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SYNTHETIC ANALGESICS. CYCLIC ANALOGS OF AMIDONE

by

John Krapcho

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of the requirements for the degree of

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John Krapcho

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GENERAL INTRODUCTION

Despite the intensive efforts of chemists to prepare a substitute for morphine, this opium alkaloid had no synthetic rival for the relief of pain until the early part of this decade. Opium, derived from the Greek word for juice, is obtained by incision of the unripe seed capsules of the poppy plant, Papaver somniferum. This plant is indigenous to Asia Minor and is cultivated in Egypt, India, China and Persia. After the milky juice is dried in air, the brown gummy mass is further dried, powdered, and deodorized to make the official powdered opium. This crude opium usually contains 10% morphine and about twenty other alkaloids.* The remaining material (75%) consists of a mixture of organic acids, resins, gums, oils, sugars and protein-like bodies, none of which contribute to the pharmacodynamic properties of the drug.

Although earlier records contain legends of the narcotic effects of the poppy, mandragora, hemp and henbane, the first written records which mention remedies for pain are probably contained in ancient Babylonian clay tablets dating back to

---

* Codeine and papaverine are the only other alkaloids in this group which find applications in medicine. The former has one-sixth the analgesic potency of morphine, and is used for the relief of dry, irritating cough. Papaverine does not exhibit analgesic properties but has been employed as an antispasmodic.

approximately 2250 B. C.[1] According to Macht,[2] the first authentic reference to the milky juice of the poppy is in the writings of Theophrastus in the third century B. C. Dioscorides, in the first century A. D., wrote extensively on drugs, and his "Greek Herbal"[3] contains a detailed discussion of the botany and medical applications of the opium poppy. The use of various opium preparations[2,4] became more popular in the following centuries but no significant contribution to opium chemistry was made until the early part of the nineteenth century. The method of isolation of the chief active ingredient of opium was first published in 1805 by Sertürner,[5] a German pharmacist. He observed the basic nature of this compound, and called it an "alkaloid" (alkali-like). It was believed previously that plants were incapable of producing compounds other than those of acidic or neutral character. Sertürner first referred to this alkaloid as "Principium Somniferum" but later, in 1817,[6] he named it morphine, after Morpheus, the Greek god of dreams.

Not long after Sertürner's pioneer work, improved methods of separation of morphine were developed, and several other opium

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(1) Prinz, in Gwathmey, "Anesthesia", p. 535. Macmillan Co., New York, N. Y. (1929).
(2) Macht, J. Am. Med. Assoc., 64, 477 (1915).
(3) "The Greek Herbal of Dioscorides", p. 456. Translated by John Goodyer in 1655. Oxford University Press (1934).
(4) Tainter, "Annals of the New York Academy of Sciences", Vol. 51, Art. I, p. 1 (1948).
(5) Sertürner, Trommsdorff's J. der Pharmazie, 13, 234 (1805); ibid., 14, 47 (1806).
(6) Sertürner, Gilbert's Ann. der Physik, 55, 56 (1817); ibid., 57, 192 (1817).

alkaloids were isolated, among them narcotine,[7] narceine,[8] codeine,[9] thebaine[10] and papaverine.[11] Quinine, strychnine, cocaine, nicotine, atropine and many other important alkaloids were also obtained from different plant sources. A number of these pure compounds found new and broader applications in medicine, some of which extend to the present day.

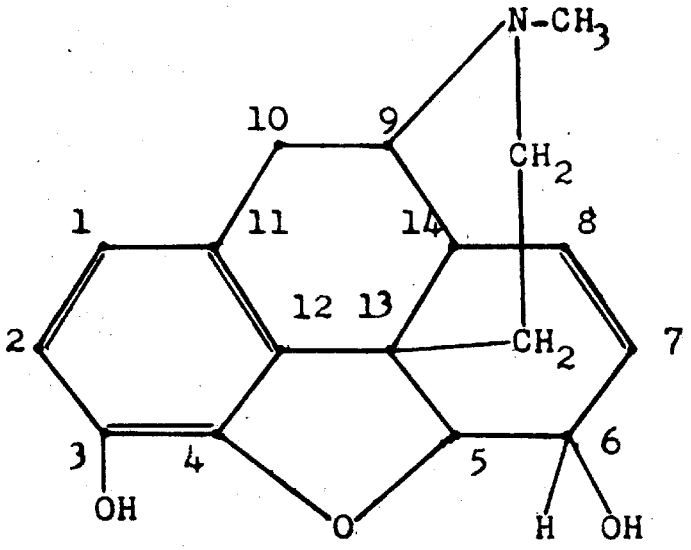
In 1884, while searching for substitute for quinine, Knorr[12] obtained Antipyrine (1-phenyl-2,3-dimethylpyrazalone-5), the first synthetic compound with significant analgesic activity. Twelve years later, Knorr and Stolz[13] prepared a closely related and more potent compound which is known as Pyramidon or Aminopyrine (4-dimethylaminoantipyrine). This latter substance remained the most powerful known synthetic analgesic until about ten years ago. Acetanilide was introduced into medicine as Antifebrine in 1886,[14] and Phenacetin (p-ethoxyacetanilide) in 1887.[15] Both drugs possess analgesic and also antipyretic properties. Dreser discovered the therapeutic value of Aspirin (acetylsalicylic acid) in 1899.[16] This compound is probably the most extensively used analgesic and antipyretic at the present time. Because of the low analgesic potency of Antipyrine, Pyramidon,

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(7) Robiquet, Ann. chim. phys., 5, 275 (1817).
(8) Pelletier, ibid., 50, 252 (1832); Ann., 5, 163 (1833).
(9) Robiquet, Ann., 5, 82 (1832).
(10) Pelletier, ibid., 16, 27 (1835).
(11) Merck, ibid., 66, 125 (1848).
(12) Knorr, Ber., 17, 2032 (1884).
(13) Knorr and Stolz, Ann., 293, 58 (1896).
(14) Cahn and Hepp. Centralbl. klin. Med., 7, 561 (1886).
(15) Hinsberg and Kast, Centralbl. med. Wissensch., 25, 145 (1887).
(16) Dreser, Arch. ges. Physiol., 76, 306 (1899).

Antifebrine, Phenacetin and Aspirin, as compared to morphine and its derivatives, Fourneau[17] prefers to call them "antalgics".

The structural formula for morphine generally accepted at present is that of Gulland and Robinson (1925);[18] this formula is supported by Schöpf [19], and is based on the chemistry of codeine and thebaine.



Morphine

In conclusion of an interesting chapter dealing with the development of earlier formulas, Small and Lutz[20] state: "The formula of Gulland and Robinson, while as yet not proved beyond dispute, probably accounts best on the whole for the

---

(17) Fourneau, Chim. et Ind., 39, 1043 (1938).
(18) Gulland and Robinson, J. Chem. Soc., 123, 980 (1923). Gulland and Robinson, Mem. Proc. Manchester Lit. Phil. Soc., 69, 79 (1925).
(19) Schöpf, Ann., 452, 211 (1927).
(20) Small and Lutz, "The Chemistry of the Opium Alkaloids", p. 336. Supplement No. 103 to Public Health Reports, U. S. Treasury Department (1932).

complicated facts of morphine chemistry, and until further more definite evidence is available may be accepted as representing the true structure of the morphine alkaloids."

Codeine is the phenolic methyl ether of morphine, and can be prepared from this substance by methylation, best with phenyltrimethylammonium hydroxide.[21] Several synthetic derivatives of morphine has been known as narcotics for a long time. Alkylation of the phenolic hydroxy group in morphine with ethyl iodide[22] yields Dionine, a drug with essentially the same properties as codeine. Diacetylation of morphine with acetic anhydride[23] produces Heroine. It is four to eight times more potent than morphine, but because of the ease of addiction to this drug its importation and manufacture in the United States has been prohibited. Catalytic hydrogenation of morphine, in the presence of a strong acid, results in a rearrangement which yields dihydromorphinone or Dilaudid.[24] Although Dilaudid is about ten times more analgesic than morphine, it is only four times as somnifacient. This allows Dilaudid to be used for the relief of pain with a minimal hypnotic effect, however, the duration of analgesia is much shorter when this drug is substituted for morphine. Dilaudid has the same margin of safety as morphine, and the ability of both drugs to produce addiction

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(21) Boehringer and Sohn, German Patent 247,180 (1909); Chem. Abst., 6, 2497 (1912).
Rodionov, Bull. soc. chim., 39, 305 (1926); Ref. 20, p. 188.
Russian Patent 18,224 (1927); Chem. Abst., 25, 1038 (1931).
(22) Merck, Arch. Pharm., 237, 211 (1899).
(23) Beckett and Wright, J. Chem. Soc., 28, 312 (1875).
(24) Knoll and Co., German Patent 365,683; Chem. Abst., 18, 1034 (1924).

and tolerance is also similar. Euphoria and side reactions are less marked after the use of Dilaudid. This compound may also be administered orally. When given by mouth, morphine produces severe nausea and vomiting.

The corresponding dihydrocodeinone (Dicodid) is readily prepared by heating dihydrothebaine with concentrated hydrochloric acid.[25] Dicodid may also be obtained by catalytic rearrangement of codeine in strongly acid solution.[26] Dicodid appears to be slowly replacing codeine for the treatment of cough because the risk of addiction is materially lower when Dicodid is used for this purpose.

The most intensive and systematic approach to the problem of finding a substitute for morphine which would be free of tolerance, addiction and undesirable side reactions,[27,28] particularly nausea and vomiting, began in 1929. This work was undertaken jointly by chemists and pharmacologists under the auspices of the National Research Council, the Universities of Virginia and Michigan, the Rockefeller Foundation and the Narcotic Bureau of the United States Public Health Service. This project covered a period of ten years, and is now continued at the National Institute of Health. The initial program resulted in numerous publications which describe the chemistry and

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(25) Mannich and Löwenheim, Arch. Pharm., 258, 295 (1920).
(26) Small, Turnbull and Fitch, J. Org. Chem., 3, 204 (1938).
(27) Krueger, Eddy and Sumwalt, "The Pharmacology of the Opium Alkaloids". Supplement No. 165 to Public Health Reports, U. S. Treasury Department (1941).
(28) Goodman and Gilman, "The Pharmacological Basis of Therapeutics", p. 186. Macmillan Co., New York, N. Y. (1941).

pharmacology of over 125 new compounds. These products consisted of derivatives of morphine, and substituted phenanthrenes, dibenzfurans and carbazoles. As a result of this work and previous investigations on morphine, Small and Eddy[29] were able to state several important relationships between chemical constitution and pharmacological action. The interpretation of these results is summarized briefly by Eddy:[30]

1. Modification of the phenolic hydroxyl decreases, and substitution or removal of the alcoholic hydroxyl increases, morphine-like activity.

2. Removal, by hydrogenation, of the double bond adjacent to the alcoholic hydroxyl usually increases potency.

3. Opening the nitrogen ring practically abolishes morphine-like activity.

4. Attachment of an alkyl group to the hydroaromatic ring results in dissociation of morphine-like effects, increasing some and decreasing others.

