the process. This method appears to possess potential advantages over others for the preparation of substituted 2-tetralones. If substituents are introduced into the phenyl ring or the aliphatic side chain prior to reaction with ethylene and aluminum chloride, new 2-tetralones with either or both rings substituted might be synthesized.

Our attention became temporarily diverted from the use of 2-tetralones as intermediates in the synthesis of morphine derivatives and became transferred to their application in the formation of the polycyclic nuclei of the steroids. Cornforth and Robinson (68) were successful in treating 2-methyl-5-methoxy-2-tetralone with the methiodide of 1-dimethylamino-3-butanone, followed by reduction, to give 13-

methyl-1-methoxy-5,6,7,8,9,10,13,14-octahydro-7-phenanthrone (LXIII). As far as could be determined, this was the only preparation of a steroid intermediate utilizing a 2-tetralone, which itself is obtained with some difficulty.

If 1- and 2-naphthylacetyl chlorides were subjected to the ethylene reaction, there is a possibility that the side chains could be lengthened and closed into the saturated rings of the 1,2,3,4-tetra-hydro-2- and 3-phenanthrones (LXI and LXII), respectively. Then the cyclopentano ring of the steroids could be introduced by exploiting the reactivity of either the keto group or its adjacent hydrogen. Of course, by beginning with 6-methoxy-2-naphthylacetyl chloride the final product (LXII, R = OCH_3), would contain a group which might be readily converted into the 3-hydroxy or keto group of the steroid series.

Despite expectations, the attempted preparation of LXI from 1-naphthylacetyl chloride by our method yielded only starting material, an unidentified white solid, acenaphthenone and ethylbenzene when benzene was the solvent. It was hoped that the low temperatures employed throughout the reaction period would eliminate formation of acenaphthenone, although the ethylbenzene was quite unexpected. Acenaphthenone is usually prepared from the acid chloride, aluminum chloride and benzene at room temperature (69); however, its formation

competes strongly with that of LXI even at lower temperatures. Although ethylbenzene is obtained by the reaction of ethylene and benzene in the presence of aluminum chloride, the temperature is usually maintained at about 75° and vigorous stirring is employed (70). Thus, its formation at the low temperatures used was surprising.

Using the same method, 2-naphthylacetyl chloride, prepared from 2-methylnaphthalene, should give LXII. A very few grams of an oil, which boiled at 220-222° (20 mm.) and solidified upon distillation, were obtained from the reaction. An attempt to convert the small amount into the semicarbazone yielded no definite product.

Mosettig and Burger (71) reported that the 1- and 4-phenanthrones, analogous to LXI and LXII, possessed surprising analgetic activity with no side effects. Thus, LXI and LXII may be true analgetics, if they can be prepared by varying the reaction conditions of the ethylene-aluminum chloride process using the corresponding acid chlorides.

TYPE IV AND TYPE V COMPOUNDS

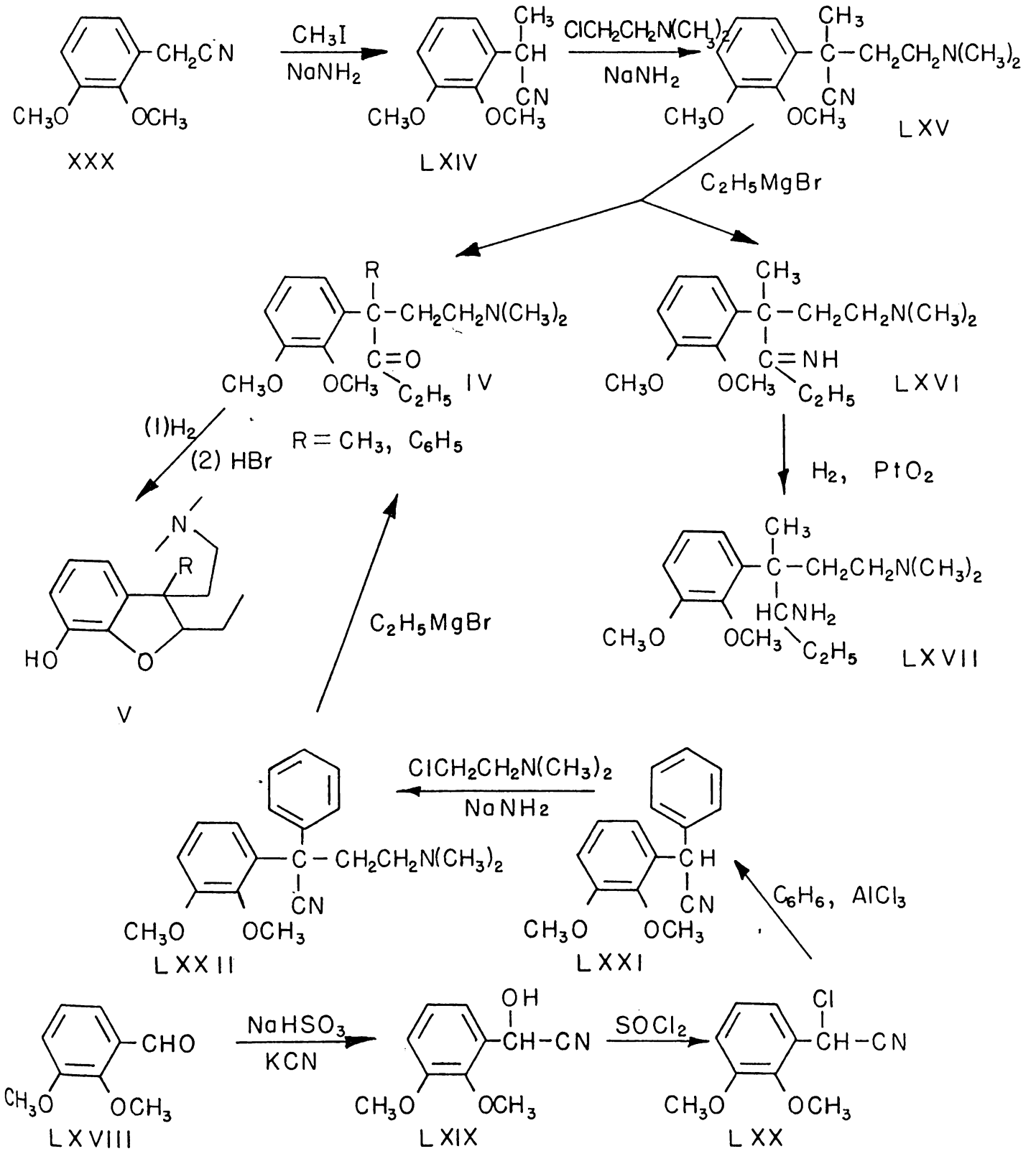
The proposed methods for the synthesis of type IV and V compounds are shown on page 44. Our aim was to prepare IV, which resembles the analgetic, Amidone (I), and convert it to V, which bears a structural relationship to the morphine structure (II). IV, where R = CH_3, differs from Amidone in that it possesses two methoxyl groups in the aromatic nucleus, a dimethylaminoethyl instead of the 2-dimethylaminopropyl side chain and a methyl in place of a phenyl group on the quaternary carbon atom. Relationship to Amidone is even more pronounced in the case of IV, where R = C_6H_5, the difference residing in the presence of the methoxyl groups and the shorter side chain. Thus, IV might be expected to exhibit some analgetic activity. The reduction of IV, followed by demethylation and cyclization, should yield V, which also could possess analgetic activity owing to its resemblance to the morphine structure. Together with previous work in this laboratory (72) the attempted conversion of IV into V, thereby proceeding from Amidone- to morphine-like compounds, appears to be the only such work in this field. However, Kagi and Miescher (73) followed a similar approach in the Demerol series.

Johnson (72) previously prepared LXIV and LXV from 2,3-dimethoxyphenylacetonitrile (XXX) through successive

alkylations with methyl iodide and dimethylaminoethyl chloride in the presence of sodamide. Utilizing the same procedure, LXIV and LXV were obtained in even better yields when the reflux period of the reactants was increased. In one case during the isolation of LXV another product which possessed the characteristics of an amino acid was obtained. An attempted conversion of the amino acid to its ester resulted in a compound which would not separate from an aqueous solution at any pH. Although Johnson succeeded in obtaining IV from LXV and ethylmagnesium bromide in low yields, the only product isolated here was the imino compound (LXVI), in a 59% yield. In spite of the very drastic conditions employed for hydrolysis of the imino to the keto group, LXVI remained untouched. This fact is not too surprising since the imine of Isoamidone (XXVI) is hydrolyzed only with difficulty (74). Compound LXVI, as the dihydrochloride, was reduced to LXVII, whose dihydrochloride was also prepared. Although analysis of the latter compound was not satisfactory, the results justify an assumption of the formation of LXVII. Following the isolation of LXVI, another product was found in the same reaction mixture. Johnson (51) also obtained this fraction, but in neither case was it identified because, at first, it was thought to consist of the intermediate imino compound.

It is well known that tertiary amines form salts with Grignard reagents; therefore, much of the reagent was used to

Proposed Synthesis of Type IV and V Compounds



form the salt in the reaction of LXV with ethylmagnesium bromide. In order to prevent this complexing of the Grignard reagent, the benzyl chloride salt of LXV was prepared and then treated with ethylmagnesium bromide. Although this method has been employed by others (73) in analogous work to give excellent yields, we only recovered starting material.

Difficulties were encountered in the preparation of the diarylacetonitrile (LXXI) which is a necessary intermediate in the synthetic approach toward IV (R = C_6H_5) and V (R = C_6H_5). Other methods (24) for the formation of such compounds by bromination of the appropriate arylacetonitrile, followed by a Friedel-Crafts reaction with benzene and aluminum chloride, were attempted. Only tars were obtained in the bromination of 2,3-dimethoxyphenylacetonitrile (XXX), even upon utilization of ultraviolet light as a catalyst. Evidently, the hydrogen bromide which formed in the bromination caused demethylation and decomposition.

A new preparatory approach to LXXI was next tried. The mandelonitrile (LXIX) was prepared from 2,3-dimethoxybenzaldehyde (LXVIII) with sodium bisulfite and potassium cyanide, and then treated with pure thionyl chloride to give the new substance (LXX) in excellent yield. This was greatly increased when the excess thionyl chloride was removed under reduced pressure rather than through decomposition with

water. Finally, LXXI was prepared from LXX by a Friedel-Crafts reaction with benzene. Sometimes a red oil was obtained in place of the crystalline LXXI, but it proved to be the desired product when hydrolysis of a portion gave the corresponding acid.

As before, the sodio salt of LXXI was alkylated with 2-dimethylaminoethyl chloride to give LXXII. Although a new compound developed upon reaction of LXXII with the Grignard reagent, it could not be positively identified as IV (R = C_6H_5). Again, there is the possibility of obtaining the intermediate imine rather than the ketone. This crude compound was subjected to hydrogenation, but only intractable oils resulted.

When 2,3-dimethoxybenzaldehyde (LXVIII) was replaced by m-hydroxybenzaldehyde in the reaction scheme above, the corresponding mandelonitrile could not be produced. This was attempted because of the high analgetic potency exhibited by a m-hydroxy analogue of Demerol, prepared by Kagi and Miescher (73).

TYPE VI COMPOUNDS

Because of considerable interest in the analgetic and spasmolytic properties of some compounds with the γ-arylpropylamine skeleton (75) prepared by the application of the Leuckart reaction (76), further work in this field was warranted. Therefore, a series of six N-alkyl- and N,N-dialkyl-3,3-diphenyl-1-methylpropylamines (Table I) were prepared according to this method from 4,4-diphenyl-2-butanone (formed from benzalacetone, benzene and aluminum chloride).

The general procedure employed consisted in heating a mixture of the ketone, the N-substituted formamide and a little formic acid at 180-200° for 10-17 hours. The intermediate formamides of LXXIII and LXXIV were not isolated, but were immediately hydrolyzed to the free amines with 30% sulfuric acid. The resulting sulfate salts of the amines proved to be insoluble in either water or organic solvents, therefore, they were dissolved in boiling water and made alkaline while hot in order to liberate the free amines. Following a modification by Bunnett and Marks (77), a little magnesium chloride hexahydrate, as catalyst, was added to those reactions in which N,N-dialkylformamides were employed. Needless to say, hydrolysis was not necessary in these cases since the tertiary amines were formed directly.

All the amines, with one exception, were extracted with ether, and without purification converted into their hydrochloride salts. The exception existed in the case of LXXVII where the excess pyrrolidine could be removed only by vacuum distillation of the reaction product.

LXXIV, LXXV and LXXVIII have been reported previously; however, the methods employed for their preparation differed from this one. Burckhalter and Johnson (75) obtained LXXIV in a 7% yield by applying the Leuckart reaction to 4,4-diphenyl-2-butanone and N-ethylformamide. LXXV has been prepared by several workers (30,31), who utilized different procedures to obtain it in 5-90% yields. The melting points varied from 115° to 158°, depending upon the percentages of the stereoisomers existing in the reaction product. Bochmuhl and Ehrhardt (31) obtained LXXVIII upon hydrogenating a mixture of the ketone and piperidine at high pressure in the presence of a catalyst.