5. No active morphine derivative has been made which is entirely free of addiction liability.

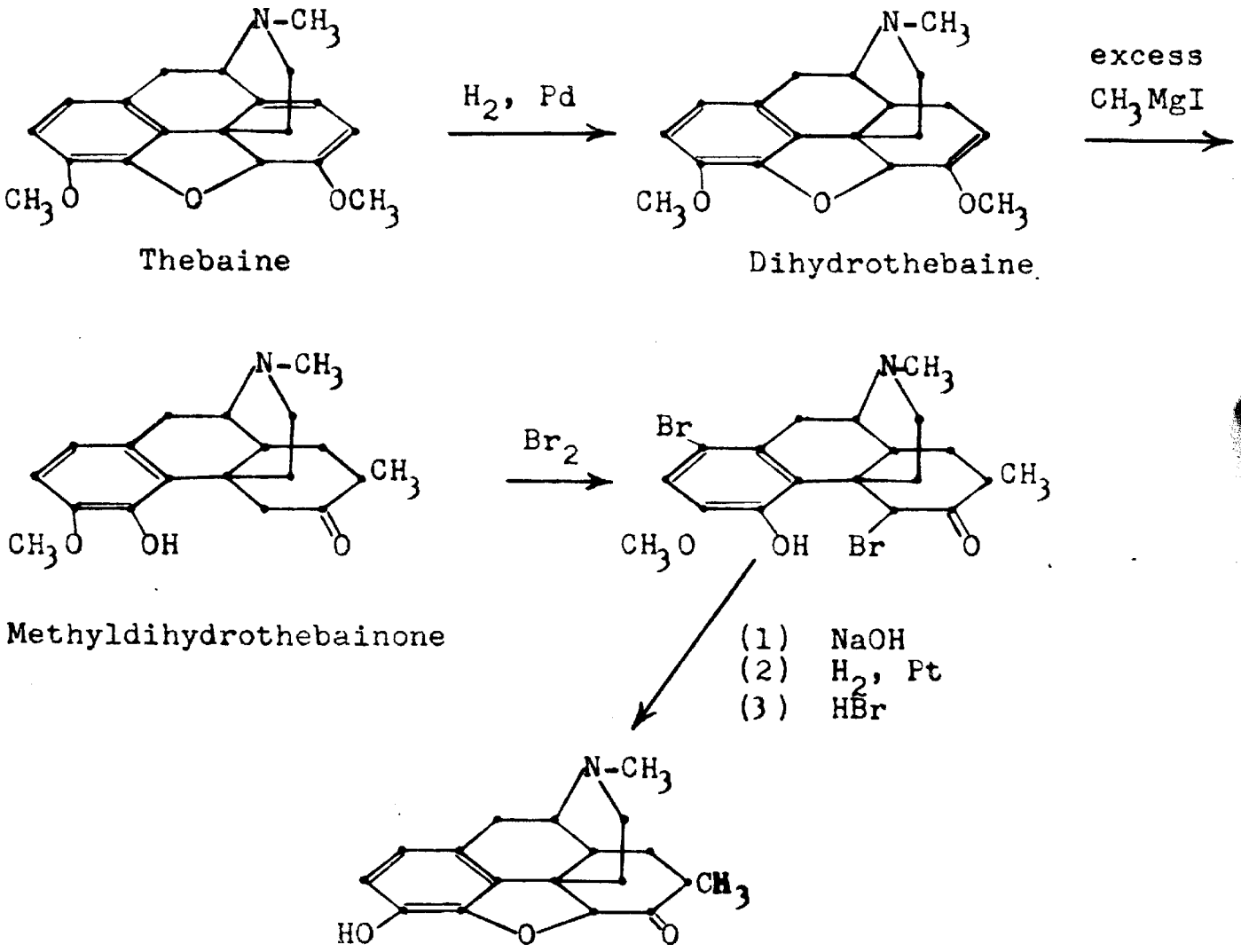
One of the most valuable drugs discovered during this research was methyldihydromorphinone (Metopon). It is a

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(29) Small, Mossetig, Himmelsbach and Eddy, "Studies on Drug Addiction". Supplement No. 138 to Public Health Reports, U. S. Treasury Department (1938).

(30) Eddy, ref. 4, p. 51.

homolog of Dilaudid, and was first prepared from thebaine* by the following reactions:(31)



Thebaine

Dihydrothebaine

Methyldihydrothebainone

Methyldihydromorphinone

The reaction of methylmagnesium iodide on dihydrothebaine resulted in the introduction of a nuclear methyl group,

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* The thebaine content of opium is usually 0.2%. It is a useless byproduct isolated during the purification of morphine. Codeine is present to the extent of 0.5% in opium.

(31)Small, Fitch and Smith, J. Am. Chem. Soc., 58, 1457 (1936).

formation of the phenolic hydroxyl group, and conversion of the enol ether group to a ketone. Small et al.[31] interpreted the nuclear methylation by the Grignard reagent as a 1,4-addition to the conjugated system comprising the oxide bridge and the 6,7-double bond. The other compound isolated was regarded as the 5-methyl isomer which formed by 1,2-addition. Schöpf[19] previously had observed a tendency of the allylic oxide bridge to undergo reductive fission. The complete mechanism of this Grignard reaction has not been elucidated. Methyldihydrothebainone was later prepared[32] by the reaction of the enol acetate of dihydrocodeinone with methylmagnesium iodide. This method is a more practical preparative route since codeine is less costly than thebaine. It is interesting to note that the morphine ketones are completely indifferent to Grignard reagents, however, it was found recently that some of these ketones are readily converted to alcohols, in excellent yield, by treatment with methyllithium, and then with dilute acetic acid.[33]

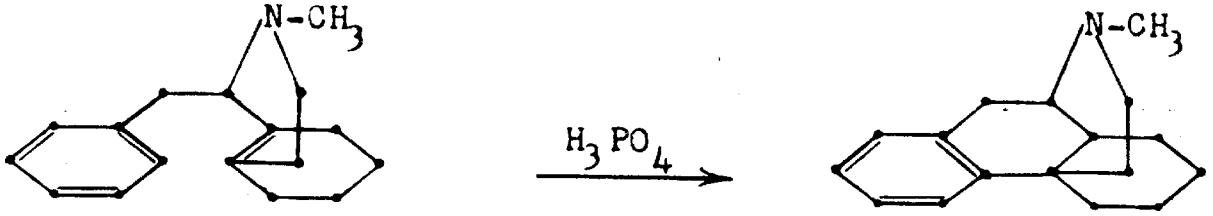
Tolerance and dependence develops more slowly with Metopon than with morphine during prolonged administration. Metopon may be used orally, and its analgesic action is attainable with relative freedom from side-actions. The effectiveness of this drug is somewhat reduced when given to patients who have previously received other narcotics. Metopon is rather difficult

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(32) Small, Turnbull and Fitch, J. Org. Chem., 3, 204 (1938).
(33) Small and Rapoport, ibid., 12, 284 (1947).

and expensive to prepare, and is not expected to be a competitor with morphine for hypodermic administration. This drug has been distributed in the United States only for the relief of chronic pain in cases of cancer.[30,34]

Thus far, the total synthesis of morphine has not been achieved, however, recent work resulted in a number of methods which may later be applied to the preparation of this complex molecule.[35,36,37,38,39,40,41,42] One of the nearest approaches to this problem has been the synthesis of N-methylmorphinan (morphan).[43,44] The smooth course of Grewe's 8-step preparation of this compound makes it readily available; 200 g. of this material were obtained from 1000 g. of ethyl cyclohexanone-2-carboxylate by the use of simple reagents. The final step in this series of reactions involved the treatment of the benzyloctahydroisoquinoline with phosphoric acid.



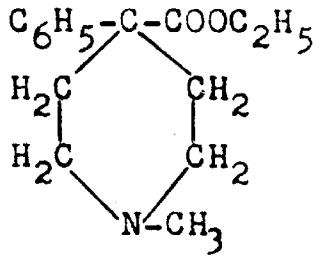
N-methylmorphinan

(34) J. Am. Med. Assoc., 134, 291 (1947).
(35) Fieser and Holmes, J. Am. Chem. Soc., 60, 2548 (1938).
(36) Grewe, Ber., 76, 1072, 1076 (1943).
(37) Ghosh and Robinson, J. Chem. Soc., 506 (1944).
(38) Koelsch, J. Am. Chem. Soc., 67, 569 (1945).
(39) Barltrop, J. Chem. Soc., 399 (1947).
(40) Newman and Magerlein, J. Am. Chem. Soc., 69, 942 (1947).
(41) Gates and Newhall, ibid., 70, 2261 (1948).
(42) Horning and Schock, ibid., 71, 1359 (1949).
(43) Grewe, Naturwiss., 11, 333 (1946).
(44) Grewe, Z. angew. Chem., 59, 194 (1947); also, Grewe and Mondon, Ber., 81, 279 (1948).

The biogenetic relationship of the benzylisoquinoline alkaloids (papaverine group) as natural precursors of the morphine compounds has been suggested by Robinson et al.,[18,45] and Schöpf.[19]

As shown in the above formula, N-methylmorphinan contains four of the five rings found in the morphine nucleus and, like morphine, it exhibits considerable analgesic action. Even more recently the 3-hydroxy-N-methylmorphinan was prepared, and it was claimed that this compound surpasses morphine in the intensity and duration of the analgesia produced, and is equally effective when administered by mouth.[46,47]

During the search for a spasmolytic agent which would exhibit the anticholinergic (antispasmodic) property of atropine, Eisleb[48,49] prepared ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride. It was stated that this substance



Demerol

was synthesized since its formula represents a modified fragment of the atropine molecule. When this compound was tested

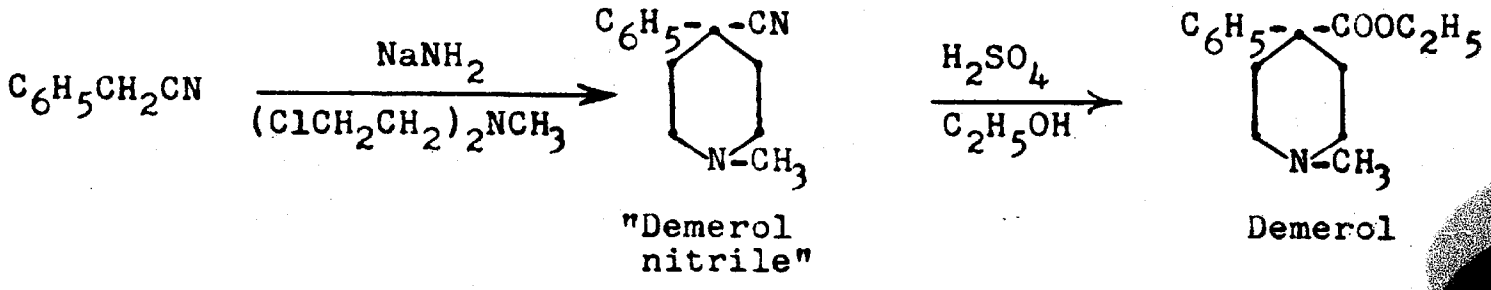
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(45) Robinson and Sugasawa, J. Chem. Soc., 3163 (1931).
(46) Swiss Patents 252,755 and 254,106. Quoted from ref. 47.
(47) Bergel and Morrison, Quarterly Reviews, 2, 349 (1948).
(48) Eisleb, U. S. Patent 2,167,351 (1939); Chem. Abst., 33, 8923 (1939).
(49) Eisleb, Ber., 74, 1433 (1941).

for toxicity in mice, the pharmacologist Schaumann noticed that some of the animals erected their tails over their backs in an S-shape.* This behavior, known as the Straub phenomenon,[50] had often been observed after the administration of morphine to mice, and it is not surprising that Schaumann suspected that the compound might possess analgesic properties. Further experiments proved this to be the case and this piperidine compound, although it did exhibit antispasmodic properties, was soon advocated as an analgesic. In a short time it appeared on the market in Germany under the names of Dolantin and Dolantal. At the present time it is known in this country and England as Demerol, Pethidine, Meperidine and Isonipecaine.

Eisleb and Schaumann first described the properties of this new compound, which approaches morphine in activity, in 1939.[51] The following year Schaumann[52] gave a more detailed description of the pharmacology of Demerol, and also reported the activity of a number of its derivatives and related compounds.

The original preparation of Demerol by Eisleb involved a simple and inexpensive synthesis:



"Demerol nitrile"

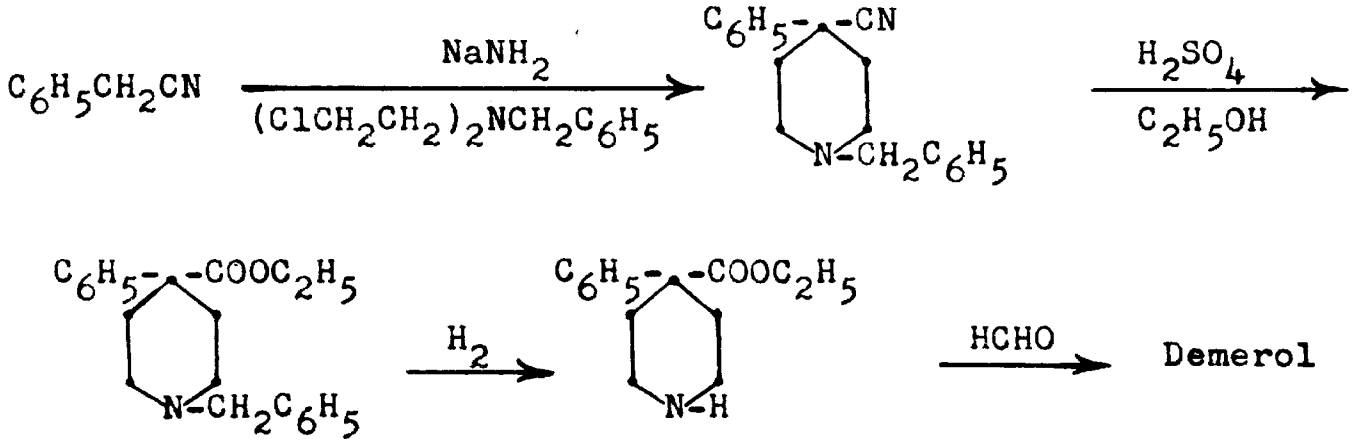
Demerol

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* Heinkamp (J. Pharmacol. Exp. Therap., 20, 107 (1922)) interpreted this reaction as due to stimulation of the spinal cord.