The Leuckart reaction was further employed in the attempted preparation of 1,3,3-triphenyl-1-(N-piperidyl)propane (LXXX) and of N,N-diethyl-1,3,3-triphenylpropylamine (LXXXI) from β,β-diphenylpropiophenone (LXXIX), and of 3-methylamino- and 3-dimethylamino-1,1,5,5-tetraphenylpentane (LXXXIII) from 1,1,5,5-tetraphenyl-3-pentanone (LXXXII). The latter ketone was obtained by the reaction of dibenzalacetone

TABLE I

3,3-Diphenyl-1-methylpropylamines, $(C_6H_5)_2$-$CHCH_2\underset{CH_3}{C}HNRR'$

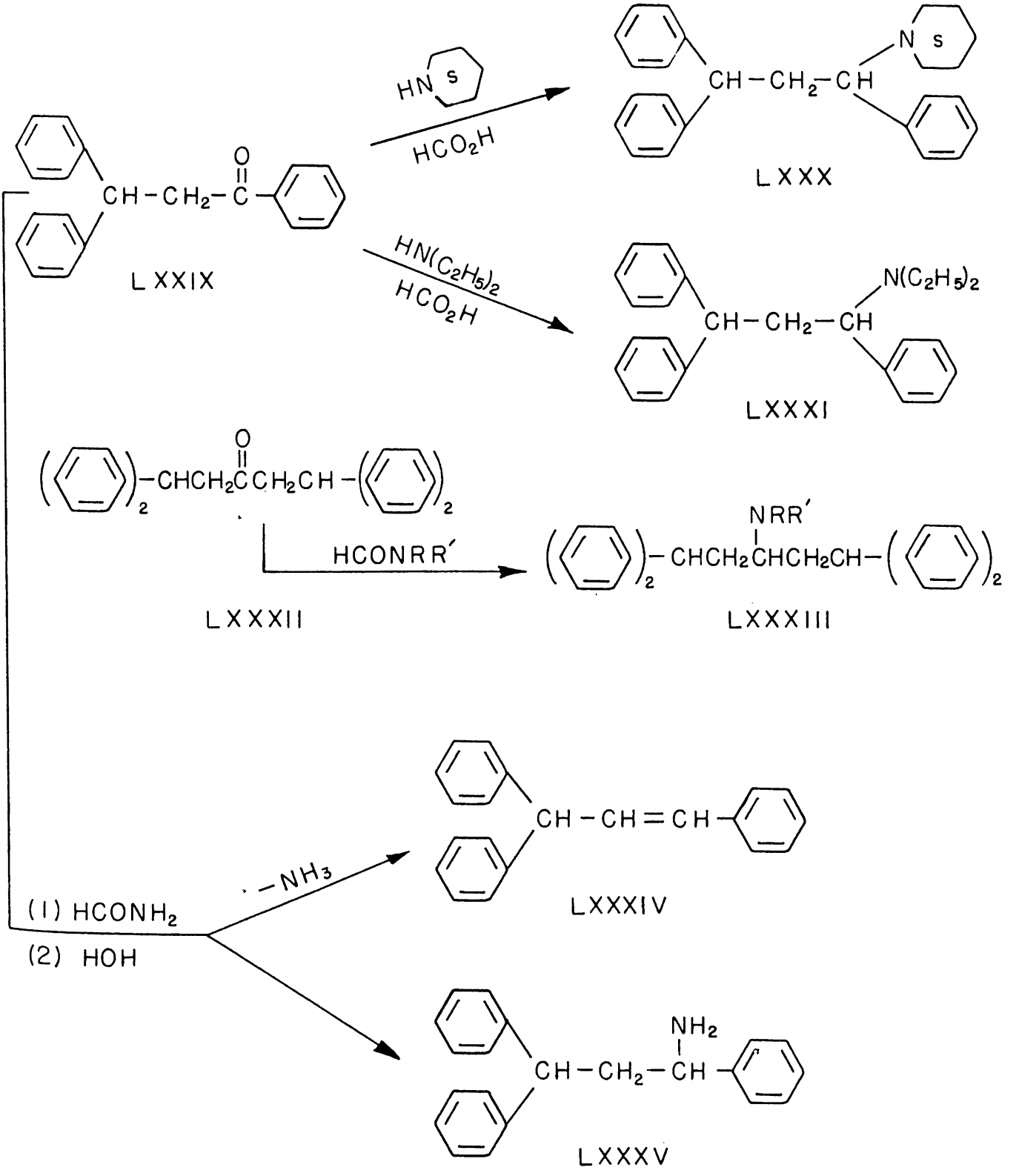
No.	R	R'	Yield%[a]	M.P. °C	Formula	Chlorine% Calcd.	Chlorine% Found
LXXIII	H	CH_3	87[b]	175	$C_{17}H_{21}N.HCl$	12.86	12.84
LXXIV	H	C_2H_5	59[c,d]	147-148	$C_{18}H_{23}N.HCl$		
LXXV	CH_3	CH_3	50[e,f]	155-156	$C_{18}H_{23}N.HCl$	12.23	12.20
LXXVI	C_2H_5	C_2H_5	18[d]	109	$C_{20}H_{27}N.HCl$	11.15	11.09
LXXVII	$-C_4H_8-$		39[d,g]	164	$C_{20}H_{25}N.HCl.H_2O$	10.62	10.78
LXXVIII	$-C_5H_{10}-$		62[e,h]	217	$C_{21}H_{27}N.HCl$	10.75	10.83

(a) Based on starting ketone. (b) From ethyl alcohol. (c) Prepared previously in 7% yield with m.p. 147° (75). (d) From acetone-ether. (e) From ethyl alcohol-ether. (f) Prepared previously by different methods (30,31) in yields of 5-90% with melting points of 115-158°. (g) Free amine boiled at 126-128° (0.1 mm.). (h) Prepared previously by a different method (31), m.p. 213-214°.

with benzene over aluminum chloride. None of the desired amines were formed, probably owing to the presence of the phenyl groups.

Since LXXXV has shown promise as an analgetic agent, more of the compound was prepared according to the procedure given by Burckhalter and Johnson (75). The formamide of LXXXV was obtained from LXXIX and formamide in a 91% yield, whereas they reported a 73% yield; however, difficulties arose upon hydrolysis of the intermediate formamide to the amine (LXXXV). Although they found that hydrolysis with 30% hydrochloric acid gave the propene (LXXXIV) through loss of ammonia, LXXXV resulted upon hydrolysis with 30% sulfuric acid. However, in one attempt only were we able to prepare LXXXV from the formamide through sulfuric acid hydrolysis, and in the others LXXXIV was obtained. This propene was also formed when hydrolytic agents such as 15% sulfuric acid, 10% hydrochloric acid and 30% sodium hydroxide were employed with the formamide. Evidently, LXXXV is very susceptible to the loss of ammonia in the presence of hydrolytic agents.

An attempt was made to prepare the m-hydroxyphenyl analogues of the amines in Table I. This was to entail preparation of 4-m-hydroxyphenyl-4-phenyl-2-butanone, the m-hydroxy derivative of the ketone used in the above syntheses, by addition of benzene across the double bond of m-hydroxy-


HN S
HCO2H
N S
CH-CH2-CH
LXXX
HN(C2H5)2
HCO2H
N(C2H5)2
CH-CH2-CH
LXXXI
LXXIX
CHCH2CCH2CH
HCONRR'
NRR'
CHCH2CHCH2CH
LXXXII
LXXXIII
(1) HCONH2
(2) HOH
-NH3
CH-CH=CH
LXXXIV
NH2
CH-CH2-CH
LXXXV

benzalacetone. However, in attempting to form this benzalacetone from m-hydroxybenzaldehyde (obtained from m-nitrobenzaldehyde) and acetone, only an intractable substance was isolated.

SYNTHESIS OF COMPOUND VII

As stated before, Amidone (I) is a potent synthetic analgetic. When its keto group is reduced to the corresponding alcohol, the activity decreases; but the acetoxy derivative of this alcohol shows a marked increase in activity. If the alcohol is dehydrated to its unsaturated derivative, a totally inactive compound is obtained. The analgetic activity of the saturated analogue (VII) of Amidone, where the keto group has been replaced by a methylene group, remains a question because it has not been prepared until now. In analogy with the relationship between structure and activity in morphine-like compounds where deletion of certain substituents enhances the activity (e.g., 3-hydroxy-N-methylmorphinan) one might speculate that VII would possess greater analgetic activity than Amidone itself. However, its true activity will remain unknown until results of pharmacological testing are reported.

Several chemists have attempted to prepare VII from Amidone by reduction (30), but they only succeeded in forming the corresponding alcohol or the unsaturated derivative, or in achieving an unusual type of split, in which the entire ketone chain is lost. We proposed to synthesize VII from readily available starting materials, with the saturated side

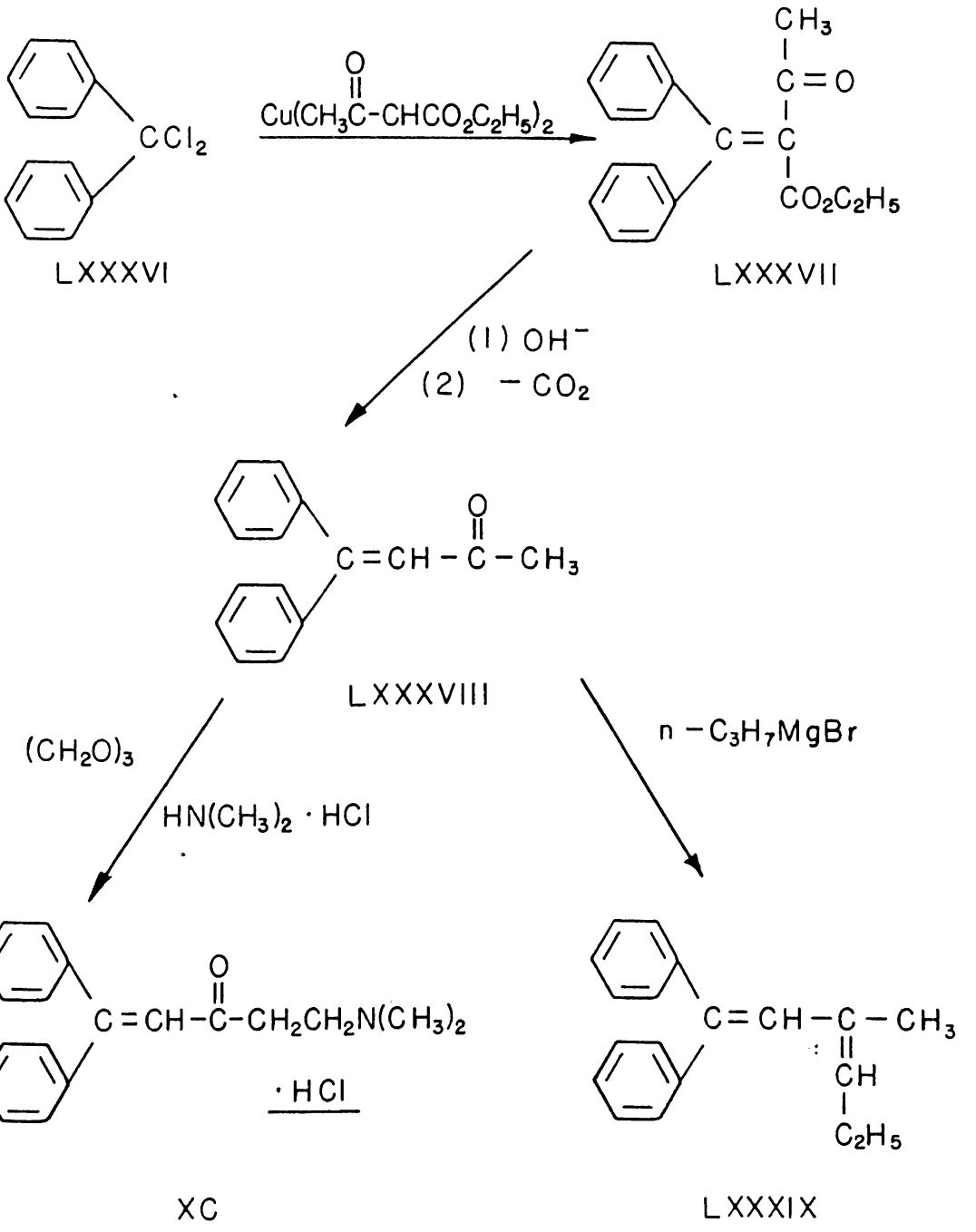
chain already present as such.

A first attempt, designed to yield the desired intermediate, 4,4-diphenyl-3-buten-2-one (LXXXVIII) in one step, failed. It involved the condensation of benzophenone and acetone in the presence of the halomagnesium derivative of N-methylaniline, according to previously reported procedures (78). However, the result was not surprising since the N-methylaniline derivative is a powerful condensing agent, and acetone readily condenses with itself to give mesityl oxide and phorone. Thus, benzophenone and phorone were the only compounds isolated.

The second attempt involved the condensation of dichlorodiphenylmethane (LXXXVI) with the copper salt of acetoacetic ester as performed by Klages and Fanto (79). In this manner LXXXVII was obtained, whereupon it led to LXXXVIII upon hydrolysis and decarboxylation. By means of the Grignard reagent it was desired to add the normal propyl residue across the double bond, thereby giving rise to the saturated ketone (XCV), through 1,4-addition. Instead, 1,2-addition and subsequent dehydration occurred to give, what appears to be, 1,1-diphenyl-3-methyl-1,3-hexadiene (LXXXIX). Although longer refluxing periods and the catalyst, cuprous chloride (which aids 1,4-addition in some Grignard reactions), were employed, the desired ketone (XCV), was not attained.