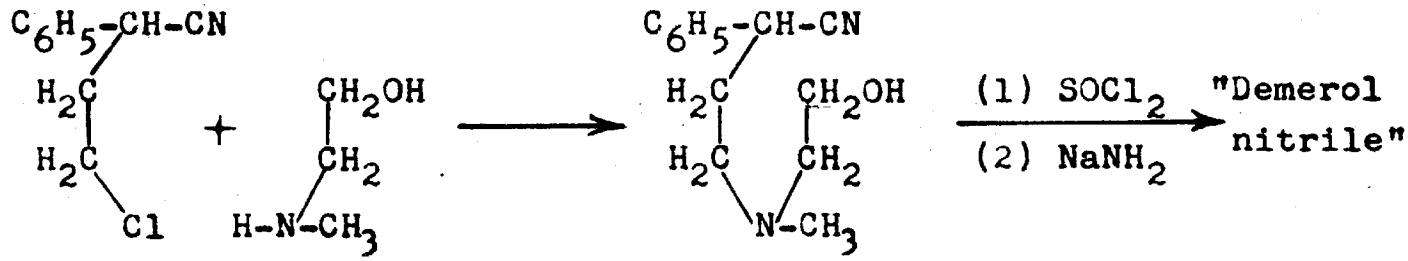
(50) Straub, Deut. med. Wochschr., 37, 1462 (1911).
(51) Eisleb and Schaumann, ibid., 65, 967 (1939).
(52) Schaumann, Arch. exp. Path. Pharmakol., 196, 109 (1940).

Because of the powerful vesicant action of methyl-bis-2-chloroethylamine, this synthesis was not used on a commercial scale. The I. G. Farbenindustrie process[53,54] utilized the benzyl- instead of the methylamine as a starting material.



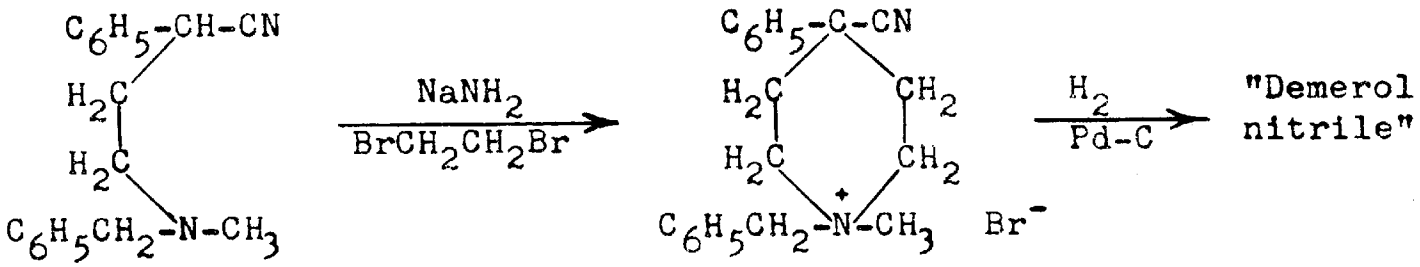
The cyclic secondary amine was also prepared by combined hydrolysis and esterification of 1-p-tosyl-4-cyano-4-phenylpiperidine.[49,55] The latter compound resulted from the reaction of p-tosyl-bis-2-chloroethylamine with phenylacetonitrile in the presence of sodamide.

Another synthesis developed at the I. G. Farbenindustrie is illustrated below:



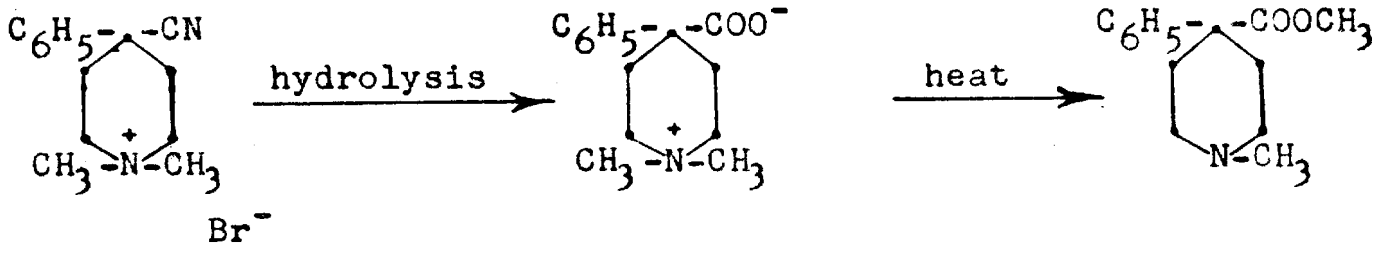
(53) I. G. Farbenindustrie A.-G., British Patent 501,135 (1939). Chem. Abst., 33, 5872 (1939).
(54) Office of the Publication Board, Department of Commerce, PB-981, p. 94 (1945).
(55) Thorp and Walton, J. Chem. Soc., 559 (1948).

A recent patent described a rather simple method of preparation:(56)



When the corresponding dimethylamino derivative was utilized as a starting material in the above reaction, the quaternary compound which formed was converted to "Demerol nitrile" by the application of heat.

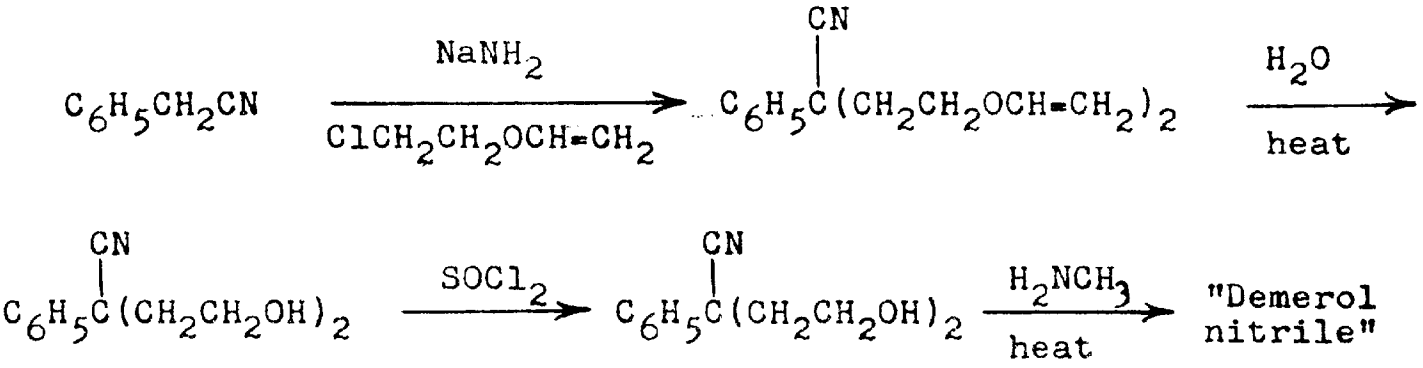
The formation and decomposition of a number of betaines are described in another patent:(57)



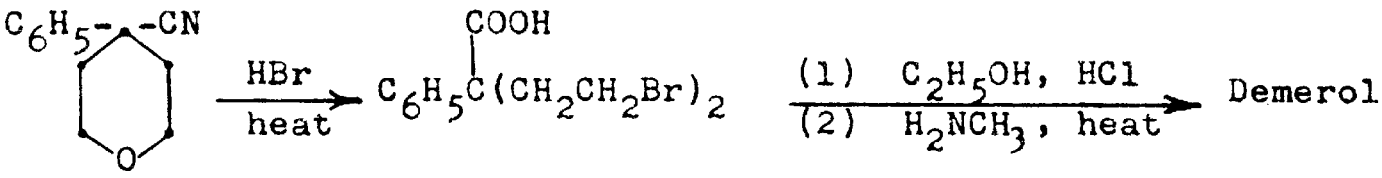
Bergel et al.(58) developed an interesting but less practical synthesis of "Demerol nitrile". The disadvantages of their method, shown below, are that the β-chloroethyl vinyl, β-chloroethyl methoxymethyl and β-chloroethyl ethoxymethyl ethers used as starting materials are not readily available, and the final step requires a sealed tube at a high temperature.

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(56) Soc. chem. Ind. Basle, British Patent 591,992 (1947); Chem. Abst., 42, 1322 (1948).
(57) Ciba Ltd., British Patent 597,794.
(58) Bergel, Morrison and Rinderknecht, J. Chem. Soc., 265, 267 (1944).

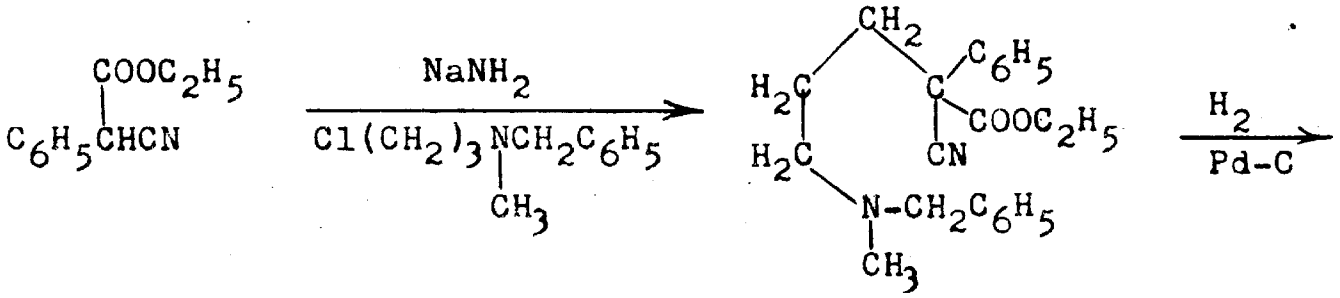


These investigators also found that 4-phenylpentamethylene oxide-4-nitrile could be converted to Demerol.

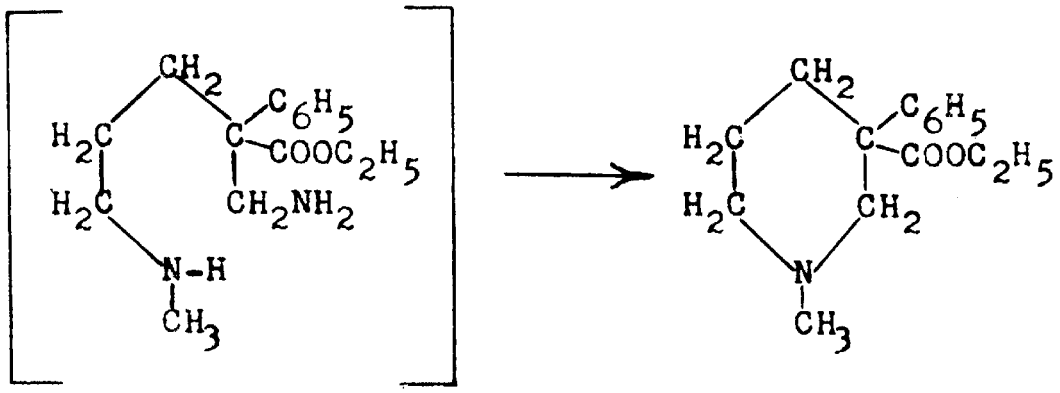


In both of the above reactions it was necessary to use a sealed tube. By treatment of the ester of the above dibromide with ammonia, Walton and Green[59] obtained 3-(β-aminoethyl)-3-phenyl-2-pyrrolidone.

By a simple procedure, Bergel et al. effected the synthesis of β-Pethidine (Iso-pethidine), an isomer of Demerol.[60]



(59) Walton and Green, J. Chem. Soc., 315 (1945).
(60) Bergel, Hindley, Morrison and Rinderknecht, J. Chem. Soc., 269 (1944).



β-Pethidine

Ethyl 1-methyl-3-phenylpyrrolidine-3-carboxylate, a lower ring homolog of β-Pethidine, was obtained by utilization of 2-chloroethylbenzylmethylamine as a starting material in the reactions indicated above.

β-Pethidine was found to be approximately 50% as potent an analgesic as Demerol. Clinical trials have indicated that the former compound was slightly toxic, did not tend to produce euphoria, and exhibited few side-effects.(61) Replacement of the phenyl by an o-tolyl group in β-Pethidine yielded a compound which possessed about 75% of the analgesic potency of Demerol. The l-isomer of this tolyl compound was superior to Demerol in the duration of analgesia.(62)

Eisleb observed that Demerol, a substituted 4-phenyl-piperidine, represented a fragment of the morphine structure. In general, further researches on Demerol-type compounds were based on attempts to obtain products which more closely simulated the morphine molecule. This approach was found to be justified.