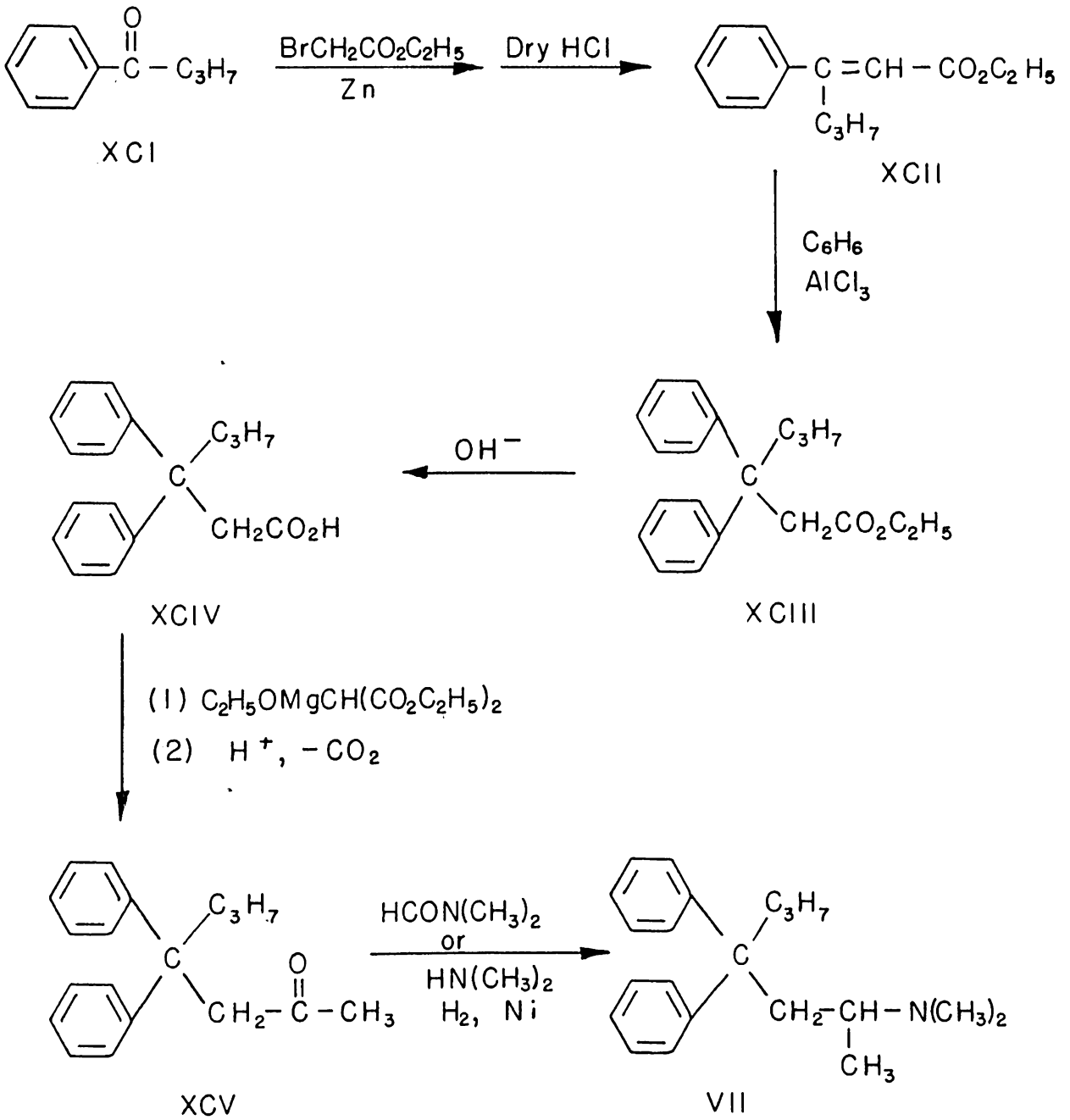
Synthesis of Compound VII

Unsuccessful Approach



Synthesis of Compound VII

Successful Approach



Again, this failure can probably be attributed to steric hindrance at the site of the diphenylmethylene carbon atom.

Compound XC was prepared as an item of side interest, but it might possess interesting pharmacological properties. Its formation involved use of the Mannich reaction (80) with LXXXVIII, paraformaldehyde and dimethylamine hydrochloride.

The successful synthesis of VII was finally accomplished with butyrophenone (XCI) acting as the starting point. A Reformatsky reaction with XCI and ethyl bromoacetate in the presence of zinc was followed by dehydration with anhydrous hydrogen chloride to produce XCII in an 87% yield. Johnson and Kon (81) also prepared it from the same reactants in a yield amounting to 55% of the theoretical, employing magnesium rather than zinc, and dehydration was effected with phosphorus oxychloride. When XCII was treated with benzene and aluminum chloride under mild conditions, the benzene added across the ethylenic group and generated the new ester (XCIII). Potassium hydroxide was utilized to hydrolyze the ester into the corresponding acid (XCIV) which could not be induced to crystallize and was analyzed as the very viscous oil.

At first, the formation of the methyl ketone (XCV) presented some difficulty. Although various acids can be converted to the corresponding methyl ketones with methyl

lithium (82), XCIV remained untouched. Therefore, a modification (83) of Walker and Hauser's procedure (84) using the ethoxymagnesium derivative of diethyl malonate with an acid chloride was employed. Thus, treatment of the acid chloride corresponding to XCIV with the diethyl malonate derivative produced the intermediate diethyl acylmalonate. It was hydrolyzed and decarboxylated under acid conditions to XCV. Either by utilizing the Leuckart reaction with N,N-dimethylformamide or by high pressure hydrogenation with dimethylamine over Raney nickel, XCV was converted into 2-dimethylamino-4,4-diphenylheptane (VII). However, hydrogenation appeared to afford better yields than were obtainable by the Leuckart reaction. The hydrochloride and hydrobromide salts, prepared in the usual manner, would not crystallize under any conditions tried.

Some of the compounds prepared during the course of this work are currently being tested by pharmacologists for their pharmacological properties, and the results will be published elsewhere.

EXPERIMENTAL*

TYPE III COMPOUNDS

2,3-Dimethoxybenzyl alcohol. -- (A). The procedure of Johnson (72) was applied. To a solution of 498 g. (3 moles) of freshly distilled 2,3-dimethoxybenzaldehyde (supplied by Monsanto Chemical Co.) in 600 ml. of ethyl alcohol was added 10 g. of Raney nickel catalyst and reduction carried out at 70-80° in a Parr low pressure hydrogenator. The catalyst was removed by filtration and the alcohol under reduced pressure. The residue was converted into the chloride without further purification.

(B). By the method of Davidson and Weiss (85), 500 g. (7.6 moles) of potassium hydroxide and 750 ml. of absolute methyl alcohol were placed in a three-liter flask fitted with a mechanical stirrer, reflux condenser, dropping funnel and thermometer. The flask was surrounded with a water bath, and a mixture of 498 g. (3 moles) of freshly distilled 2,3-dimethoxybenzaldehyde, 300 ml. of absolute methyl alcohol and 400 ml. of 35-40% formaldehyde solution was added with stirring and at such a rate that the temperature did not exceed 70°. After the addition was complete, the water bath

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* C and H analyses are by Mr. C. M. Beazley, Skokie, Illinois.

was replaced by a Glas-col heating mantle and the temperature maintained at 65-70° for three hours. The reflux condenser was replaced with a downward condenser and the methyl alcohol distilled until the internal temperature reached 101°. To the hot residue was added 900 ml. of cold water, and the resulting mixture was cooled and immediately extracted with benzene. The aqueous layer was separated and extracted twice with 250 ml. portions of benzene, which were combined with the original benzene and washed with two 500 ml. portions of water. The benzene was shaken with anhydrous sodium sulfate until the solution was clear and the solvent removed under diminished pressure. The residue was vacuum distilled to give 498 g. (98%) of the colorless oil, b.p. 88-92° (0.15 mm.) (46).

2,3-Dimethoxybenzyl chloride -- (A). To 500 g. (4.2 moles) of thionyl chloride cooled by an ice bath was slowly added a solution of the residue left from part A above dissolved in 300 ml. of anhydrous benzene. The rate of addition was adjusted so as to maintain a continuous evolution of sulfur dioxide. After the addition was complete, the ice bath was removed and the solution allowed to stand overnight. The flask was again surrounded by an ice bath and 300 ml. of water slowly added. The contents of the flask were then thoroughly washed with water, and the benzene layer separated and dried over anhydrous potassium carbonate. The benzene

was removed under reduced pressure and the residue distilled under high vacuum to yield 460 g. (83%) of the water clear oil, b.p. 72° (0.1 mm.). Johnson reported the boiling point of 86-89° (0.8 mm.).

(B). Following the procedure given by Jackson (86), 498 g. (3 moles) of 2,3-dimethoxybenzyl alcohol dissolved in 1500 ml. of dry, thiophene-free benzene was placed in a four-liter separatory funnel and anhydrous hydrogen chloride passed through the solution for three hours. Throughout the reaction period the mixture darkened and concentrated hydrochloric acid separated as a second layer. After standing for eight hours, the acid was removed and the benzene completely neutralized by thorough washing with two 700 ml. portions of a saturated sodium carbonate solution. Without purification this benzene solution of the chloride was converted into the nitrile.

2,3-Dimethoxyphenylacetonitrile (XXX). -- (A). According to the method of Johnson (72), 130 g. (2.7 moles) of sodium cyanide and 300 ml. of water were placed in a two-liter flask placed upon a steam bath. Warming was necessary to effect solution, and under these reflux conditions 460 g. (2.5 moles) of 2,3-dimethoxybenzyl chloride in 500 ml. of ethyl alcohol was slowly added. In this same way the benzene solution of the chloride from part B was reacted with the theoretical amount of sodium cyanide using the benzene as

solvent in place of ethyl alcohol. After the addition was complete, the mixture was refluxed for five hours and then cooled. The sodium chloride was removed by filtration and the filtrate heated on the steam bath to remove as much alcohol as possible. Upon cooling the mixture was extracted with 500 ml. of ether, which was washed twice with 100 ml. portions of water and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and the residue distilled under high vacuum, yielding 394 g. (89%) of the colorless liquid, b.p. 110° (0.5 mm.); n_D^{20} 1.5245. Johnson reported a boiling point of 106-108° (0.4 mm.) and 96% yield.

(B). Following the procedure of Kindler and Schrader (50), a mixture of 166 g. (1 mole) of 2,3-dimethoxybenzaldehyde, dissolved in enough ethyl alcohol to hinder solidification, 130 g. (1.2 moles) of ethyl chlorocarbonate, 91 g. (1.4 moles) of potassium cyanide in 250 ml. of water and 300 g. of magnesium sulfate heptahydrate in 500 ml. of water was stirred and cooled in an ice bath for four hours, and then placed in the refrigerator overnight. The cold mixture was extracted with ether, which in turn was washed with water, two 200 ml. portions of 10% sodium hydroxide, two 150 ml. portions of a dilute sodium bisulfite solution and finally with water again. The ether was dried over sodium sulfate and removed on the steam bath.

Upon dissolving the residue in xylene, 30 g. of 5%

palladium on charcoal was added, and hydrogen passed through the mixture until carbon dioxide ceased to evolve. The solvent was removed under reduced pressure, and the residue vacuum distilled to give 112 g. of the intermediate ester, b.p. 121-126° (0.5 mm.), together with 47 g. (14%) of the nitrile, b.p. 101-110° (0.5 mm.). Evidently more of the catalyst is required in order to increase the yield of nitrile.

α-2,3-Dimethoxyphenylacetoacetonitrile (XXXI). -- (A). By the general procedure of Julian and co-workers (87). To a hot solution of 0.8 mole of sodium ethoxide in ethyl alcohol, prepared from 18.4 g. (0.8 mole) of metallic sodium and 300 ml. of anhydrous ethyl alcohol, was slowly added 106 g. (0.6 mole) of 2,3-dimethoxyphenylacetonitrile followed by 80 g. (0.9 mole) of anhydrous ethyl acetate, dried by refluxing over phosphorous pentoxide. The mixture was refluxed for fourteen hours, allowed to stand at room temperature for three hours and finally cooled in an ice-salt bath for two hours. The ice-cold contents of the flask were poured into 500 ml. of ice-cold water, and 50 ml. of glacial acetic acid added to precipitate an oil. After extracting the oil with 300 ml. of ether, the ether was thoroughly washed with water and dried over anhydrous potassium carbonate. The ether was evaporated and the residue distilled to give 78.6 g. (61%) of the water-clear oil, b.p. 130-137° (0.3 mm.); n_D^{20} 1.5320.

Upon redistillation and standing at room temperature the oil solidified. The white solid was recrystallized from Skelly A to give 75 g. of the pure nitrile, m.p. 64-65°. Johnson (51) reports a boiling point of 139-141° (0.7 mm.), a melting point of 64° and a yield of 75%.

(B). In general the method described above gave less than 50% yields; therefore, the procedure outlined by Levine and Hauser (88) was utilized to increase the yields. To a refluxing suspension of 90 g. (2.3 moles) of sodamide in 600 ml. of dry benzene was slowly added 200 g. (1.13 moles) of 2,3-dimethoxyphenylacetonitrile and the refluxing continued for four hours. A solution of 180 g. (2 moles) of anhydrous ethyl acetate in 100 ml. of dry benzene was then added very cautiously and the mixture refluxed for five additional hours. After standing overnight at room temperature, a solid formed and was decomposed with two liters of ice. This was acidified with concentrated hydrochloric acid, and the benzene was separated from the aqueous layer, which was extracted three times with 250 ml. portions of ether. The benzene and ether extracts were combined, washed with water and dried with sodium sulfate. The solvents were removed under reduced pressure and the residue distilled to give 137.1 g. (55.5%) of the colorless oil, b.p. 146° (0.9 mm.), which crystallized upon standing.

Ethyl α-2,3-Dimethoxyphenylacetoacetate (XXXII). -- Since only poor yields of the ester were obtained by Kimball's method (52), that of McElvain and co-workers (53) was used. A solution of 31 g. (0.14 mole) of α-2.3-dimethoxy phenylacetonitrile in 250 ml. of absolute ethyl alcohol, cooled to 0° in an ice-salt bath, was saturated with anhydrous hydrogen chloride and allowed to stand at room temperature overnight. The excess hydrogen chloride and alcohol were removed under diminished pressure, and the following added: 100 ml. of absolute ethyl alcohol containing three ml. of conc. hydrochloric acid and three times the theoretical quantity of water necessary to hydrolyze the imino ether. After heating this solution on the steam bath for forty-five minutes, it was poured into 800 ml. of cold water. The mixture was extracted with ether, which was dried over sodium sulfate and then removed under reduced pressure. Upon vacuum distillation of the residue 25 g. (67%) of the light yellow oil were obtained, b.p. 107-120° with decomposition (0.2-1 mm.). The residue was redistilled to give 20 g. of the oil, b.p. 117° (0.2 mm.); n_D^{20} 1.5296.

Anal. Calcd. for $C_{14}H_{18}O_5$: C, 63.14; H, 6.81.
Found: C, 63.46; H, 7.08.

β-Methoxyethyl chloride. -- (A). According to standard procedures utilizing thionyl chloride, 504 g. (6 moles) of ethylene glycol monomethyl ether was converted into the

chloride with 708 g. (6 moles) of thionyl chloride. The excess gases were removed under reduced pressure and the residue distilled to yield 452 g. (72%) of the colorless liquid, b.p. 89.5-91°.

(B). Following the directions of Palomaa and Kenetti (89) for the synthesis of this haloether, 456 g. (6 moles) of ethylene glycol monomethyl ether, 329 g. (2.4 moles) of phosphorous trichloride and 104 g. (1.32 moles) of pyridine gave 394 g. (57%) of the oil, b.p. 86-91°.

β-Methoxyethyl iodide. -- By way of the condenser 390 g. (4.1 moles) of β-chloroethyl methyl ether was added to a solution of 690 g. (4.6 moles) of sodium iodide dissolved in 3500 ml. of acetone. The solution was heated to reflux temperatures which were maintained for forty-eight hours. After it had cooled to room temperature, the sodium chloride was filtered and the acetone distilled from the filtrate to leave a residue of unchanged sodium iodide, sodium chloride and a dark liquid. The inorganic salts were removed by filtration and the liquid distilled to yield a dark-colored oil, b.p. 90-130°. After washing the oil with a dilute sodium thiosulfate solution to remove the excess iodine, it was redistilled to give the water-clear haloether in a yield of 339 g. (44%), b.p. 110-136°. Karvonen (90) reported the boiling point as 138° from ethylene iodide and methyl alcohol.

β-Methoxyethyl benzenesulfonate. -- By the procedure of Bachmann and Fornefeld (54). To a mixture of 205 g. (2.7 moles) of ethylene glycol monomethyl ether, 300 ml. of dry pyridine and 400 ml. of dry benzene cooled to 0° was added 500 g. (2.84 moles) of benzenesulfonyl chloride. The solution was stirred for two hours and 800 ml. of ice-cold 6N hydrochloric acid added. Following extraction with ether, which was washed with water and dried over sodium sulfate, the solvents were removed *in vacuo* and the residue vacuum distilled to yield 484 g. (83%) of the colorless sulfonate, b.p. 110-121° (0.5 mm.). Bachmann and Fornefeld reported b.p. 136-141° (0.2 mm.); yield 61%.

β-Methoxyethyl methylsulfonate. -- According to the method of Newman and Magerlein (42), 80 g. (1 mole) of dry pyridine was added to a solution of 100 g. (0.88 mole) of methanesulfonyl chloride, 67 g. (0.88 mole) of ethylene glycol monomethyl ether and 150 ml. of dry ether cooled in a Dry Ice-acetone bath. When the addition was complete, the temperature was allowed to rise to 0° where it was maintained for two hours. The cold ether solution was washed with ice-cold, concentrated hydrochloric acid, ice-cold saturated sodium bicarbonate and ice-cold water. The ether was dried with anhydrous potassium carbonate and removed on the steam bath. Upon distillation of the residue, 46 g. (34%) of the

colorless liquid was obtained, b.p. 80-82° (0.3 mm.). Newman and Magerlein reported b.p. 122-124° (7 mm.), and 67% yield.

<u>α-2,3-Dimethoxyphenyl-α-(β-methoxyethyl)-acetoaceto-nitrile (XXXIII)</u>. -- (A). In applying the general procedure of Bachmann and Fornefeld (54), 39 g. (0.18 mole) of α-2,3-dimethoxyphenylacetoacetonitrile in 120 ml. of dry benzene was slowly added to a stirred, refluxing suspension of 7.8 g. (0.2 mole) of sodamide in 100 ml. of dry benzene. After refluxing the mixture for six hours and then treating it with 46 g. (0.21 mole) of β-methoxyethyl benzenesulfonate, it was refluxed for twelve additional hours. Two hundred ml. of water was added, and the product, which was isolated by ether extraction from the organic layer, was refluxed with 100 ml. of glacial acetic acid, 20 ml. of concentrated hydrochloric acid and 20 ml. of water for one-half hour in order to hydrolyze the excess alkylating agent. From the alkaline layer upon acidification was obtained starting material.

The acid solution was neutralized with a sodium hydroxide solution, and the oil which separated was extracted with ether. The ether was washed with water and dried over sodium sulfate. After removal of the solvent under diminished pressure, the disubstituted acetoacetonitrile distilled as a light yellow oil at 125-135° and 0.07-0.1 mm; weight 23 g. (47%); n_D^{20} 1.5188.

Anal. Calcd. for $C_{15}H_{19}O_4N$: C, 64.96; H, 6.91.

Found: C, 63.16; H, 6.91.

The 2,4-dinitrophenylhydrazone crystallized from ethyl alcohol in red-orange leaflets; m.p. 187°.

Anal. Calcd. for $C_{21}H_{23}O_7N_5$: C, 55.14; H, 5.07.

Found: C, 54.77; H, 4.53.

(B). Very poor yields were realized when either the β-chloro- or β-iodoethylmethyl ethers were substituted as alkylating agents in the above procedure.

After a slow addition of 45 g. (0.21 mole) of α-2,3-dimethoxyphenylacetoacetonitrile to a stirred, refluxing suspension of 10 g. (0.25 mole) of finely divided sodamide in 150 ml. of dry benzene, the mixture was refluxed for four hours, and then treated with 28.2 g. (0.3 mole) of β-chloroethylmethyl ether. The mixture was refluxed for fourteen hours, cooled and poured into one liter of water. The benzene layer was separated, washed with water and dried with sodium sulfate. The aqueous layer liberated starting material upon acidification.

Following removal of the benzene, distillation of the residue yielded 10 g. (17.5%) of the product, b.p. 110-120° (0.05 mm.).

In the same manner 140 g. (0.63 mole) of α-2,3-dimethoxyphenylacetoacetonitrile, 39 g. (1 mole) of sodamide and 186 g. (1 mole) of β-iodoethylmethyl ether gave 10 g. (6%) of

the oil.

Ethyl α-cyano-2,3-dimethoxyphenylacetate (XLI). -- Following general methods (88, 91) a solution of 107 g. (0.6 mole) of 2,3-dimethoxyphenylacetonitrile in 100 ml. of anhydrous ether was slowly added to a refluxing suspension of 24 g. (0.62 mole) of sodamide in 400 ml. of anhydrous ether. After the addition was complete and refluxing had continued for four and one-half hours, 83 g. (0.7 mole) of diethylcarbonate was slowly introduced. The mixture was refluxed for five and one-half hours and allowed to stand at room temperature overnight. It was then poured onto 300 g. of ice and acidified with concentrated hydrochloric acid. The product was extracted with ether, which was washed with water and dried over sodium sulfate. Upon removal of the ether, the residue was distilled, yielding 62.3 g. (42%) of the viscous, yellow oil, b.p. 140-142° (0.3 mm.); n_D^{20} 1.5138.

Anal. Calcd. for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07.
Found: C, 62.64; H, 6.08.

A portion of the above mentioned ester was converted into what appeared to consist of 2,3-dimethoxyphenylacetic acid through elimination of the nitrile grouping together with hydrolysis by treatment with 25% sodium hydroxide under reflux conditions. Isolation of the acid was performed in the usual manner through acidification, extraction with ether and washing the ether with dilute sodium hydroxide and/or

sodium bicarbonate; followed by reacidification and extraction with ether. The ether was removed and the residue distilled under reduced pressure; yielding 10 g. of a light yellow, highly viscous oil, b.p. 125-128° (01 mm.); n_D^{20} 1.5298.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17.
Found: C, 62.40; H, 6.56.

The acid was converted into the corresponding 2,3-dimethoxyphenylacetyl chloride by refluxing a benzene solution of the acid with thionyl chloride until the gases ceased to be evolved. The excess reagents were removed under reduced pressure and the crude, residual acid chloride was utilized below without purification.

α-2,3-Dimethoxyphenyl-2,x-dimethylacetophenone. -- This compound was obtained instead of the desired product, 7,8-dimethoxy-2-tetralone, in the following reaction.

After the addition of 6.7 g. (0.05 mole) of anhydrous aluminum chloride to a solution of 10.8 g. (0.045 mole) of the crude 2,3-dimethoxyphenylacetyl chloride (from above) in 70 ml. of dry xylene cooled in an ice-salt bath, dry ethylene was passed through the mixture for six hours while the temperature was maintained at 0°. After remaining overnight in the refrigerator, the mixture was poured onto ice and concentrated hydrochloric acid, and the product extracted with benzene. The solvent layer was washed with a saturated

sodium bicarbonate solution and water, and dried over magnesium sulfate. Following distillation of the benzene and xylene under diminished pressure, distillation of what was assumed to be the substituted acetophenone gave 6 g. (58%) of the viscous oil, b.p. 160-163° (0.4 mm.); n_D^{20} 1.5796. The 2,4-dinitrophenylhydrazone crystallized from ethyl alcohol-ethyl acetate in red-orange crystals; m.p. 181°.

Anal. Calcd. for $C_{24}H_{24}O_6N_4$; C, 62.06; H, 5.21.
Found: C, 61.40; H, 5.40.

Ethyl α-cyano-α-(β-methoxyethyl)-2,3-dimethoxyphenylacetate (XLII). -- To 11.7 g. (0.3 mole) of sodamide suspended in 100 ml. of dry benzene was slowly added 62.3 g (0.25 mole) of ethyl α-cyano-2,3-dimethoxyphenylacetate dissolved in 50 ml. of dry benzene, and the mixture refluxed for five hours. Following this period 46 g. (0.3 mole) of β-methoxyethyl methylsulfonate in 50 ml. of dry benzene was slowly added, and the resulting solution was refluxed for six hours and allowed to stand overnight at room temperature. After pouring the solution onto ice in water, it was extracted with benzene, which was washed with dilute hydrochloric acid and water, and dried with magnesium sulfate. The solvent was removed under reduced pressure and the crude product vacuum distilled to give 56 g. (73%) of the water-clear, viscous oil, b.p. 142-145° (0.25 mm.); n_D^{20} 1.5100.

Anal. Calcd. for $C_{16}H_{21}O_5N$: C, 62.52; H, 6.89.
Found: C, 62.57; H, 6.82.

α-(β-Methoxyethyl)-2,3-dimethoxyphenylacetic acid (XLIII). -- A mixture of 50 g. (0.16 mole) of ethyl α-cyano-α-(β-methoxyethyl)-2,3-dimethoxyphenylacetate and 100 ml. of a 25% sodium hydroxide solution was heated under reflux conditions until a homogeneous solution was formed. Following cooling and acidification with concentrated hydrochloric acid three layers were formed - a dark oil, a white oil and an aqueous layer. The dark oil was extracted with ether; the white oil proved to be a very fine powder which was collected on a filter, but could not be identified and was insoluble in acids, base and organic solvents. Yield 3.2 g.

The ether was washed with water, and dried over magnesium sulfate. Upon evaporation of the ether a dark oil remained which gave 33 g. (75%) of the viscous, water-clear oil by distillation in vacuo; b.p. 158-162° (0.4 mm.); n_D^{20} 1.5239.

Anal. Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.13.
Found: C, 61.15; H, 7.02.

According to standard procedures α-(β-methoxyethyl)-2,3-dimethoxyphenylacetyl chloride was prepared from 24.5 g. (0.09 mole) of the above acid in dry benzene and 12 g. (0.1 mole) of thionyl chloride. The excess benzene and thionyl chloride were removed under reduced pressure, and the dark

red liquid used without purification.