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(61) Glazenbrook and Branwood, Lancet, 249, 528 (1945).
(62) MacDonald, Woolfe, Bergel, Morrison and Rinderknecht, Brit. J. Pharmacol., 1, 4 (1946).

The pharmacological data of Schaumann[52] showed that replacement of the N-methyl group in Demerol by other radicals produced compounds of lower activity. Decrease in potency was noted also when the 4-carbethoxy group was replaced by other carbalkoxy radicals. Substitution of an o-tolyl or m-hydroxyphenyl radical for the phenyl group in Demerol yielded compounds which exhibited slightly more activity than Demerol.[52,62] The product which contains the m-hydroxy group is known as Bemidone.[54,66] The acetyl derivative of Bemidone possessed essentially the same activity as the parent compound.[62] When the phenyl group of Demerol was replaced by some other aryl group, the products obtained exhibited little or no analgesic activity.[52] The pharmacology of the 2-thienyl analog of Demerol and a number of related compounds has not been reported.[63]

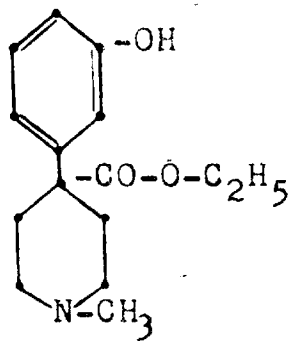
Substitution of a butyryl group for the carbethoxy radical in Demerol yielded a product which possessed about the same potency of Demerol,[52] however, when the carbethoxy radical of Bemidone was exchanged for a propionyl group, a highly potent compound was obtained. The later substance is known as Ketobemidone and was reported to be ten times more active than Demerol.[54,64,65]

Probably the most potent compound related to Demerol is

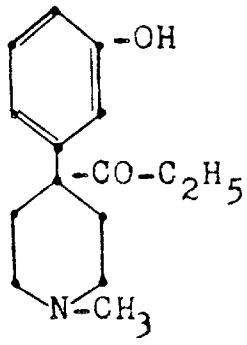
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(63) Blicke, U. S. Patents 2,425,721, 2,425,722 and 2,425,723; Chem. Abst., 42, 613 (1948).
(64) Kirchhof, Fed. Proc., 7, 234 (1948).
(65) Ciba, Ltd., British Patent 609,763 (1948); Chem. Abst., 43, 2240 (1949).

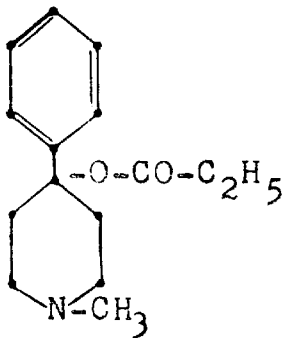
1-methyl-4-propionoxy-4-phenylpiperidine (Nu-718).[66]



Bemidone



Ketobemidone



Nu-718

This substance was stated to be thirty times more active than Demerol,[67] and was prepared readily by the reaction of phenylmagnesium bromide on 1-methyl-4-piperidone, followed by treatment of the resulting organometallic complex with propionic anhydride.[68,69]

In view of the high activity of Nu-718, the investigators at Hoffmann-LaRoche, Inc. studied the 4-acyloxy modifications of Demerol further, and were able to make the following generalizations relating activity to chemical structure in this series:[67,70]

1. The 4-phenyl group was essential; upon replacement by hydrogen, an almost inert compound was obtained.

2. Replacement of the phenyl group by a benzyl, naphthyl, p-tolyl or p-methoxyphenyl radical greatly decreased activity.

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(66) Code number, Hoffmann-LaRoche, Inc.
(67) Foster and Carman, J. Pharmacol. Exp. Therap., 94, 195 (1947).
(68) Jensen, Lundquist, Rekling and Wolffbrandt, Dansk. Tidsskr. Farm., 17, 173 (1943); Chem. Abst., 39, 2506 (1945).
(69) Ziering, Berger, Heineman and Lee, J. Org. Chem., 12, 894 (1947).
(70) Lee, Berger, Ziering and Heineman, "Jubilee Volume Emil Barrell, p. 264 (1946). Basel.

3. The acyloxy group was necessary since deviation from this structure reduced activity.

4. Shifting of both the phenyl and acyloxy radicals from the 4 to the 2 position eliminated analgesic activity.

5. The carbon-oxygen linkage at the 4 position produced greater analgesia than the carbon-carbon linkage found in Demerol.

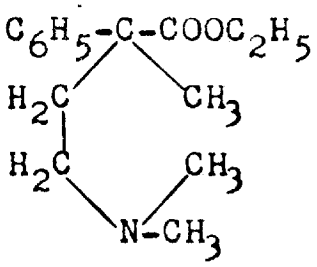
From examination of the Stuart atom models, Ziering and Lee[71] expected that the 3-methyl substituted Nu-718 would simulate the cyclohexane ring of dihydrodesoxymorphine-D rather closely. The latter compound is more potent than morphine, but the duration of analgesia produced by it is rather short. It was found that the trans form of the 3-methyl compound was 5.5 times more active than morphine, and the cis modification about as active as morphine but only one-fourth as active as Nu-718. These pharmacological results were verified and extended by Holland and Gross.[72] When tested on dogs, these workers found the cis form produced the same degree of analgesia as morphine but of shorter duration. Its administration was accompanied by mild sedation and side-actions. The trans form was four to five times more potent than morphine, and the duration of analgesia was about the same, however, the trans modification caused marked sedation and frequent side-effects such as dizziness, sweating, itching, nausea and vomiting.

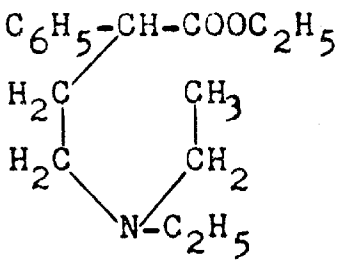
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(71) Ziering and Lee, J. Org. Chem., 12, 911 (1947).
(72) Holland and Gross, Fed. Proc., 7, 227 (1948).

In addition to the compounds already discussed, many other substituted 3- and 4-phenylpiperidines have been prepared.[73,74,75,76,77,78] None of these products was reported to possess activity comparable to Demerol.

A number of intestigators have synthesized compounds which represent an "open ring" structure of Demerol.[75,79,80,81] Compounds represented by the following formulas were reported to exhibit markedly less analgesic action than Demerol.[62,75]





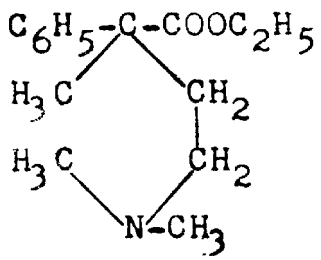
"Open ring" structures of the Demerol type

Demerol is slightly less effective than morphine as an analgesic, and is somewhat less apt to produce addiction. Unlike morphine, Demerol does not depress respiration, and for this reason is the drug of choice by many obstetricians. It is also used as a preanesthetic agent, however, in many cases it does not produce the sometimes desirable sedative effect.[82]

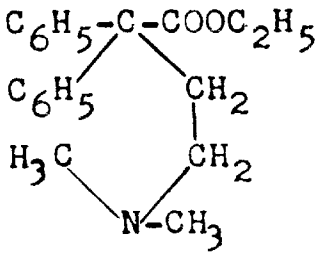
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(73) Koelsch, J. Am. Chem. Soc., 65, 2093, 2458 (1943).
(74) Cook and Barr, J. Chem. Soc., 438 (1945).
(75) Kwartler and Lucas, J. Am. Chem. Soc., 69, 2582 (1947).
(76) Badger, Cook, Donald, Graham and Walker, Nature, 162, 21 (1948).
(77) McElvain and Vozza, J. Am. Chem. Soc., 71, 896 (1949).
(78) McElvain and McMahon, ibid., 71, 901 (1949).
(79) Billman and Rendall, ibid., 66, 745 (1944).
(80) Chanin, Dissertation, University of Michigan (1945).
(81) Billman, Smith and Rendall, J. Am. Chem. Soc., 69, 2058 (1947).
(82) Yonkman, ref. 4, p. 59.

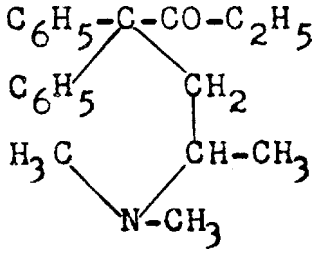
Because of the almost complete loss of analgesic activity when the piperidine ring in morphine and in Demerol were ruptured, it is surprising to note the analgesic, and also the spasmolytic, properties of the 4-alkylaminoalkyldiphenylacetic acid esters,(83) for example, ethyl 2,2-diphenyl-4-dimethylamino-



An inactive "open ring" analog of Demerol.



Ethyl 2,2-diphenyl-4-dimethylamino-butyrate.



Amidone

butyrate. During the recent war study of such compounds was extended in the laboratories of the I. G. Farbenindustrie at Hoechst-am-Main to include ketones which corresponded to the above esters. Of the original compounds prepared,(54) the most active, five to ten times more potent than Demerol, was 6-dimethylamino-4,4-diphenyl-3-heptanone (Amidone). The name, Amidone, was derived from Pyramidon by omission of the first syllable.(84) Recently the Council on Pharmacy and Chemistry of the American Medical Association adopted the name of Methadone.(84) This drug, marketed as the hydrochloride, is also known in this country as Dolophine and Adanon, and in England as Miadone. Several other interesting compounds related to Amidone have been

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(83) Bockmühl and Ehrhart, German Patent 711,069. U. S. Patent 2,230,774; Chem. Abst., 35, 3391 (1941).
(84) Chen, ref. 4, p. 83.
(85) J. Am. Med. Assoc., 134, 1483 (1947).

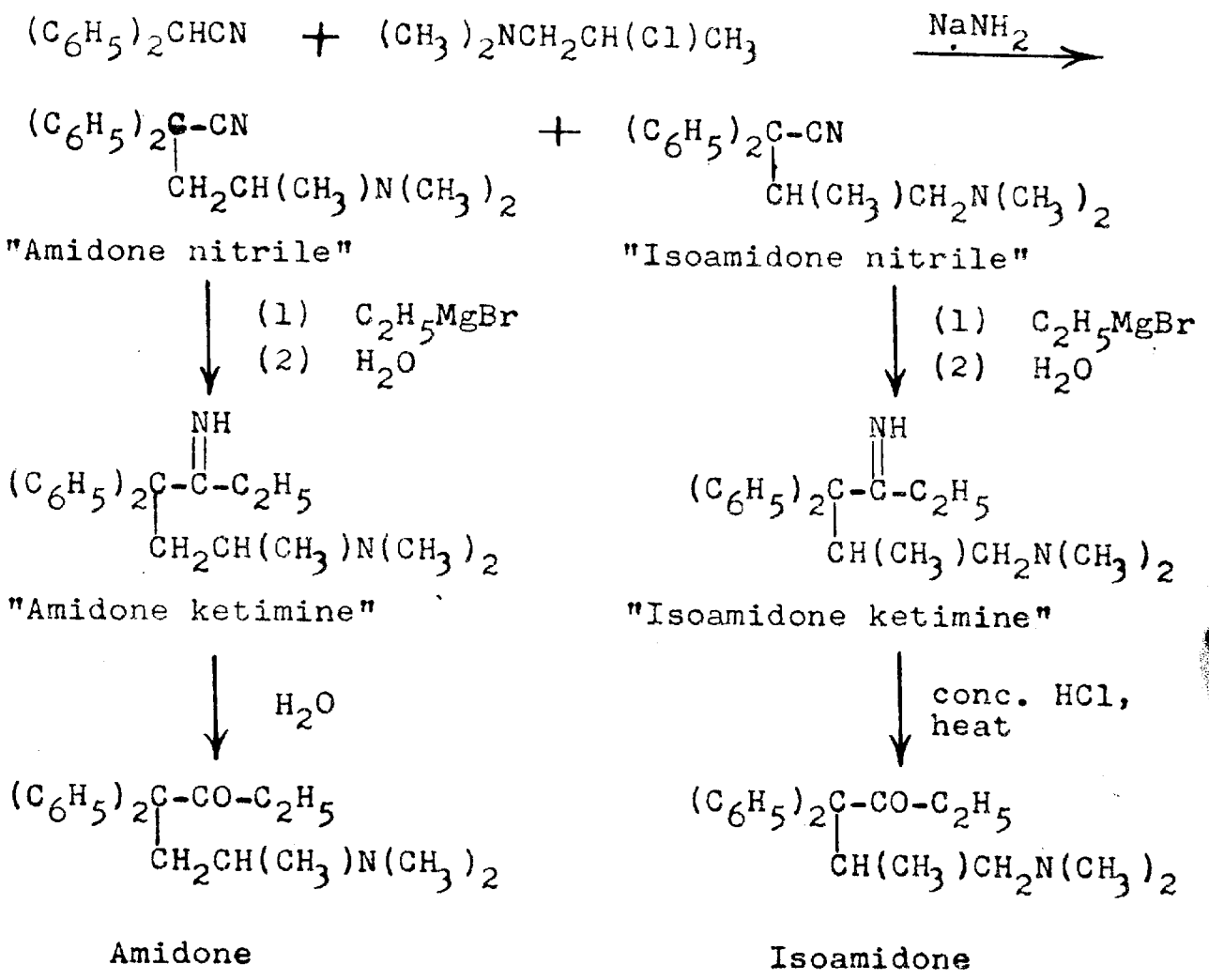
discovered. The Hoechst workers found that replacement of a phenyl, or the ethyl, group in Amidone yielded products less active than Amidone, however, substitution of the basic side chain, 2-dimethylaminopropyl, by 2-dimethylaminoethyl, 2-morpholinoethyl and 2-pyrrolidinopropyl radicals produced compounds which were about five times more potent than Demerol.(54)