Ethyl 2,3-dimethoxyphenylacetate. -- By the procedure used for the preparation of ethyl α-2,3-dimethoxyphenylacetoacetate, 177 g. (1 mole) of 2,3-dimethoxyphenylacetonitrile in 1200 ml. of absolute ethyl alcohol gave 158 g. (71%) of the water-clear oil; b.p. 108-111° (0.3 mm.); n_D^{20} 1.5101. Sugasawa and Sigehara (92) prepared the ester by a different method, but reported no properties or yield. Those given above appear to be the first recorded.

Ethyl hydracrylate.--Following the directions of Gresham and co-workers (93), 478 g. (6.6 moles) of propiolactone (supplied by Mr. T. L. Gresham of the B. F. Goodrich Co.) was added very slowly to 2 g. of concentrated sulfuric acid cooled by a water bath, and the addition was performed at such a rate that the temperature did not exceed 80°. The semi-solid reaction product was melted and poured into two liters of acetone, which in turn was evaporated to a volume of one liter and poured into three liters of cold water. The water was placed in the refrigerator overnight and the solid, semi-crystalline product precipitated. After the solid was filtered, washed with water and dried, 391 g. of the polymer remained.

After refluxing a mixture of 391 g. of this polymer, 775 g. of anhydrous ethyl alcohol and 2 g. of concentrated

sulfuric acid for forty-seven hours, the acid catalyst was neutralized with calcium carbonate, the excess ethyl alcohol removed by distillation and the residual oil filtered to remove the calcium salts. Distillation of the oil at 20 mm. yielded 433.2 g. (55%) of the colorless liquid, b.p. 93-96°; n_D^{20} 1.4222. Gresham reported 81-83° (13 mm.); n_D^{20} 1.4222, yield 84%.

2-Tetrahydropyranyl ether of ethyl hydracrylate. -- By the procedure of Parham and Anderson (94), a mixture of 59 g. (0.5 mole) of ethyl hydracrylate, 101 g. (0.5 mole) of dihydropyran and a few drops of concentrated hydrochloric acid was allowed to stand for three hours with occasional shaking. Ether was added and the resulting solution thoroughly washed with cold 10% sodium hydroxide in order to remove all traces of acid. The ether was dried with sodium sulfate and evaporated on the steam bath. The residue was distilled, yielding 90 g. (89%) of the colorless oil, b.p. 132-137° (20 mm.) and 59° (0.1 mm.); n_D^{20} 1.4430.

Anal. Calcd. for $C_{10}H_{18}O_4$: C, 59.38; H, 8.97.
Found: C, 59.72; H, 9.21.

α-(β-Hydroxypropionyl)-2,3-dimethoxyphenylacetonitrile (XLIV). -- After the slow addition of a solution of 89 g. (0.5 mole) of 2,3-dimethoxyphenylacetonitrile in dry benzene

to a stirred, refluxing suspension of 40 g. (1 mole) of sodamide in 200 ml. of dry benzene, the mixture was refluxed for one hour, cooled and slowly treated with 90 g. (0.45 mole) of the 2-tetrahydropyranyl ether of ethyl hydracrylate. The temperature was slowly raised to that necessary for refluxing, which was maintained for two hours. After standing overnight, the mixture was poured onto ice and water, and acidified with concentrated hydrochloric acid. The benzene was separated and the aqueous layer extracted twice with ether. The combined solvents were washed with water and dried over sodium sulfate. The solvents were distilled under diminished pressure, and treatment of the residue with hot ethyl alcohol yielded only a few grams of the white crystals, which on recrystallization from ethyl alcohol melt at 157-158°. Even under alkaline conditions the 2-tetrahydropyranyl ether group was hydrolyzed in this case; acetyl chloride, benzoyl chloride and the iodoform reaction gave positive indications for the presence of the alcoholic group.

<u>Anal.</u> Calcd. for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07
N, 5.62.

Found: C, 62.79; H, 6.10.
C, 62.45; H, 6.12;
N, 5.74.

α-(β-Ethoxypropionyl)-2,3-dimethoxyphenylacetonitrile (XLIV). -- To a stirred, refluxing suspension of 20 g. (0.5 mole) of sodamide in 200 ml. of dry benzene was slowly added 89 g. (0.5 mole) of 2,3-dimethoxyphenylacetonitrile. The mixture was stirred and refluxed for an additional hour, cooled in an ice bath and treated slowly with 102 g. (0.7 mole) of ethyl β-ethoxypropionate (from Carbide and Carbon Chemicals Co.). After completion of the addition and removal of the ice bath, the solution was stirred at room temperature for two hours, then refluxed for two hours and finally allowed to stand at room temperature overnight. It was poured onto ice in water, acidified with concentrated hydrochloric acid and extracted with benzene, which was washed with water and dried over sodium sulfate. The benzene was removed under reduced pressure and 30 g. (21%) of the white solid precipitated on treatment with benzene-Skelly B. After recrystallization from benzene-Skelly B, it melted at 135°.

Anal. Calcd. for $C_{15}H_{19}O_4N$: C, 64.96; H, 6.91; N, 5.05.

Found: C, 69.11; H, 6.81
C, 69.81; H, 6.70; N, 5.52.

Phenylacetyl chloride (XLV). -- A mixture of 31 g. (0.2 mole) of phenylacetic acid and 24 g. (0.2 mole) of thionyl chloride was refluxed until the gases ceased to be

evolved. Distillation of the solution yielded a slight amount of unreacted thionyl chloride and 33 g. (94%) of the reddish liquid, b.p. 122° (70 mm.). Raiford and Lankelma (95) reported b.p. 110-111° (23 mm.).

2-Tetralone (LIII). -- After the addition of 16 g. (0.104 mole) of phenylacetyl chloride dissolved in 300 ml. of dry carbon disulfide to a stirred suspension of 26.6 g. (0.2 mole) of anhydrous aluminum chloride in 400 ml. of dry carbon disulfide cooled in an ice bath, dry ethylene was passed through the stirred, cooled mixture for four hours. The dark red mixture was poured onto ice and concentrated hydrochloric acid, and extracted with ether. The latter was washed with water, dilute sodium hydroxide and dried over sodium sulfate. The ether was evaporated on the steam bath leaving a dark residue, which gave 11.4 g. (75%) of the colorless liquid on distillation under reduced pressure, b.p. 140-145° (19 mm.). Mosettig and Burger (96) reported the boiling point as 142° (15 mm.).

A saturated sodium bisulfite solution reacted with the product yielding the white leaflets of the water-soluble addition compound.

The phenylhydrazone was crystallized from ethyl alcohol in yellow plates, m.p. 105°. After recrystallization, white plates were obtained, m.p. 108°. Bamberger (60) reported

m.p. 107.5-108°.

The semicarbazone was recrystallized several times from ethyl alcohol and melts at 188°. Mosettig and Burger (96) reported the pure product melting at 189-191°.

An intense purple-blue color was obtained on applying the "tetralone blue" test (63), which consists in treating and shaking a solution of the 2-tetralone in ethyl alcohol with dilute sodium hydroxide. Upon acidification of the alkaline solution an orange-red oil separated. This result conforms to the known facts as reported by Straus (97).

2,3-Dimethoxyphenylacetic acid -- (A). Following the procedure developed above, 79 g. (0.32 mole) of ethyl α-cyano-2,3-dimethoxyphenylacetate gave 53.8 g. (87%) of the viscous, yellow oil, b.p. 147-152° (0.9 mm.). The oil solidified on standing and, after recrystallization from petroleum ether-acetone or water, was obtained in a yield of 42 g. (68%); white crystals which melt at 83°. Chakravarti and Swaminathan (98) reported 84°.

(B). After refluxing overnight a mixture of 36 g. (0.2 mole) of 2,3-dimethoxyphenylacetonitrile, 100 ml. of 50% sodium hydroxide and 250 ml. of ethyl alcohol, the ethyl alcohol was evaporated on the steam bath and the aqueous solution washed with ether. Upon acidification of the alkaline layer the white solid precipitated, and was collected on a

filter in a yield of 38.7 g. (97%). The air-dried crude product melts at 79-81°.

2,3-Dimethoxyphenylacetyl chloride (LIV). -- According to standard methods of synthesis, 42 g. (0.2 mole) of 2,3-dimethoxyphenylacetic acid dissolved in 250 ml. of dry benzene was refluxed with a slight excess of thionyl chloride until gas evolution had ceased. The excess reagents were removed under reduced pressure with no heat applied. All attempts to purify the acid chloride by distillation failed because it decomposes in the presence of the slightest amount of heat.

7-Methoxy-2-oxo-2,3-dihydrobenzofuran (LVIIa). -- During the course of this reaction, the benzofuran was formed in place of the desired 7,8-dimethoxy-2-tetralone.

To a suspension of 26.6 g. (0.2 mole) of anhydrous aluminum chloride in 700 ml. of dry carbon disulfide cooled to 0° was slowly added 21.9 g. (0.1 mole the theoretical quantity from the corresponding acid) of crude 2,3-dimethoxyphenylacetyl chloride dissolved in 100 ml. of carbon disulfide. The large amount of solvent was employed in order to eliminate any gumming and clumping. After completion of the addition, dry ethylene was passed through the stirred and cooled mixture for six hours; however, the ethylene probably had no effect upon the reaction.

The mixture was decomposed on ice and concentrated hydrochloric acid, the carbon disulfide layer separated and the aqueous layer extracted with ether. The combined solvents were washed with water and dried over sodium sulfate. After evaporating the solvents on the steam bath, the residue was distilled giving 10.3 g. (62%) of the yellow oil, b.p. 120° (0.2 mm.), which solidified immediately. Colorless plates which melt at 79° were obtained upon recrystallization of the solid from Skelly B. Mosimann and Tambor (64) prepared the compound in a low yield and reported a melting point of 80°.

Anal. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91.
Found: C, 65.88; H, 5.17.

A portion of this lactone was hydrolyzed with 10% sodium hydroxide yielding 2-hydroxy-3-methoxyphenylacetic acid which melts at 124° and gives a green color with 5% ferric chloride in ethyl alcohol solution. Mosimann and Tambor report 124° and the green color with ferric chloride.

p-Methoxyphenylacetic acid. -- Following the procedures given previously for the preparation of 2,3-dimethoxybenzyl chloride (part B), of 2,3-dimethoxyphenylacetonitrile (part A) and of 2,3-dimethoxyphenylacetic acid (part B), 138 g. (1 mole) of anisyl alcohol (Givaudan-Delawanna, Inc.) gave 141 g. (85%) of the crude acid, m.p. 83-84°. The final product was the only intermediate isolated throughout the entire

synthesis. Hromatka (99) reported a melting point of 86° for the pure product.

p-Methoxyphenylacetyl chloride. -- According to standard methods utilizing thionyl chloride, 23.8 g. (0.14 mole) of p-methoxyphenylacetic acid yielded 22.4 g. (85%) of the acid chloride, b.p. 92° (1 mm.) and 144-145° (20 mm.). Sosa (100) reported 139° (12.5 mm.); yield 90%.

6-Methoxy-2-tetralone (LVIII). -- By the directions employed for the synthesis of 2-tetralone, 30 g. (0.16 mole) of p-methoxyphenylacetyl chloride and 43 g. (0.32 mole) of anhydrous aluminum chloride gave 16 g. (56%) of the oil, b.p. 183° (30 mm.) and 111-116° (0.2 mm.). Crowley and Robinson (61) obtained the oil, b.p. 164° (11 mm.), by a very complicated procedure.

The product rendered a positive "tetralone-blue test" (63).

The semicarbazone crystallized from ethyl alcohol, m.p. 158-159°. Salzer (66) reported a melting point of 159°.

The 2,4-dinitrophenylhydrazone formed red-orange crystals from ethyl alcohol and melts at 136°. Crowley and Robinson reported 132°.

Diphenylacetyl chloride. -- Following standard procedures using thionyl chloride, 40.5 g. (89%) of the crude, tan solid, m.p. 55°, was obtained from 42 g. (0.2 mole) of

diphenylacetic acid. Staudinger (101) reported the pure compound melts at 56-57°.

p-Nitrophenylacetyl chloride. -- In the same manner as described above 40 g. (0.22 mole) of p-nitrophenylacetic acid gave 41.5 g. (94%) of the solid product, which melts at 48° from carbon disulfide-Skelly B. Pyman (102) obtained crystals melting at 48° from light petroleum ether.

α-Naphthylacetyl chloride. -- By the same general procedure given above 26 g. (0.14 mole) of α-naphthylacetic acid yielded 24.5 g. (86%) of the liquid, b.p. 127-133° (0.5 mm.). I.G.F. (103) reported the higher boiling point of 148-155° (0.05 mm.).

Ethylbenzene and Acenaphthenone. -- In the attempted synthesis of 1,2,3,4-tetrahydro-3-phenanthrone by the method employed for the preparation of 2-tetralone using benzene as the solvent, 20 g. of ethylbenzene, b.p. 134-135° and 52-72° (25-30 mm.); n_D^{25} 1.4931, was obtained from 29.2 g. (0.14 mole) of α-naphthylacetyl chloride, 26.6 g. (0.2 mole) of anhydrous aluminum chloride and ethylene. Further distillation yielded a higher boiling fraction, b.p. 95-115°, which probably consisted of di- and triethylbenzenes.

Upon treatment of the distillation residue with hot ethyl alcohol, 7 g. of acenaphthenone were obtained, m.p.

115-117°. Recrystallization from ethyl alcohol, Skelly A or Skelly B raised the melting point to 121°. A mixed melting point with a known sample gave no depression. Also isolated were a few grams of a mixture of acenaphthenone and α-naphthylacetic acid, and 3 g. of a white, crystalline solid which could not be identified.

Ethylbenzenes can be prepared from the reactants employed here, however, higher temperatures are usually employed. The same applies for the formation of acenaphthenone (69,70).

β-Naphthylacetic acid. -- (A). According to the method developed by Buu-Hoi (104) a mixture of 192 g. (1.35 moles) of β-methylnaphthalene, 120 g. (0.68 mole) of N-bromosuccinimide and 400 ml. of carbon tetrachloride was refluxed for seven hours. After cooling and filtering the succinimide which had separated, the filtrate was washed with ice-cold dilute sodium hydroxide and water, and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue, β-bromomethylnapthalene, used without further purification.

(B). After addition of a solution of the crude bromide in 600 ml. of ethyl alcohol to the stirred, refluxing solution of 147 g. (3 mole) of sodium cyanide in 300 ml. of water, refluxing was continued for nine hours, and cold water was

added to the hot mixture. Most of the ethyl alcohol was evaporated on the steam bath, the mixture cooled and the product extracted with ether. The ether was washed with water, dried with sodium sulfate and removed. Upon distillation under diminished pressure the oil, which solidified, b.p. 205-210° (30 mm.), was obtained. After recrystallization of the solid from ethyl alcohol-water, 37 g. (33%) of the impure β-naphthylacetonitrile was obtained, m.p. 77-78°. Newman (105) reported the pure compound, prepared by another method melts at 86°; yield 90%.

(C). After refluxing the above nitrile with 50% sodium hydroxide and ethyl alcohol for twenty-four hours, the ethyl alcohol was evaporated in a current of air, water added and the insoluble organic material extracted with ether. The alkaline layer was acidified with concentrated hydrochloric acid, which precipitated the white solid. The acid was collected on a filter and dried to give 25.8 g. (63%), m.p. 143°. Newman reported 142°; yield 77% by another method.

β-Naphthylacetyl chloride. -- In the same general way as above 25.8 g. (0.14 mole) of β-naphthylacetic acid in dry benzene was reluxed with an excess of thionyl chloride until there was no more evolution of gases. After standing overnight, the benzene and thionyl chloride were distilled, and the residue vacuum distilled yielding a colorless oil,

b.p. 120° (0.2 mm.), which solidified immediately. The white solid was recrystallized from Skelly B to give 25 g. (88%), m.p. 61°. Repeated recrystallization of a portion for analysis raised the melting point to 62.5°. This acid chloride decomposes upon contact with the air, which likely explains the nature of the analytical results.

Anal. Calcd. for $C_{12}H_9OCl$: C, 70.42; H, 4.43.

Found: C, 73.39; H, 5.10.

TYPE IV AND V COMPOUNDS

α-(2,3-dimethoxyphenyl)-propionitrile (LXIV). -- According to the procedure of Burckhalter and Johnson (1), 177 g. (1 mole) of 2,3-dimethoxyphenylacetonitrile was slowly added to a stirred, refluxing suspension of 40 g. (1 mole) of sodamide in 400 ml. of dry benzene, and refluxing was continued for one and one-half hours after the addition was complete. To the cooled and stirred mixture, 175 g. (1.23 mole) of methyl iodide was slowly added. After the addition was complete, reflux temperature was maintained for three and one-half hours, the mixture cooled and a theoretical amount of sodium iodide collected on a filter. The benzene was washed with water and dried over potassium carbonate. The solvent was removed, and the residue distilled under high vacuum to give 155.2 g. (81%) of the colorless oil, b.p. 91-94° (0.2 mm.). Burckhalter and Johnson obtained the product in a 75% yield with a boiling point of 106-108° (0.4 mm.).

α-Methyl-α-(2-dimethylaminoethyl)-2,3-dimethoxyphenylacetonitrile (LXV). -- (A). In the same way as was described by Burckhalter, Stephens and Hall (106), 72 g. (0.5 mole) of β-dimethylaminoethyl chloride was isolated from its hydrochloride and extracted with benzene. The benzene was dried over anhydrous potassium carbonate.

(B). By the method of Burckhalter and Johnson (1), 59.1 g. (0.31 mole) of α-(2,3-dimethoxyphenyl)-propionitrile dissolved in 100 ml. of dry benzene was slowly added to a stirred, refluxing mixture of 15.6 g. (0.4 mole) of sodamide in 300 ml. of dry benzene. After refluxing for two hours, the mixture was cooled and treated with the dry benzene solution of β-dimethylaminoethylchloride from part A. The resulting solution was maintained at reflux temperature for six hours, cooled and washed with water. The benzene was dried over potassium carbonate, and then removed under reduced pressure. Distillation of the residue yielded 66 g. (82%) of the light yellow oil, b.p. 127-131° (0.3 mm.); n_D^{20} 1.5160. The oil was obtained in a yield of 55% with a boiling point of 148° (0.8 mm.) by Burckhalter and Johnson.

In the course of one such preparation, the benzene was extracted with dilute hydrochloric acid from which the amine above was liberated by making the solution alkaline. Upon making it more basic, another oil separated. This oil was soluble in a sodium bicarbonate solution and dilute acid, but could not be purified. On the basis of its characteristics, it appears to be the corresponding amino acid.

6-Dimethylamino-4-methyl-4-(2,3-dimethoxyphenyl)-3-iminohexane Di hydrochloride (LXVI). -- To a cool solution of 0.6 mole of ethylmagnesium bromide in 200 ml. of anhydrous

ether was added a solution of 50 g. (0.2 mole) of α-methyl-α-(2-dimethylaminoethyl)-2,3-dimethoxyphenylacetonitrile in 150 ml. of dry xylene. The solution was refluxed for six hours, during which time most of the ether was removed and the solution changed in color from black to dark green. The hot mixture was poured into 200 ml. of concentrated hydrochloric acid and 400 ml. of water. The heat of reaction removed most of the xylene and left a yellow acidic solution which was heated on the steam bath for three hours. After the solution was cooled, 200 ml. of benzene was added, and the aqueous layer separated, neutralized with sodium hydroxide and extracted with ether. The basic solution was reacidified and boiled on a hot plate for two hours. After it was cooled, the solution was made basic again, and extracted with ether. The ether and benzene extracts were combined, washed with water and dried over potassium carbonate. The solvents were removed under reduced pressure and the residue distilled to give 33 g. (59%) of the light yellow, viscous oil, b.p. 138-146° (0.3 mm.). A small amount was converted to the dihydrochloride in the usual way; it melted at 214-215° when recrystallized from acetone.*

In spite of the drastic conditions employed for

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* The product was assumed to be the same ketone obtained by Johnson, and was used in the next reaction without being analyzed.

hydrolysis, the imino compound remained intact.

Following the distillation of the product above 19.4 g. of a yellow, highly viscous oil, b.p. 147-151° (0.3 mm.), was obtained in one case; its hydrochloride melts at 187-189°. These results were identical with those of Johnson (51), but in neither case was the substance identified.

3-Amino-6-dimethylamino-4-methyl-4-(2,3-dimethoxyphenyl)-hexane Dihydrochloride (LXVII). -- To a solution of 33 g. (0.11 mole) of 6-dimethylamino-4-methyl-4-(2,3-dimethoxyphenyl)-3-iminohexane in 200 ml. of ethyl alcohol was added about 0.5 g. of platinum oxide catalyst and reduction carried out at 50-60° in a Parr low pressure hydrogenator. The catalyst was removed by filtration and the ethyl alcohol under reduced pressure. The residue was distilled to yield 32.6 g. (98%) of the very viscous, colorless oil, b.p. 125-140° (0.2 mm.). A small portion was converted into its hydrochloride in the usual manner, and the white crystals precipitated from acetone on standing, m.p. 219-220°. Upon recrystallization from ethyl alcohol-ether the melting point was raised to 223°.

Anal. Calcd. for $C_{17}H_{30}O_2N_2 \cdot 2HCl$:

C, 55.58; H, 8.78; N, 7.63; Cl, 19.30.

Found: C, 54.60; H, 8.93; Cl, 18.98.

C, 54.58; H, 8.90; N, 7.70.

2,3-Dimethoxymandelonitrile (LXIX). -- By the general method developed by Hahn and co-workers (107). After forming the solid sodium bisulfite addition compound by stirring 149 g. (0.9 mole) of 2,3-dimethoxybenzaldehyde with a saturated solution of sodium bisulfite, it was filtered and made into a thick paste with water. To this cooled mixture was added 160 g. (2.5 moles) of potassium cyanide dissolved in 75 ml. of water. After stirring the cooled solution for forty-five minutes, a white powder separated and was collected on a filter. It is insoluble in all reagents, melts above 310° and decomposes completely in a flame with a brilliant pinkish hue. The filtrate was made acidic with dilute acid and extracted with ether. The ether was washed with a dilute solution of sodium bisulfite and water. It was evaporated leaving a white solid, which was recrystallized from ether-Skelly A to give 152.8 g. (88%) of the pure product, m.p. 76-77°. Krannichfeldt (108) reported a melting point of 76° using a different process.

α-Chloro-2,3-dimethoxyphenylacetonitrile (LXX). -- To 119 g. (1 mole) of pure thionyl chloride cooled in an ice bath, was added a solution of 170 g. (0.88 mole) of 2,3-dimethoxymandelonitrile in dry benzene. After the addition was complete, the ice bath was removed, and the solution stirred at room temperature for two hours and finally at reflux temperature until the evolution of gases had stopped.

The excess reagents were removed under reduced pressure, and the residue distilled at a high vacuum yielding 155 g. (85%) of the light yellow liquid, b.p. 109° (0.7 mm.); n_D^{25} 1.5387. Upon standing, the liquid solidified into light yellow crystals, m.p. 41-42°.

Anal. Calcd. for $C_{10}H_{20}O_2NCl$: C, 56.75; H, 4.76.
Found: C, 56.74; H, 4.67.

α-Phenyl-2,3-dimethoxyphenylacetonitrile (LXXI). -- Following the general procedure described by Schultz and coworkers (24), a solution of 5.5 g. (0.03 mole) of α-chloro-2,3-dimethoxyphenylacetonitrile in a little dry benzene was slowly added to a refluxing suspension of 6.6 g. (0.05 mole) of anhydrous aluminum chloride in 300 ml. of dry benzene. After completion of the addition, the mixture was heated at reflux temperature for two hours during which time it turned milky. The reaction mixture was poured onto a mixture of 200 g. of ice and 20 ml. of concentrated hydrochloric acid, the benzene separated and the aqueous layer extracted twice with ether. The benzene and ether were combined; washed with water, a saturated solution of sodium bicarbonate and water again; and dried over sodium sulfate. The solvents were removed leaving a solid, which gave 5 g. (76%) of the light yellow crystals, m.p. 137°, upon recrystallization from Skelly B-benzene.

Anal. Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97.
Found: C, 76.27; H, 5.51.

A small portion of the nitrile was hydrolyzed with 50% potassium hydroxide to give α-phenyl-2,3-dimethoxyphenylacetic acid. After repeated recrystallizations from benzene-Skelly B the light tan crystals melt at 152°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92.
Found: C, 70.60; H, 6.16.

N. E.: Calcd.: 272.3. Found: 275.

α-(2-Dimethylaminoethyl)-α-phenyl-2,3-dimethoxyphenylacetonitrile (LXXII). -- Essentially by the procedure utilized for the preparation of α-methyl-α-(2-dimethylaminoethyl)-2,3-dimethoxyphenylacetonitrile, 48 g. (0.19 mole) of α-phenyl-2,3-dimethoxyphenylacetonitrile, 8 g. (0.2 mole) of sodamide and 43 g. (0.3 mole) of β-dimethylaminoethylchloride gave 45.2 g. (74%) of the very viscous oil, b.p. 195-196° (1.1 mm.). Anhydrous hydrogen chloride was passed through an ether solution of a small portion of the oil to precipitate the white salt, which melts at 189° after recrystallization from acetone-ether.

Anal. Calcd. for $C_{20}H_{24}O_2N_2.HCl$: Cl, 9.82.
Found: Cl, 9.69.

Attempted preparation of 6-Dimethylamino-4-phenyl-4-(2,3-dimethoxyphenyl)-3-hexanone (IV). -- According to the

method of Speeter and co-workers (109). After the addition of a mixture of 42.6 g. (0.13 mole) of α-(2-dimethylamino-ethyl)-α-phenyl-2,3-dimethoxyphenylacetonitrile in 100 ml. of anhydrous ether to a solution of 0.3 mole of ethylmagnesium bromide in 100 ml. of anhydrous ether, the red-yellow mixture was heated at reflux temperature for six hours. The boiling mixture was poured as swiftly as possible into a solution of 200 ml. of water and 100 ml. of concentrated hydrochloric acid, the heat of reaction removing most of the ether. The solution was cooled and 100 ml. of benzene added. The aqueous layer was separated, made alkaline with sodium hydroxide and extracted with ether. The ether was dried over potassium carbonate and evaporated on the steam bath, leaving a dark residue, which was distilled to give 25 g. (54%) of a light yellow, viscous liquid, b.p. 176-183° (0.4-0.5 mm.).

Prepared in the usual way, the hydrochloride would not crystallize. The picrate was obtained in a very small amount and, recrystallized from chloroform, it melted at 181°. No analysis was performed, because the above oil could very possibly be starting material or a mixture of it with the product.