The Germans did not exploit Amidone since it was discredited by both the I. G. Farbenindustrie and the military authorities because of its side-effects. It is probable that the doses employed were larger than necessary.(84)

During the investigation of the research activities of the I. G. Farbenindustrie at Hoechst-am-Main, a Technical Industrial Intelligence Committee, composed of Kleiderer, Rice, Conquest and Williams, was impressed by the reports which described the high analgesic activity of Amidone,(54) and decided that this compound merited further study. Following the encouraging results of Amidone on experimental animals,(86,87) obtained in this country, many American and British workers rapidly repeated and expanded the original German work on this series of compounds. The complete German work on Amidone has been published recently by Bockmühl and Ehrhart.(88) These workers reported the general preparation, and the spasmolytic and analgesic activity of sixty compounds. The first, and only practical, method for the synthesis of Amidone consists of the following reactions.(54,88)

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(86) Scott and Chen, J. Pharmacol. Exp. Therap., 87, 63 (1946).
(87) Scott, Robbins and Chen., Science, 104, 587 (1946).
(88) Bockmühl and Ehrhart, Ann., 561, 52 (1948); Chem. Abst., 43, 4243 (1949).

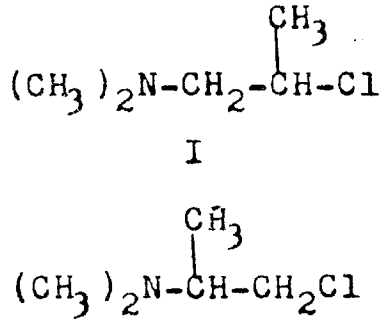


Equal quantities of the above nitriles were obtained when either 1-dimethylamino-2-chloropropane (I) or 1-chloro-2-dimethylaminopropane (II) was used in the sodamide condensation.[89] The use of potassium t-butoxide[90] or lithium amide[91] had no effect on the yield of the isomeric nitriles. The separation of these isomers was readily effected because of the insolubility of "Amidone nitrile" in hexane. Schultz and Sprague[89]

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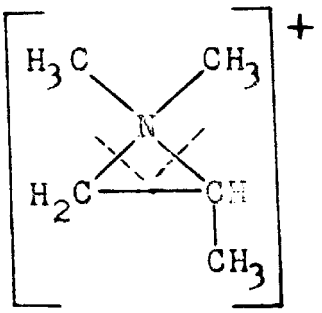
(89) Schultz and Sprague, J. Am. Chem. Soc., 70, 48 (1948).
(90) Schultz, Robb and Sprague, ibid., 69, 188, 2454 (1947).
(91) Cheney, Smith and Binkley, ibid., 71, 53 (1949).

interpreted the condensation of I, or II, with diphenylacetonitrile, in the presence of sodamide, as proceeding through the formation of the intermediate ethylenimonium ion, III. The point of cleavage of III is governed by



I

II



III

steric and polar factors of the ion itself, and also of the anion with which it reacts. These workers prepared the dimethylaminochloropropanes, I and II, from their respective alcohols and found that II was converted into I by distillation. However, Attenburrow et al.[92] reported that II did not isomerize during their distillation of this compound. The hydrochloride of II was converted into the corresponding salt of I when the former was heated to its melting point.[89] The rearrangement of dialkylaminochloropropanes had been studied previously by other investigators.[93,94,95]

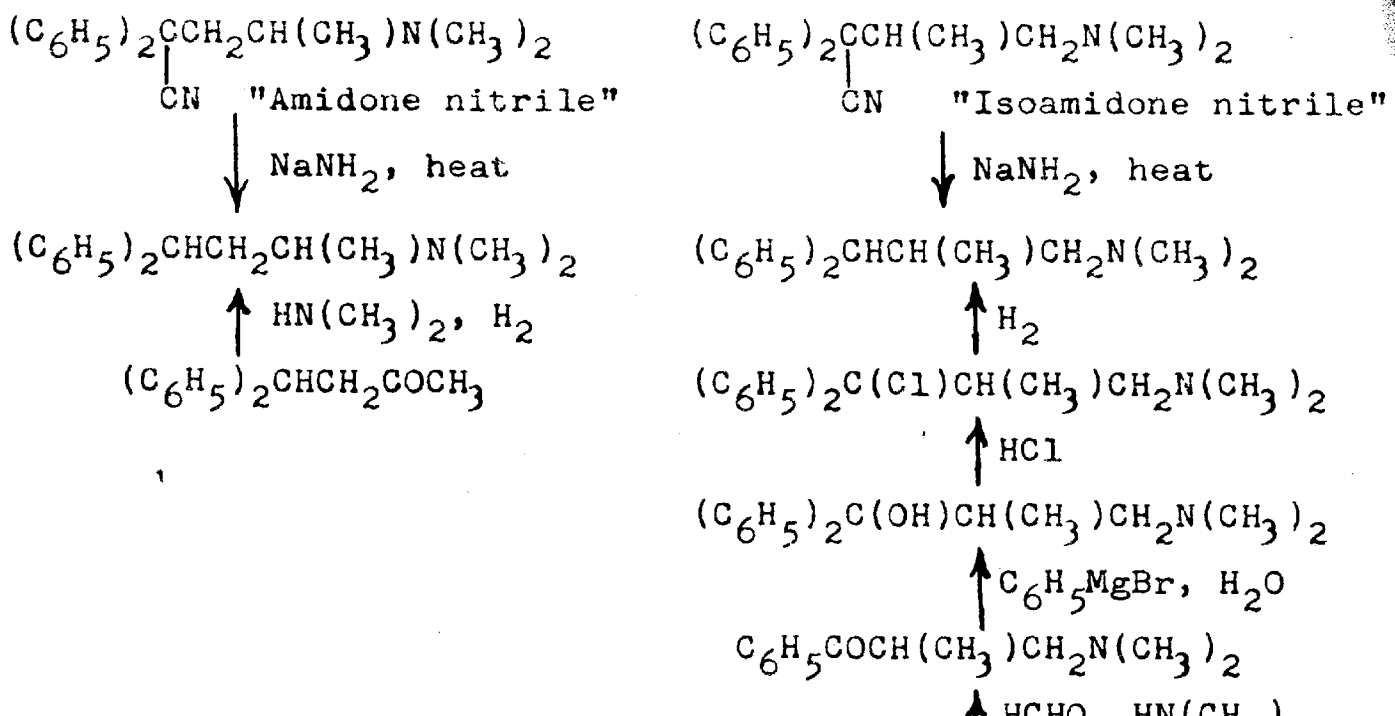
Reaction of "Amidone nitrile" with ethylmagnesium bromide, followed by mild hydrolysis, yielded Amidone. When "Isoamidone

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(92) Attenburrow, Elks, Hems and Speyer, J. Chem. Soc., 510 (1949).
(93) Brode and Hill, J. Am. Chem. Soc., 69, 724 (1947).
(94) Kerwin, Ullyot, Fuson and Zirkle, ibid., 69, 2961 (1947).
(95) Ross, ibid., 69, 2982 (1947).

nitrile" was treated in the same manner, the stable ketimine was obtained. Vigorous hydrolysis of this ketimine converted it into the ketone, Isoamidone.

In view of the difference in the analgesic activity of Amidone and Isoamidone, it was desirable to know the position of the C-methyl group in "Amidone nitrile" and in "Isoamidone nitrile". Bockmühl[96,88] proved the structures of the nitriles by replacement of the cyano group by hydrogen, and synthesis of the resulting products.

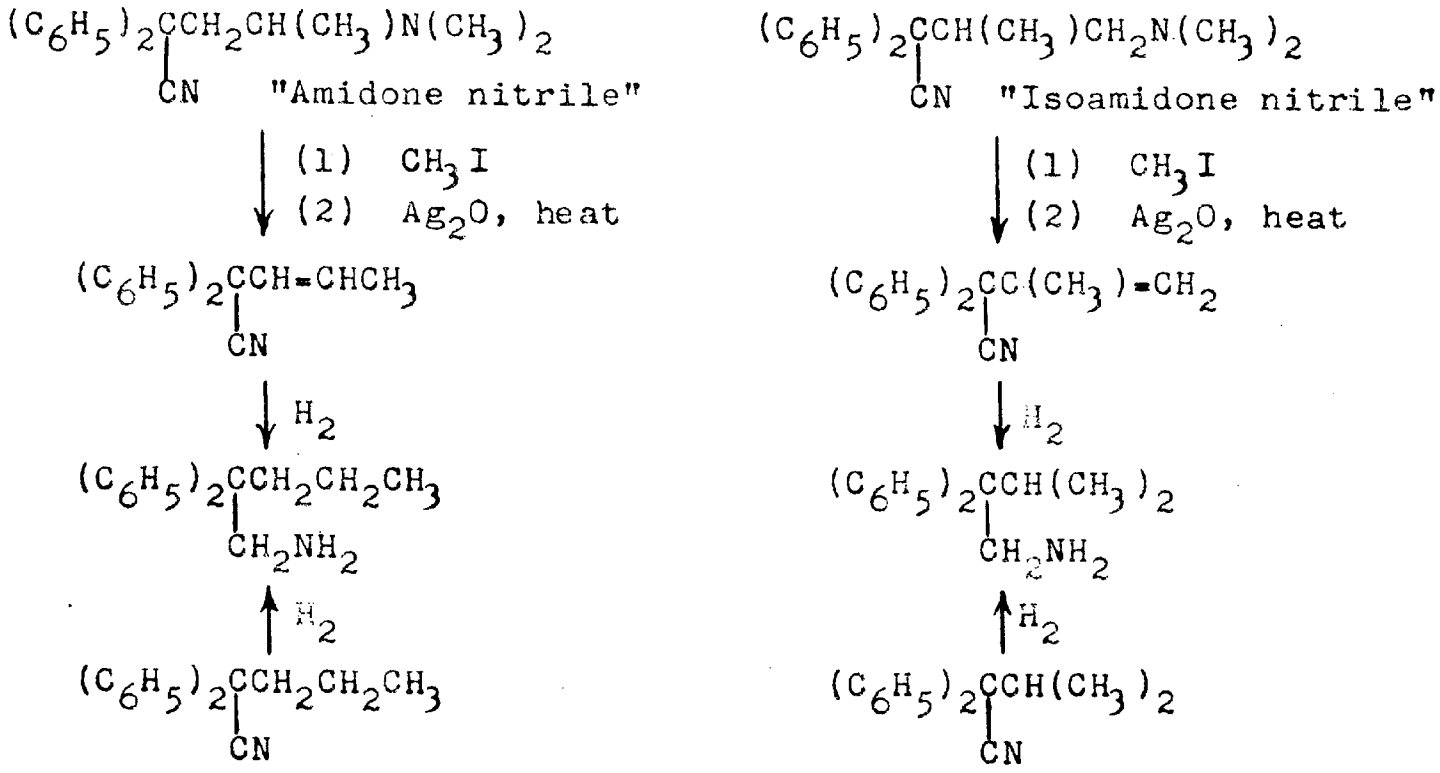


The above structure proof was not published until recently[88] and, therefore, was unknown to many of the early