TYPE VI COMPOUNDS

Benzalacetone. -- The procedure of Drake and Allen (110) was applied. A mixture of 636 g. (6 moles) of benzaldehyde, 500 ml. of water and 1200 ml. of acetone was cooled to 10°. With stirring, 125 ml. of 10% sodium hydroxide solution was added at such a rate that the temperature did not exceed 30°. The solution was stirred at room temperature for three and one-fourth hours, then made acidic to litmus with dilute hydrochloric acid. The oily layer was separated and the water layer extracted with 200 ml. of bengene. After combining the oil and the benzene extract, the solution was washed with water and the benzene removed under diminished pressure. The residue was distilled yielding 778.7 g. (89%) of the light yellow oil, b.p. 145-150° (20 mm.). Drake and Allen obtained the product in 78% yield, b.p. 123-128° (8 mm.).

4,4-Diphenyl-2-butanone. -- Following the general method of Shildneck (111), a solution of 146 g. (1 mole) of benzalacetone in 300 ml. of dry benzene was added to a stirred suspension of 266 g. (2 moles) of anhydrous aluminum chloride in two liters of dry benzene cooled to 10°. The temperature was maintained at 20-25° during the addition, and the mixture turned a dark brown. After stirring the mixture for three hours at room temperature, the benzene was decanted from the

inorganic salt into one liter of cold water containing 150 ml. of concentrated hydrochloric acid. The aluminum chloride was collected on a filter and washed with dry benzene. The filtrate was combined with the original benzene, mixed thoroughly with the acid solution, and finally washed twice with one liter portions of water. The solvent was removed, and the residue vacuum distilled giving 185.2 g. (83%) of the light yellow oil, b.p. 127-128° (0.1 mm.), which solidified upon standing, m.p. 46° (112,75).

1,1,5,5-Tetraphenyl-3-pentanone (LXXXII). -- By the above procedure, 96 g. (0.41 mole) of dibenzalacetone (prepared by Mr. W. L. Nobles), 120 g. (0.9 mole) of anhydrous aluminum chloride and 900 ml. of dry benzene yielded 62 g. (39%) of the white solid, m.p. 121°. Repeated recrystalization from ethyl alcohol raised the melting point to 124°. Kohler and Heritage (113) reported, 130°, when the product was isolated as a side product.

N-(1,3,3-triphenyl-1-propyl)-formamide. -- According to the procedure given by Burckhalter and Johnson (75). To 57 g. (0.5 mole) of ammonium carbonate was slowly added 45 g. (0.87 mole) of 90% formic acid. The temperature was slowly raised to 165° allowing the water and carbon dioxide to escape. To the hot solution was added 50 g. (0.17 mole) of β,β-diphenylpropiophenone (supplied by Mr. W. L. Nobles), and

the temperature raised to 195° where it was maintained for seven hours. The hot mixture was poured into 200 ml. of ethyl alcohol from which 50 g. (91%) of the white solid crystallized. It melts at 175°. Burckhalter and Johnson reported a yield of 73%, m.p. 175°.

1,3,3-Triphenyl-1-propylamine (LXXXV). -- Following Burckhalter and Johnson (75), a mixture of 50 g. (0.16 mole) of N-(1,3,3-triphenyl-1-propyl)-formamide and 300 ml. of 30% sulfuric acid was refluxed for two hours. When hydrolysis was attempted with 10% hydrochloric acid, 30% sodium hydroxide and 15% sulfuric acid, either starting material or 1,3,3-triphenyl-1-propene (LXXXIV) was obtained. Although two layers still remained, the solution was cooled and extracted with ether, which yielded a few grams of the propene, m.p. 98-100°.

The acid layer was neutralized with a sodium hydroxide solution and the liberated amine extracted with ether. The ether was dried over anhydrous potassium carbonate and removed by evaporation. Upon distillation the residue gave 35 g. (77%) of the colorless, viscous oil, b.p. 138-140° (0.3 mm.). The hydrochloride was prepared in the usual manner yielding 13 g. (26%) of the white solid, which was recrystallized from acetone, m.p. 175-176°. This melting point was depressed upon a mixed melting point determination with a sample of the starting material. Burckhalter and

Johnson reported a 58% yield of the amine b.p. 184-186° (4 mm.); a 40% yield, of the amine salt m.p. 168-169°; and a melting point of 98-99° for the propene.

N-Methyl-1-methyl-3,3-diphenylpropylamine Hydrochloride (LXXIII). -- By the general method described by Moore (76). To 41 g. (0.8 mole) of 90% formic acid cooled in an ice bath was slowly added 100 g. (0.8 mole) of 25% methylamine. After the addition was complete, the ice bath was removed and the temperature slowly raised to 180° with the evolution of water. The temperature was allowed to fall to 120°, and a mixture of 45 g. (0.2 mole) of 4,4-diphenyl-2-butanone and 20 g. of 90% formic acid added. After maintaining a temperature of 175° overnight, it was finally raised to 195°, and the hot mixture poured into twice its volume of water. The oil, which separated, was refluxed for twenty hours with 30% sulfuric acid and poured into 200 ml. of water. Upon extraction with benzene and/or ether a white solid formed between the two layers. The solid was filtered and dissolved in hot water, which was made alkaline with a sodium hydroxide solution while hot. The liberated amine was extracted with ether after the solution had been cooled. No steam distillation was employed to remove excess reagents, although many others have used it.

After combining the two solvent extracts, they were dried over potassium carbonate. Anhydrous hydrogen chloride

was passed through the solvent solution of the amine, precipitating the white salt. Recrystallization of the hydrochloride from ethyl alcohol gave 48 g. (87%), m.p. 175°.

Anal. Calcd. for $C_{17}H_{21}N.HCl$: Cl, 12.86.
Found: Cl, 12.84.

N-Ethyl-1-methyl-3,3-diphenylpropylamine Hydrochloride (LXXIV). -- Following the above procedure, 45 g. (0.2 mole) of 4,4-diphenyl-2-butanone, 41 g. (0.8 mole) of 90% formic acid and 109 g. (0.8 mole) of 33% ethyl amine yielded 34.1 g. (59%) of the white salt. After recrystallization from acetone-ether, it melts at 147-148°. Burckhalter and Johnson (75) obtained the product in a 7% yield and a melting point of 147°.

N,N-Dimethyl-1-methyl-3,3-diphenylpropylamine Hydrochloride (LXXV). -- According to the general method of Bunnett and Marks (77). The temperature of a mixture of 45 g. (0.2 mole) of 4,4-diphenyl-2-butanone, 58.5 g. (0.8 mole) of dimethylformamide, 0.2 mole of 90% formic acid and 0.03 mole of magnesium chloride hexahydrate was slowly raised to 180° while the distillate temperature rose to 134°. After maintaining this temperature for three hours, the solution was diluted with twice its volume of water and acidified with concentrated hydrochloric acid. The unreacted ketone was extracted with benzene, yielding 15.4 g. upon removal of the

solvent. The aqueous layer was made strongly alkaline with sodium hydroxide and the oil extracted with ether. The ether was dried over potassium carbonate and the hydrochloride prepared in the usual way. After recrystallization from ethyl alcohol-ether, the salt was obtained in a yield of 29 g. (50%), m.p. 155-156°.

Anal. Calcd. for $C_{18}H_{23}N.HCl$: Cl, 12.23.

Found: Cl, 12.20.

Other workers (30,31) prepared this compound by different methods in yields ranging from 5 to 90 per cent and with melting points of 115° to 158°.

N,N-Diethyl-1-methyl-3,3-diphenylpropylamine Hydrochloride (LXXVI). -- To 15.4 g. (0.3 mole) of 90% formic acid cooled in an ice bath was slowly added 22 g. (0.3 mole) of diethylamine. After removal of the ice bath, the temperature was slowly raised to 180° and then allowed to fall to 130°. To the hot solution was added 16 g. (0.07 mole) of 4,4-diphenyl-2-butanone, and the temperature raised to 190° where it was maintained for twenty hours. After the solution had cooled, it was acidified with hydrochloric acid and extracted with benzene, from which was obtained 6.7 g. of pure starting material. The acid layer was made basic with sodium hydroxide and the amine extracted with ether. The ether was dried over potassium carbonate, and the hydrochloride precipitated with anhydrous hydrogen chloride. After recrystalliza-

tion from acetone-ether, 4 g. (18%) of the white salt were obtained, m.p. 109°.

Anal. Calcd. for $C_{20}H_{27}N.HCl$: Cl, 11.15.

Found: Cl, 11.09.

2-(N-Piperidyl)-4,4-diphenylbutane Hydrochloride (LXXVIII). -- According to the procedure of Bunnett and Marks described above. A mixture of 45. g. (0.2 mole) of 4,4-diphenyl-2-butanone, 0.8 mole of N-piperidylformamide (prepared from equivalent amounts of 90% formic acid and piperidine), 0.2 mole of 90% formic acid and 0.03 mole of magnesium chloride hexahydrate was heated at 175-200° overnight. After isolation of the amine in ether and formation of the hydrochloride in the usual manner, 40 g. (61.5%) of the white crystals were obtained. Recrystallization from ether and/or ethyl alcohol gave a melting point of 216-217°.

Anal. Calcd. for $C_{21}H_{27}N.HCl$: Cl, 10.75.

Found: Cl, 10.83.

Bochmuhl and Ehrhardt (31) reported 213-214° by a different method.

2-(N-Pyrrolidyl)-4,4-diphenylbutane (LXXVII). -- By the above method, 67 g. (0.3 mole) of 4,4-diphenyl-2-butanone, 1.2 mole of N-pyrrolidylformamide (formed from equimolecular quantities of pyrrolidine and 90% formic acid), 0.05 mole of magnesium chloride hexahydrate and 0.3 mole of formic acid

reacted to give a dark solution. After the isolation procedure, the ether was removed and the residue distilled under diminished pressure giving 63.3 g. (76%) of the colorless oil, b.p. 126-128° (0.1 mm.). The hydrochloride was prepared in the usual manner, and was obtained in a yield of 37 g. (39%) upon recrystallization from acetone-ether. It melts at 164°.

Anal. Calcd. for $C_{20}H_{25}N.HCl.H_2O$: Cl, 10.62.

Found: Cl, 10.78.

Attempted preparation of 3-Dimethylamino-1,1,5,5-tetraphenylpentane (LXXXIII). Following the above procedure, none of the desired product could be obtained from a mixture of 26 g. (0.067 mole) of 1,1,5,5-tetraphenyl-3-pentanone, 21 g. (0.3 mole) of dimethylformamide, 0.07 mole of 90% formic acid and 0.01 mole of magnesium chloride hexahydrate. Almost a quantitative recovery of starting material was made.

Attempted preparation of 3-Methylamino-1,1,5,5-tetraphenylpentane (LXXXIII). -- According to the same general method employed above for the preparation of the secondary amines, 27 g. (0.07 mole) of 1,1,5,5-tetraphenyl-3-pentanone, and 0.3 mole of N-methylformamide were heated at a temperature of 200-220°. After the usual hydrolysis, isolation of the amine in ether and precipitation of the hydrochloride, a very small amount of the salt was obtained; therefore, it could not be positively identified. It was soluble in

organic solvents and recrystallized from water-concentrated hydrochloric acid.

Attempted preparation of N,N-Diethyl-1,3,3-triphenylpropylamine (LXXXI). -- Following the general procedure above, none of the amine was isolated from a mixture of 29 g. (0.1 mole) of β,β-diphenylpropiophenone, 0.5 mole of N,N-diethylformamide, 0.1 mole of formic acid and 0.01 mole of magnesium chloride hexahydrate. The only result was a quantitative recovery of starting material.

COMPOUND VII

Dichlorodiphenylmethane (LXXXVI). -- By the procedure of Gomberg and Jickling (114). To a suspension of 200 g. (1.5 moles) of anhydrous aluminum chloride in 400 ml. of carbon tetrachloride cooled in an ice bath was slowly added a mixture of 234 g. (3 moles) of dry benzene and 400 ml. of carbon tetrachloride, at such a rate that the temperature did not rise above 30°. After the addition was complete, the dark red mixture was stirred and cooled for one-half hour. The ice bath was removed and stirring at room temperature continued for nine hours. The mixture was poured onto ice, and the carbon tetrachloride thoroughly mixed with the acid solution. The solvent layer was separated, dried over calcium chloride and removed by evaporation. Upon distillation of the residue under reduced pressure 322.7 g. (91%) of the water-clear liquid was obtained, b.p. 102-105° (0.1 mm.). Klages and Fanto (79) reported, 172° (16 mm.).

Ethyl α-diphenylmethyleneacetoacetate (LXXXVII). -- (A). To 600 g. of basic copper acetate in three liters of water was added a 26% ammonia solution until a clear, dark blue solution was obtained. The solution was cooled to 10° and a mixture of 390 g. (3 moles) of acetoacetic ester in one liter of ethyl alcohol added. As the cooled mixture was stirred for two hours, the green solid precipitated. The

crystals were collected on a filter, and dried in a desiccator over calcium chloride to give 424 g. (44%) of the crude copper salt of acetoacetic ester. A small portion was recrystallized from benzene yielding green crystals, m.p. 193-194°. Klages and Fanto (79) reported 192-193° by another method.