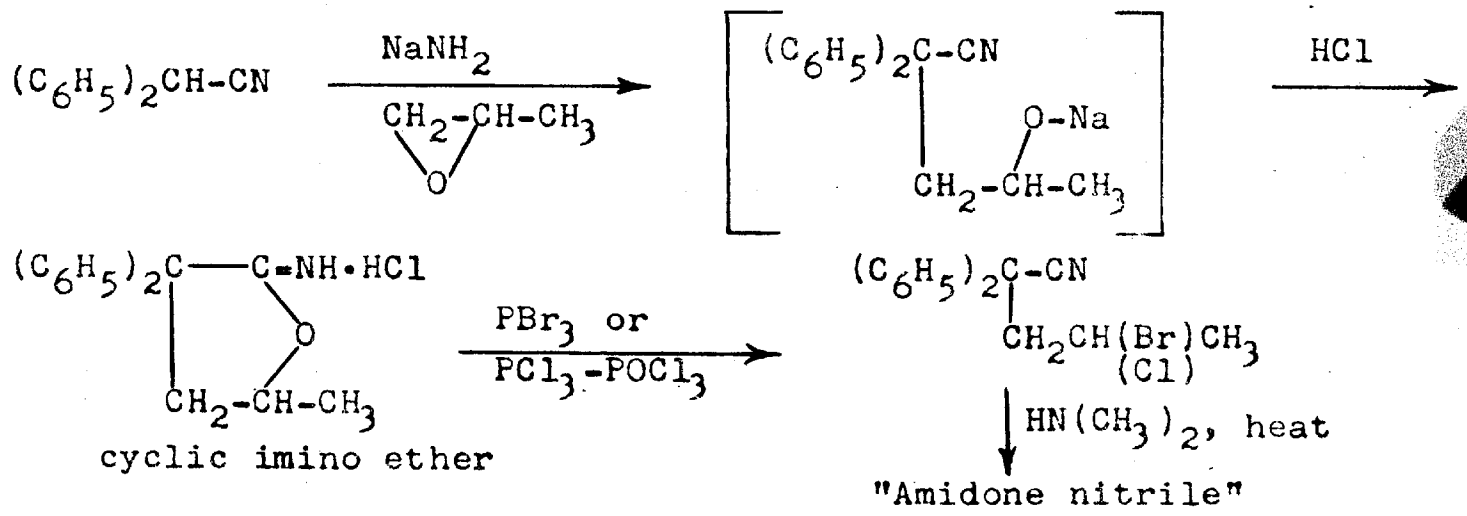
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(96) Bockmühl, private communication to Kleiderer (1946).

American and British investigators in this field. Shultz et al.[90] verified the structures of the nitriles by exhaustive methylation, followed by hydrogenation to known products.



Easton and co-workers[97] employed another method for the preparation of "Amidone nitrile" in which a cyclic imino ether was obtained as an intermediate. This procedure, however, is

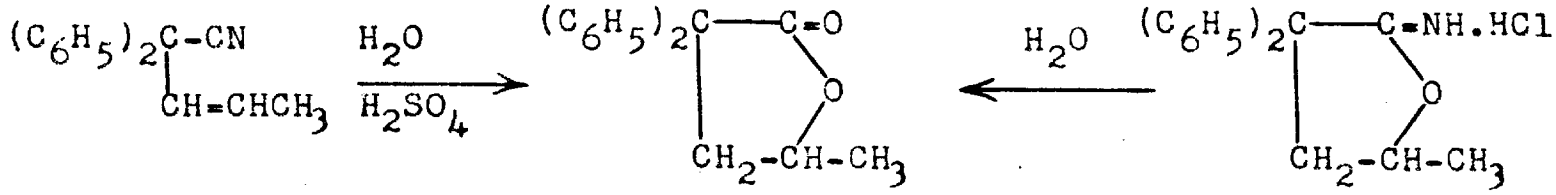


(97) Easton, Gardner and Stevens, J. Am. Chem. Soc., 69, 2941 (1947).

of no practical importance because replacement of the halogen atom in the side chain by the dimethylamino group resulted in less than 10% of "Amidone nitrile". The main product was a neutral, unsaturated substance, presumably 2,2-diphenyl-3-pentenenitrile. Attenburrow et al.[92] obtained a 25% yield of the morpholino compound, 2,2-diphenyl-4-morpholinopentanenitrile, when the above chloronitrile was heated with morpholine in a sealed tube. Easton and co-workers[97] also showed that hydrolysis of the product obtained by exhaustive methylation of "Amidone nitrile" yielded the same lactone which was produced by hydrolysis of the above cyclic imino ether.

"Amidone nitrile"

↓ exhaustive methylation



The condensation of diphenylacetonitrile with propylene oxide, followed by hydrolysis of the product to the above lactone, has been reported by other investigators.[90,98] Wilson[98] obtained the acetyl derivative of the imino ether by heating it with acetic anhydride, and also prepared a substituted tetrahydrofuran by the reaction of the lactone with ethylmagnesium bromide.

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(98) Wilson, J. Chem. Soc., 1993 (1948).

In their study of the chemistry of Amidone, May and Moesetig[99] found that Amidone was not attacked by a Clemmensen reduction, and a modified Wolff-Kishner reaction on this compound resulted in cleavage of the entire ketone chain. The product, 1,1-diphenyl-3-dimethylaminobutane, had no analgesic activity but was claimed to exhibit antihistiminic properties.[100] Catalytic hydrogenation,[99] or treatment with sodium and alcohol,[88] coverted Amidone into the corresponding alcohol. This alcohol possessed lower analgesic activity than Amidone, however, the acetyl derivative exhibited approximately the same potency as Amidone. Treatment of the alcohol with thionyl chloride yielded the inactive chloro compound, in addition to a considerable quantity of the olefin. This olefin, 6-dimethylamino-4,4-diphenyl-2-heptene, exhibited about the same activity as the alcohol.

The steric effect of the C-methyl group in "Isoamidone nitrile" and Isoamidone is very pronounced. Walton and co-workers[100] readily cleaved the cyano group from "Amidone nitrile" with sodamide but were unsuccessful in eliminating the same group from "Isoamidone nitrile". Bockmühl[88,96] apparently used more drastic conditions to effect this change. Walton et al. readily converted "Amidone nitrile" into the corresponding acid but were unable to carry out the same hydrolysis with "Isoamidone nitrile". Isoamidone was converted into the alcohol

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(99) May and Mosettig, J. Org. Chem., 13, 459 (1948).
(100) Walton, Ofner and Thorp, J. Chem. Soc., 648 (1949).

by prolonged treatment with lithiumaluminum hydride, however, catalytic reduction, under a variety of conditions, was unsuccessful.[99,101]

The stability of "Isoamidone ketimine" had been observed by several groups of workers. In their early work, Easton et al.[102] isolated this ketimine, and found that it was only partially converted into the ketone by mild hydrolysis. In a later publication,[103] these workers described the preparation of the acetyl derivative of this ketimine and, in addition, the dipicrate, and the acetyl derivative, of the less stable "Amidone ketimine". Other examples of sterically hindered, stable ketimines recorded in the literature are the ketimines of 1,2-diphenyl-2-methyl-1-propanone[104] and trichloroacetomesitylene.[105]

The difference in the stability of the isomeric ketimines made it unnecessary to separate the intermediate nitriles in some cases. For example, in the preparation of the morpholino analogs of Amidone and Isoamidone, the mixture of isomeric nitriles obtained from the reaction of diphenylacetonitrile and 1-morpholino-2-chloropropane, in the presence of sodamide, was treated with ethylmagnesium bromide and then poured onto cold dilute hydrochloric acid. The salt of the ketone (morpholino analog of Amidone) crystallized from the mixture, and the mother liquor contained the stable ketimine salt. This ketimine

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(101) Speeter, Byrd, Cheney and Binkley, J. Am. Chem. Soc., 71, 57 (1949).
(102) Easton, Gardner and Stevens, ibid., 69, 976 (1947).
(103) Easton, Gardner, Evanich and Stevens, ibid., 70, 76 (1948).
(104) Bruzau, Compt. rend., 190, 496 (1930).
(105) Houben and Fisher, Ber., 63, 2455 (1930).

was isolated and converted into the ketone (morpholino analog of Isoamidone) by refluxing it with constant-boiling hydrochloric acid. The same principle was utilized in the preparation of the fluorene analog of Amidone.[106] Attenburrow et al.[92] reacted 1-chloro-2-morpholinopropane with diphenylacetonitrile, in the presence of sodamide, and obtained a mixture of 40% 1,1-diphenyl-2-methyl-3-morpholinopropyl cyanide and 60% 1,1-diphenyl-3-morpholinobutyl cyanide. After crystallization from petroleum ether, the mixture of isomeric nitriles - plate-like crystals of the one isomer and cube-like crystals of the other - were separated by hand. These nitriles were converted into the corresponding ketones in the manner described above. Bockmühl and Ehrhart[88] also described the above-mentioned morpholino nitriles and ketones. As a result of successful clinical investigations in England,[107] the morpholino analog of Amidone, ten times more potent than Demerol,[88] is now marketed by the British under the name of Heptalgin.[108] The acetyl derivative of the "heptalgin alcohol," 2-morpholino-4,4-diphenyl-5-acetoxyheptane,[101] appears to be more promising than Heptalgin. Sherrod and co-workers[109] found that the therapeutic index, ratio of effective to toxic dose, of the above acetoxy compound was 40; the value for the acetoxy derivative of Amidone was 14, and the Amidone index was 2.3.

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(106) Ginsburg and Baizer, J. Am. Chem. Soc., 71, 1500 (1949).
(107) Wilson and Hunter, Brit. Med. J., 553 (1948).
(108) Chem. Eng. News, 27, 712 (1949).
(109) Sherrod, Kaiser, Santos-Martinez and Pfeiffer, Fed. Proc., 7, 255 (1948).

In their study of the ketimines and acylketimines of the Amidone and Isoamidone series, Cheney et al.[110] determined that in both series the order of decreasing toxicity and increasing activity was ketone, ketimine, acylketimine. Because of the comparable potency and significantly lower toxicity, all the ketimines and their acyl derivatives studied possessed as high or more favorable activity indices than those of Amidone and Isoamidone. Of the compounds tested, the acetyl derivative of "Amidone ketimine" exhibited the highest activity index.

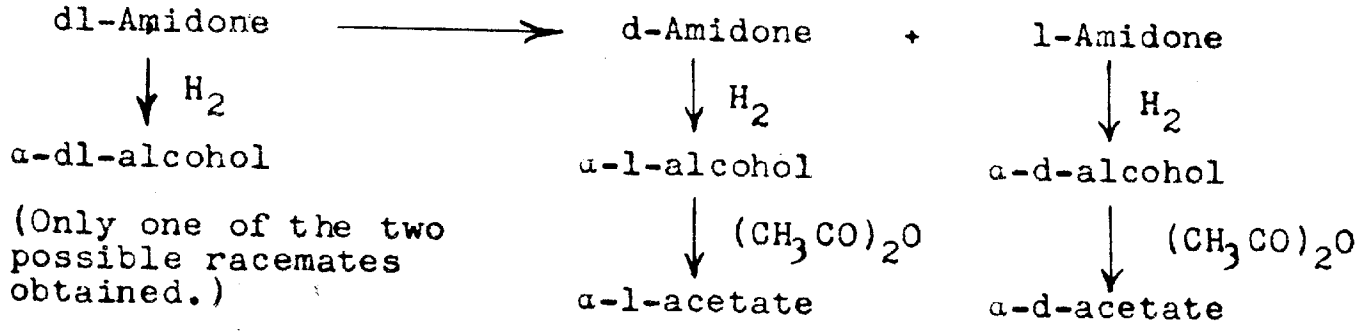
Probably as a result of a British Intelligence report,[111] which stated that the German workers found the levo[112] isomer of Amidone possessed greater analgesic activity than the racemic modification, several groups of investigators studied further the resolution of Amidone and related compounds. Thorp and co-workers[113] failed in their attempt to resolve Amidone with the use of d-tartaric acid or other optically active acids, but they were able to resolve "Amidone nitrile" with this acid. The optically active ketones were obtained by the reaction of the d- and l-nitriles with ethylmagnesium bromide, followed by hydrolysis of the intermediate ketimines. Brode and Hill[114] obtained seed-crystals of l-Amidone-d-acid tartrate and, consequently, were able to isolate both isomers. Bockmühl and

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(110) Cheney, Smith and Binkley, J. Am. Chem. Soc., 71, 53 (1949).
(111) B. I. O. S., Final Report No. 116, Item 24, pp. 51, 52, and 65.
(112) The use of levo, dextro, "l", and "d" is restricted to designation of direction of rotation.
(113) Thorp, Walton and Ofner, Nature, 159, 679; 160, 605 (1947).
(114) Brode and Hill, J. Org. Chem., 13, 191 (1948).

Ehrhart[88] also reported the separation of the l-isomer of Amidone by the use of tartaric acid. Larsen et al.[115] described, in more detail, the resolution of Amidone and "Amidone nitrile". They also applied the same procedure to effect the resolution of Isoamidone and "Isoamidone nitrile." These workers found that resolution of Amidone yielded 85% l-Amidone-d-bitartrate and 42% d-Amidone-d-bitartrate monohydrate. Resolution of "Amidone nitrile" yielded 56% of the l-nitrile and 63% of the d-isomer; these nitriles were converted into l- and d-Amidone in 92% yield.

Pohland et al.[116] prepared the optically active forms of Amidone, and studied some of their derivatives.



The optically active "Amidone nitriles" were also converted into the d- and l-ethyl esters by combined hydrolysis and esterification. When tested on rats, the above isomers exhibited a great difference in analgesic potency. Using Amidone (dl-Amidone) as a standard, these investigators found that the d-isomer of Amidone was only 8% as active as Amidone while the l-isomer was

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(115) Larsen, Tullar, Elpern and Buck, J. Am. Chem. Soc., 70, 4194 (1948).

(116) Pohland, Marshall and Carney, J. Am. Chem. Soc., 71, 460 (1949).

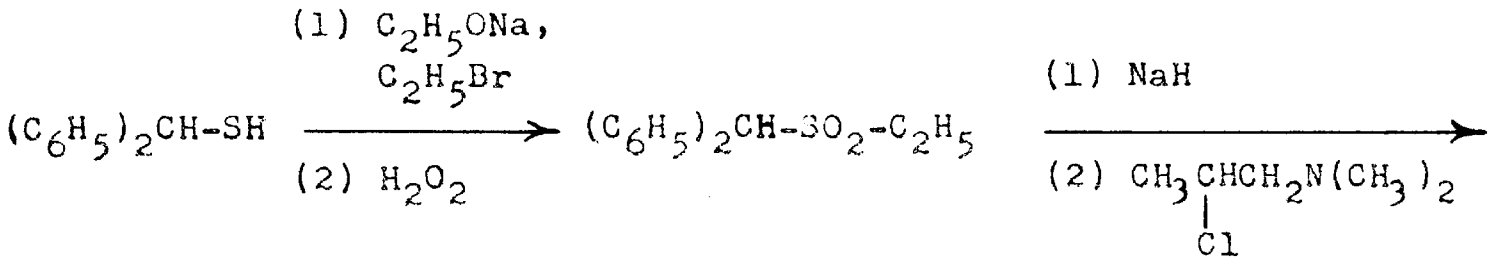
160% more potent. In the alcohol series, the α-dl-isomer was 20% as potent as Amidone, the α-d-form 3%, and the α-l-form 40% as active. The α-dl-acetate exhibited 133% of the Amidone potency; the α-d-acetate, 200%; and the α-l-isomer, only 37%. In the ethyl ester series, the dl- and d-forms possessed 40%, and the l-form 3%, of the Amidone potency.

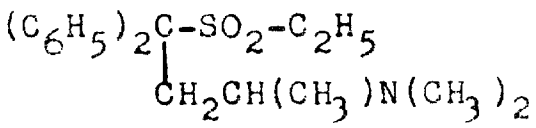
The reported values for the analgesic activity of compounds usually are not in complete agreement since the results vary with the animals used, and the method of testing employed.(117,118) Chen(84) found that, in rats, l-Amidone was seven times more active than the d-isomer; in dogs, twenty-five times more active; and in man, fifty times more potent than the d-form. Jenney and Pfeiffer(119) reported that l-Isoamidone has a higher therapeutic index than l-Amidone. Although the latter compound is slightly more potent, it is also more toxic. It is probable that both of these isomers are under clinical investigation at the present time. In contrast to the analgesic properties, the spasmolytic activity of Amidone was shown to be a function of the general structure of the compound, and not associated with optical isomerism.(120)

The synthesis of the sulfone analog of Amidone was readily accomplished by means of the following reactions:(121,122)

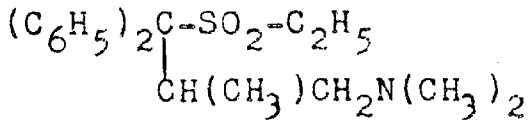
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(117) Pfeiffer, Sonnenchein, Glassman, Jenney and Bogolub, ref. 4, p. 21.
(118) Miller, ref. 4, p. 34.
(119) Jenney and Pfeiffer, Fed. Proc., 7, 231 (1948).
(120) Thorp, Brit. J. Pharmacol., 4, 98 (1949).
(121) Klenk, Suter and Archer, J. Am. Chem. Soc., 70, 3846 (1948).
(122) Tullar, Wetterau and Archer, ibid., 70, 3960 (1948).





"Amidone sulfone"



"Isoamidone sulfone"
(not isolated)

In the last step, sodium hydride was found to be a slightly better condensation agent than sodamide. In view of the fact that two isomers were obtained when diphenylacetonitrile, in the presence of sodamide, was treated with the above dimethylaminochloropropane, it is interesting that only the "Amidone sulfone" (45% yield) and starting material were isolated from this reaction. The structure of this isomer was verified by hydrogenolysis of the sulfone. The latter reaction yielded the same compound, 1,1-diphenyl-3-dimethylaminobutane, obtained from "Amidone nitrile" by replacement of the cyano group by hydrogen. The sulfone analog of Amidone was claimed to exhibit the same analgesic potency, but only one-half the toxicity of Amidone. Lewis[123] observed that tolerance developed most rapidly with this compound when compared with morphine, l-Amidone, l-Isoamidone and Ketobemidone. On resolution of "Amidone sulfone" by means of d-tartaric acid, the l-isomer

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(123) Lewis, Fed. Proc., 8, 315 (1949).

was found to be twenty times more potent than the d-form.[122] A number of other sulfones were also prepared, but none of these substances possessed higher analgesic potency than the analog of Amidone.

Zambito[124] prepared a number of products similar to Amidone. He utilized the simpler 2-dimethylaminoethyl, instead of the 2-dimethylaminopropyl, side chain and studied the effect of replacement of one or both of the phenyl groups by radicals such as cyclohexyl, benzyl, α-thienyl and alkyl. Products in which phenyl and cyclohexyl, phenyl and n-hexyl or α-thienyl and cyclohexyl had been substituted for the two phenyl groups seemed to be worthy of further pharmacological study. A number of other, less active, compounds were also reported.

Im summarizing the pharmacological data of approximately 200 compounds related to Amidone, Chen[84] stated that it was necessary to have the $(C_6H_5)_2C$ radical between the ketone and amino group in order to retain analgesic action. Replacement of one or both of the phenyl groups decreased or abolished activity. It was also essential that both phenyl groups should be attached to the same carbon atom. Substitution, by similar radicals, of the basic and ketone side chains, attached to the $(C_6H_5)_2C$ group resulted in less active, or inactive, compounds. Most of the above modifications of the Amidone structure were also reported by Bockmühl and Ehrhart.[88]

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(124) Zambito, Dissertation, University of Michigan (1947).

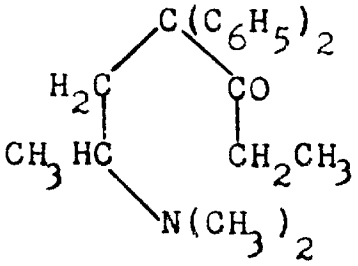
On a weight basis, in man, Amidone (hydrochloride) is twice as active an analgesic as morphine sulfate. Amidone produces a sedative effect, but the amount required is greater than that necessary for analgesia. In this respect Amidone is less effective than morphine. Amidone is more toxic than morphine; it is particularly toxic to rats. Tolerance to the sedative and analgesic action of Amidone has been demonstrated. Physical dependence can develop with Amidone, but the withdrawal symptoms are so slight that it used for treatment of morphine addiction. From the above summary of the pharmacology of Amidone,[84] it can be concluded that it is by no means an ideal analgesic but it seems that it may find a limited application in medicine.

Many of the derivatives and related compounds of the Amidone and Demerol type have promising properties on experimental animals, and some of these substances may prove to be of clinical value.

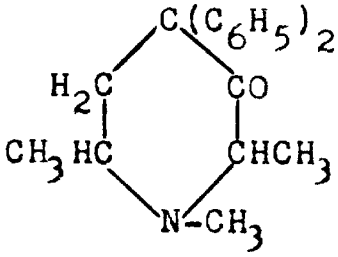
Bergel and Morrison[47] classified compounds which are structurally related to morphine into sixteen groups, and also cited the literature references for the preparation of these substances. Of these groups, only the phenylpiperidine (Demerol type), diphenylpropylamine (Amidone type) and N-methylmorphinan structures exhibited analgesic activity comparable to morphine. A lesser degree of potency has been claimed for compounds representing the diphenylethylamine and basic isocoumarin classifications.

DISCUSSION OF THIS INVESTIGATION

In view of the analgesic activity of 1-ethyl-3,3-diphenyl-2-pyrrolidone,[125] and the presence of the piperidine ring in both morphine and Demerol, it appeared interesting to prepare a series of substituted 3-piperidones, including cyclic analogs of Amidone and Isoamidone.

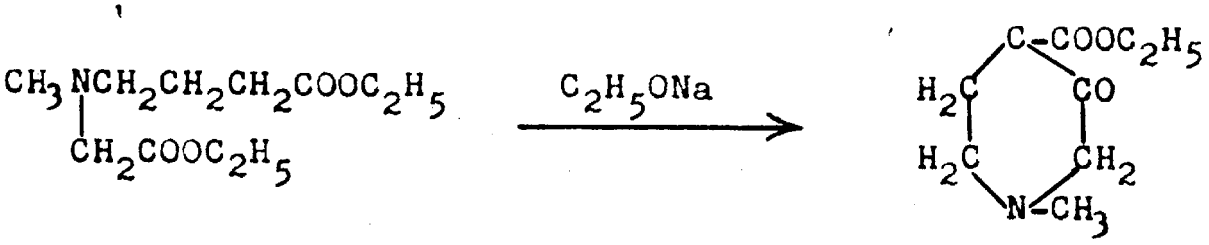


Amidone



Cyclic Amidone

The two previous syntheses of 3-piperidones reported in the literature are long processes, and would not be suitable for the preparation of the more highly substituted products which we wished to obtain. McElvain and Vozza[77] prepared 1-methyl-4-carbethoxy-3-piperidone by cyclization of a diester.

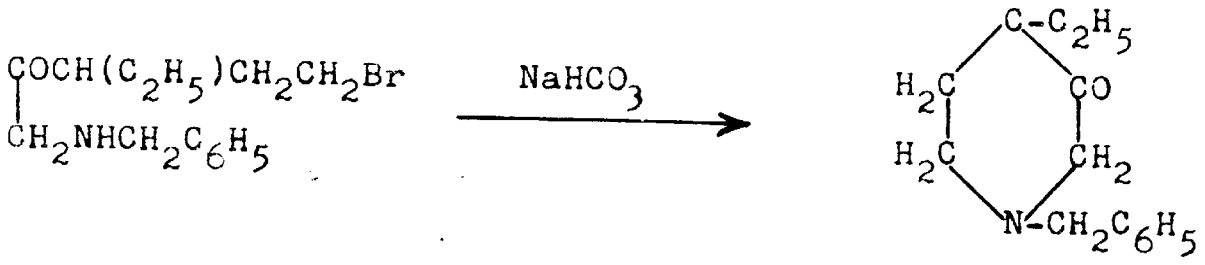


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(125) Blicke and Zambito. Abstracts of the American Chemical Society meeting, April, 1947, p. 3K.

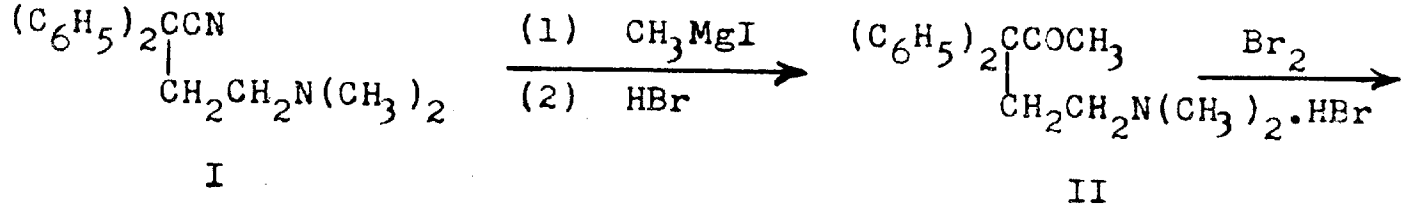
The latter compound was isolated in 40% yield by a series of five reactions beginning with butyrolactone. These workers found that the above method for the preparation of the diester was more advantageous than an earlier procedure[126] in which ethyl γ-bromobutyrate was allowed to react with the required sarcosine ester.