(B). Following the method of Klages and Fanto, 196 g. (0.83 mole) of dichlorodiphenylmethane was slowly added to a stirred mixture of 272 g. (0.83 mole) of the copper salt of acetoacetic ester in two liters of dry benzene. After completion of the addition, the dark mixture was stirred for two hours at room temperature and then refluxed for five hours on the steam bath. The mixture was allowed to cool to room temperature. A theoretical quantity of copper chloride was collected on a funnel and washed with benzene. The filtrate was washed with water, a dilute sodium hydroxide solution and water again. After drying over sodium sulfate, the benzene was removed under reduced pressure leaving a dark oil. The oil was distilled to yield 70 g. of the chloride and 128 g. (53%) of the colorless liquid, b.p. 163-165° (0.8 mm.), which solidified and melted at 74-75°. Klages and Fanto reported a melting point of 76° and a boiling point of 200-240° (30 mm.).

4,4-Diphenyl-3-buten-2-one (LXXXVIII). -- (A). A mixture of 128 g. (0.44 mole) of ethyl α-diphenylmethyleneacetoacetate and 500 ml. of a 10% solution of potassium hydroxide was

stirred and heated at 65-75° until the two layers disappeared. Stirring was continued while the mixture cooled to room temperature. After extracting with ether, the alkaline layer was acidified with dilute hydrochloric acid precipitating the α-diphenylmethyleneacetoacetic acid. Upon recrystallization of a few grams from ethyl alcohol-water, it melts at 158-159°, and at 162-163° from Skelly B. Klages and Fanto reported 143°.

(B). The crude acid was distilled under reduced pressure with evolution of carbon dioxide to give 83.6 g. (87%) of the light yellow oil, b.p. 217-225° (20 mm.) and 126-132° (0.4 mm.); n_D^{25} 1.6169.

The oxime, when recrystallized from Skelly C, melts at 83-84°; when from Skelly B, it melts at 92°. Klages and Fanto crystallized the oxime from ligroin, m.p. 88°, and reported a boiling point of 190° for the ketone.

1,1-Diphenyl-3-methyl-1,3-hexadiene (LXXXIX). To a solution of 0.1 mole of n-propylmagnesium bromide in 200 ml. of anhydrous ether was added 22 g. (0.1 mole) 4,4-diphenyl-3-buten-2-one dissolved in 150 ml. of dry benzene. The reaction was exothermic and produced a light yellow solution. After being stirred at room temperature for two hours, the solution was refluxed for one hour. Although the reflux time was increased and cuprous chloride added in order to catalyze 1,4-

addition, only 1,2-addition followed by dehydration occurred in every case. The solution was cooled and poured into dilute hydrochloric acid. The benzene layer was removed, washed with water and dried over sodium sulfate. The solvent was removed under diminished pressure leaving a yellow residue, which was distilled to yield 18.6 g. (71%) of the colorless oil, b.p. 85-95° (0.1 mm.). A middle fraction boiling at 85-86° was obtained for analysis; n_D^{25} 1.6022.

Anal. Calcd. for $C_{19}H_{20}$; C, 91.88; H, 8.12.
Found: C, 91.54; H, 7.05.
C, 91.36; H, 7.52.

5-Dimethylamino-1,1-diphenyl-1-penten-3-one Hydrochloride (XC). -- By the general procedure described by Blicke (80), a mixture of 37 g. (0.17 mole) of 4,4-diphenyl-3-penten-2-one, 14.5 g. (0.18 mole) of dimethylamine hydrochloride, 12 g. (0.4 mole) of paraformaldehyde and a few drops of concentrated hydrochloric acid was refluxed for five hours. The hot solution was poured into 200 ml. of acetone, and the hydrochloride precipitated on cooling. The salt was separated by filtration and dried in a vacuum desiccator, yielding 27.7 g. (53%) of the light yellow crystals, m.p. 169°. Purification by recrystallization from absolute ethyl alcohol gave 23 g. (52.5%), m.p. 173.5-174°.

Anal. Calcd. for $C_{19}H_{21}ON.HCl$: Cl, 11.23.
Found: Cl, 11.24.

Butyrophenone (XCI). -- To a suspension of 600 g. (4.5 moles) of anhydrous aluminum chloride in 2300 ml. of dry benzene was slowly added 318 g. (3 moles) of butyryl chloride, and the mixture refluxed for two and one-half hours. The solution was cooled and poured onto ice and concentrated hydrochloric acid. After the benzene layer was separated, washed with water, a 10% solution of sodium hydroxide and water again, it was dried over sodium sulfate. The benzene was removed under reduced pressure and the residue distilled to give 383 g. (86%) of the colorless oil, b.p. 230°. By a different procedure (115) the ketone was obtained in an 82% yield, b.p. 123° (20 mm.).

Ethyl 3-phenyl-2-hexenoate (XCII). -- By the general method outlined by Shriner (116). To 195 g. (3 mole) of 30-mesh zinc dust (purified by washing with 2% hydrochloric acid, water, ethyl alcohol and acetone, and followed by drying at 110°) was added about 50 ml. of a mixture of 148 g. (1 mole) of butyrophenone, 362 g. (2 mole) of ethyl bromoacetate and 300 ml. of dry benzene. A crystal of iodine was added and the mixture heated until a vigorous reaction ensued. When this reaction had subsided, the remaining portion of the benzene solution was added at such a rate that the benzene refluxed continuously. After the addition was complete, the mixture was heated at reflux temperature for three hours. It was cooled in an ice bath and decomposed with

ice-cold 20% sulfuric acid. The benzene layer was removed, washed with water and dried over sodium sulfate.

The solvent was distilled, and the residue, heated on the steam bath, was treated with anhydrous hydrogen chloride for three hours to effect dehydration. The excess hydrogen chloride and water were removed under reduced pressure leaving a dark oil. It was distilled giving 190 g. (87%) of the light yellow oil, b.p. 167-168° (25 mm.); n_D^{21} 1.5264. Using a similar procedure with magnesium Johnson and Kon (81) obtained the ester in a 55% yield, b.p. 158-160° (19 mm.); n_D^{21} 1.5264.

Ethyl 3,3-diphenylcaproate (XCIII). -- To 133 g. (1 mole) of anhydrous aluminum chloride suspended in 800 ml. of dry benzene, which was cooled in an ice bath, was slowly added a solution of 190 g. (0.87 mole) of ethyl 3-phenyl-2-hexenoate in 200 ml. of dry benzene. After the addition was complete, the brown mixture was stirred at room temperature for three hours and then at reflux temperature for one hour. The solution was cooled and poured onto ice and concentrated hydrochloric acid. The benzene was separated, washed with water and dried over sodium sulfate. The benzene was removed and the residue vacuum distilled to yield 91 g. of starting material and 104.4 g. (41%) of the light yellow oil. A middle fraction for analysis boiled at 125-127° (0.1 mm.); n_D^{25} 1.5390.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16.
Found: C, 80.25; H, 8.25.

3,3-Diphenylcaproic acid (XCIV). -- A mixture of 98.7 g. (0.33 mole) of ethyl 3,3-diphenylcaproate and 400 ml. of a 15% potassium hydroxide solution was refluxed for two hours, or until it became a homogeneous solution. This solution was poured into 500 ml. of water and acidified with dilute hydrochloric acid, precipitating the acid in a semi-solid state. The product was extracted with ether, which was washed with water and evaporated. The residual oil was distilled under high vacuum to give 20.3 g. of starting material and 64.2 g. (72%) of a very viscous, light yellow oil, b.p. 155-160° (0.2 mm.). The acid would not crystallize, therefore, a middle fraction was obtained by distillation for analysis, b.p. 157-159° (0.1 mm.); n_D^{28} 1.5576.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51.
Found: C, 80.70; H, 7.74.

4,4-Diphenyl-2-heptanone (XCV). -- A solution of 45 g. (0.17 mole) of 3,3-diphenylcaproic acid in dry benzene and an excess of thionyl chloride was refluxed until the evolution of gases had ceased. After standing overnight, the excess reagents were removed by distillation leaving the dark, crude acid chloride.

Following the work of Nobles (83), a mixture of 4.1 g.

(0.17 mole) of magnesium ribbon, 0.5 ml. of dry carbon tetrachloride and 4 ml. of anhydrous ethyl alcohol was placed in a 300 ml. flask fitted with a thermometer, mechanical stirrer and dropping funnel. As soon as the reaction had started 25 ml. of dry chlorobenzene was added rapidly, and the reaction allowed to proceed to completion.

A solution of 27.2 g. (0.17 mole) of diethylmalonate, 20 ml. of chlorobenzene and 15 ml. of anhydrous ethyl alcohol was added to the stirred and cooled mixture at such a rate that the temperature did not exceed 35°. When the reaction had proceeded to the extent that removal of the cooling bath did not result in a rise of temperature, the mixture was heated to 55° and kept there until all the magnesium had reacted (about one hour).

The clear, light green solution was cooled to 20°, and a solution of the above acid chloride in 20 ml. of chlorobenzene was added with stirring and cooling so that the temperature did not exceed 30°. After the addition was complete, the cooling bath was removed, and the solution stirred at room temperature for one hour and finally heated to 55° for one-half hour. The flask was cooled in an ice bath, and a solution of 11 ml. of concentrated sulfuric acid in 80 ml. of water slowly added. The mixture was transferred to a separatory funnel, and the chlorobenzene layer separated. The acid layer was extracted with benzene, which was combined with the

chlorobenzene and concentrated by distillation under diminished pressure.

The residue was refluxed with a solution of 8 ml. of concentrated sulfuric acid, 60 ml. of glacial acetic acid and 40 ml. of water until decarboxylation was complete (about eleven hours). The mixture was poured onto ice, made alkaline with a 20% sodium hydroxide solution and extracted with ether. The ether was dried over sodium sulfate and evaporated on the steam bath. The dark residue was distilled yielding 39.2 g. (88%) of the light yellow oil, b.p. 132-135° (0.2 mm.). A middle fraction for analysis boiled at 133° (0.1 mm.); n_D^{25} 1.5516.

Anal. Calcd. for $C_{19}H_{22}O$: C, 85.66; H, 8.33.
Found: C, 85.44; H, 8.63.

The methyl ketone gave positive reactions with a 2,4-dinitrophenylhydrazone solution, a saturated sodium bisulfite solution and the iodoform reaction.

The 2,4-dinitrophenylhydrazone was recrystallized from absolute ethyl alcohol-chloroform in bright orange plates, m.p. 203°.

Anal. Calcd. for $C_{25}H_{26}O_4N_4$: C, 67.25; H, 5.87.
Found: C, 67.70; H, 5.73.

2-Dimethylamino-4,4-diphenylheptane (VII). -- (A). In applying the procedure of Bunnett and Marks (77), a mixture

of 25 g. (0.094 mole) of 4,4-diphenyl-2-heptanone, 30 g. (0.4 mole) of dimethylformamide, 6 g. (0.1 mole) of 90% formic acid and 3 g. (0.015 mole) of magnesium chloride hexahydrate was heated at 170-175° for ten hours while the water and carbon dioxide escaped. The solution was acidified with concentrated hydrochloric acid and extracted with ether. Upon removal of the ether, 19 g. of starting material was recovered. The acid layer was made alkaline with sodium hydroxide to liberate the free amine. The oil was extracted with ether, which was washed with water and dried over potassium carbonate. After treatment of the ether solution with anhydrous hydrogen chloride, the hydrochloride separated as an oil. This oil solidified upon triturating with Skelly A, but the resulting solid could not be recrystallized to give a stable form of the salt. Therefore, the amine was isolated as given above, and distilled giving a few grams of a colorless oil, b.p. 126-129° (0.25 mm.).

(B). According to the general method of Bochmuhl and Ehrhardt (31), to a mixture of 19 g. (0.075 mole) of 4,4-diphenyl-2-heptanone, 55 g. (0.3 mole) of a 25% aqueous solution of dimethylamine and 200 ml. of ethyl alcohol was added 2 g. of Raney nickel catalyst. The mixture was treated with hydrogen under 60-90 atmospheres for twenty-four hours at 125°. The catalyst was filtered and the ethyl alcohol

removed under reduced pressure. The residual aqueous mixture was extracted with ether, which was washed with water and dried over potassium carbonate. The ether was removed, and the residue was distilled under high vacuum to give 16 g. (76%) of a water-clear oil, b.p. 126-129° (0.25 mm.). A middle fraction was distilled for analysis, b.p. 134° (0.4 mm.); n_D^{25} 1.5475.

Anal. Calcd. for $C_{21}H_{29}N$: C, 85.36; H, 9.89.

Found: C, 85.14; H, 9.51.

SUMMARY

1. Five different methods were employed in the attempted preparation of III (page 2), a valuable intermediate for proposed syntheses of morphine-like compounds. One of these methods led to a new preparative method for 2-tetralones. The method also offers a means of providing interesting intermediates for steroidal intermediates. Further, a novel synthesis of substituted benzofurans was discovered during the course of these particular studies.

2. The preparation of type IV and V compounds failed owing to the difficulty of hydrolyzing the corresponding ketimines. A new method by which the intermediate diarylacetonitriles can be obtained was developed.

3. A series of six 3,3-diphenyl-1-methylpropylamines was prepared from the corresponding ketone by utilization of the Leuckart reaction or the Bunnett and Marks modification. These compounds are currently being tested for analgetic and spasmolytic activity.

4. The saturated analogue of Amidone, VII, was prepared in good yield from readily available starting materials through intermediates containing the saturated side chain.

5. A new substance, 5-dimethylamino-1,1-diphenyl-1-penten-3-one (XC), was prepared from 4,4-diphenyl-3-buten-2-one by use of the Mannich reaction.

6. Compounds of pharmacological interest, selected from the described experimental results, are currently being tested by pharmacologists.

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