Work[127] employed a different method for the synthesis of a 3-piperidone. The starting material for this reaction

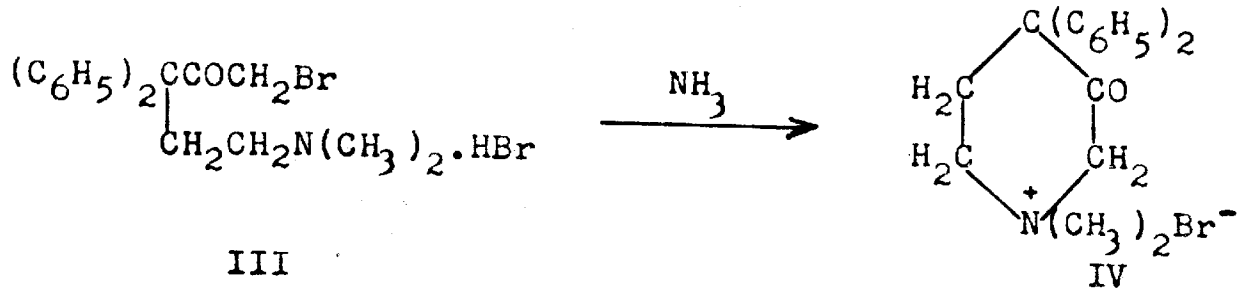


was prepared from ethyl acetoacetate by means of a 6-step procedure.

The synthesis of 3-piperidones was readily achieved by us by means of the following reactions:

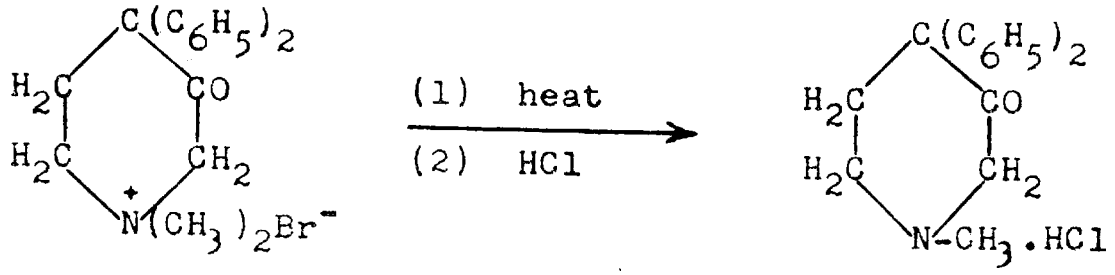


I II



III IV

(126) Prill and McElvain, J. Am. Chem. Soc., 55, 1233 (1933).
(127) Work, J. Chem. Soc., 194 (1946).



IV V

The yields, in all of these processes, exceeded 80%; the overall yield, starting with diphenylacetonitrile, was 46%.

The nitrile (I) was prepared by the reaction of 2-dimethylaminoethyl chloride with diphenylacetonitrile in the presence of sodamide. On treatment of I with excess methylmagnesium iodide, followed by hydrolysis of the intermediate ketimine-magnesium iodide complex, the methyl ketone was obtained. The hydrobromide salt of this ketone, II, was readily brominated in refluxing glacial acetic acid to yield III. The corresponding dibromo compound of III was prepared by the addition of two equivalents of bromine to II. Suspension of the salt (III) in water, and addition of excess aqueous ammonia resulted in complete solution from which the insoluble quaternary salt (IV) separated almost immediately.*

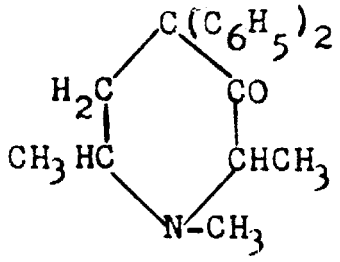
Thermal decomposition of IV proceeded smoothly when the salt was heated to its melting point under reduced pressure; methyl bromide was evolved, and the free base which formed was

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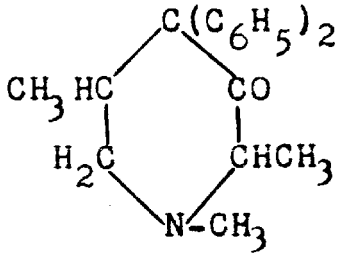
* Of the eleven quaternary salts prepared, four were very soluble in water. The latter compounds were purified by evaporation of the aqueous solutions to dryness, followed by separation of the organic salts from the ammonium bromide by extraction with hot isopropyl alcohol. The quaternary salts, with the exception of 1-methyl-4-phenyl-3-piperidone, crystallized from the alcoholic extract.

purified by distillation. The nearly colorless distillate was dissolved in ether and converted into a salt by the addition of hydrogen chloride. One crystallization of this salt from ethanol yielded the pure hydrochloride (V). On treatment of the free base of V with excess methyl bromide, the methobromide (IV) was obtained.*

Amidone and Isoamidone hydrobromides were brominated and the bromo products cyclized. Thermal decomposition of the resulting methobromides yielded the cyclic analogs of Amidone and Isoamidone.



Cyclic Amidone

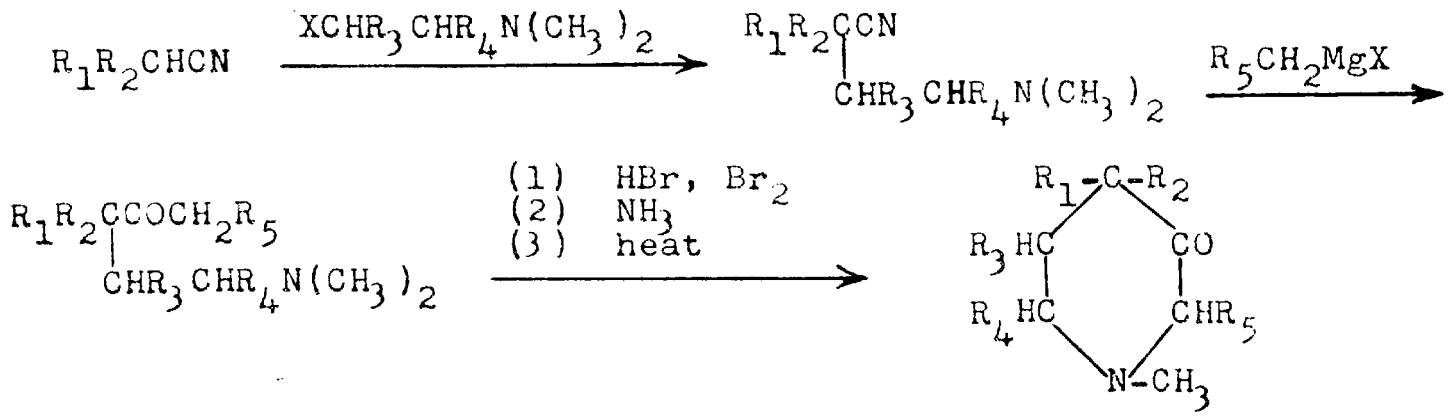


Cyclic Isoamidone

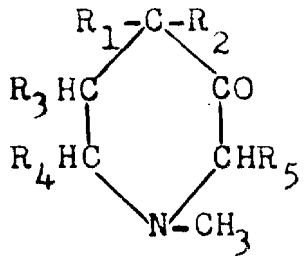
Inspection of the equations used in the preparation of V will indicate that by variation of the essential reactants, that is the disubstituted nitrile, basic side chain and Grignard reagent, it should be possible to prepare 3-piperidones which contained substituents in any or all of the 1, 2, 4, 5, and 6 nuclear positions. The general equation, and table of examples illustrates the scope of this synthesis.

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* This reaction indicated that no rearrangement (contraction of the ring) occurred during the conversion of the methobromide (IV) into the free base of V.



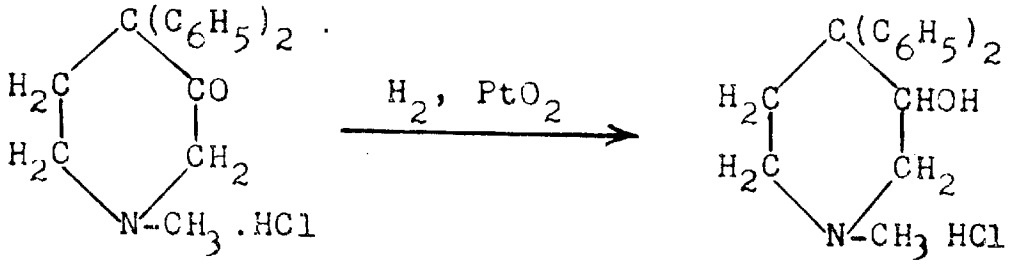
Substituted 3-Piperidones Prepared



	R_1	R_2	R_3	R_4	R_5
1.	C_6H_5	C_6H_5	H	H	H
2.	C_6H_5	CH_3	H	H	H
3.	C_6H_5	C_6H_{13}	H	H	H
4.	C_6H_5	$C_6H_{11}CH_2CH_2$	H	H	H
5.	C_6H_5	C_6H_{11}	H	H	H
6.	C_4H_2BrS*	C_6H_{11}	H	H	CH_3
7.	C_6H_5	C_6H_5	H	H	CH_3
8.	C_6H_5	C_6H_5	H	H	$C_6H_5CH_2$
9.	C_6H_5	C_6H_5	H	CH_3	CH_3
10.	C_6H_5	C_6H_5	CH_3	H	CH_3

* 5-bromo-2-thienyl

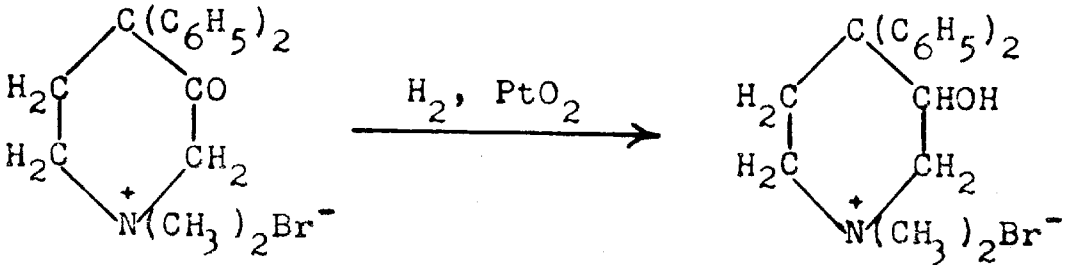
The ketone (V) was rapidly hydrogenated to the alcohol (VI). The latter compound was acetylated rapidly, and in



V VI

quantitative yield, when it was heated with acetic anhydride; it also yielded the p-nitrobenzoate derivative when treated with p-nitrobenzoyl chloride in the presence of pyridine. Cyclic Amidone hydrochloride was also readily hydrogenated, but the alcohol which was formed could not be acetylated with acetic anhydride.

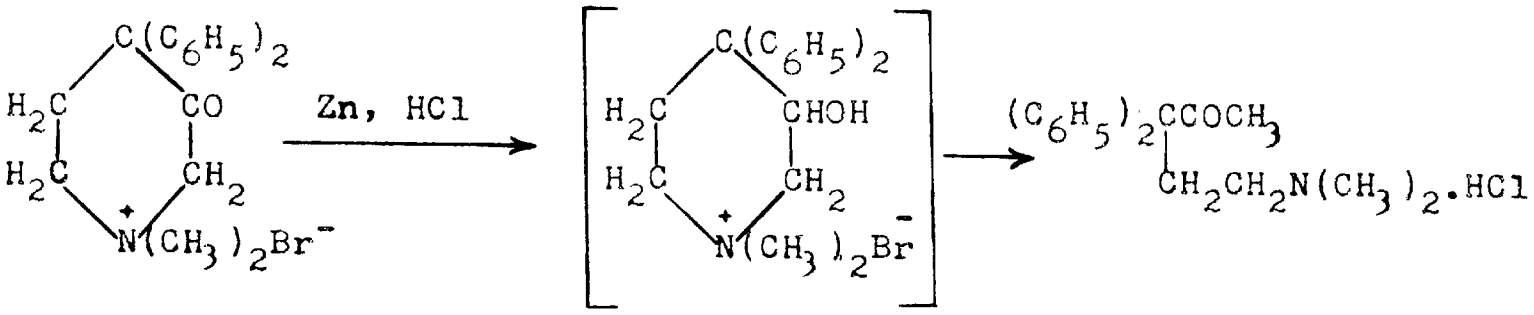
Catalytic reduction of IV yielded the corresponding alcohol methobromide (VII). When heated to its melting point



IV VII

under reduced pressure, VII liberated methyl bromide, and the free base of VI (previous equation) which formed sublimed on the walls of the flask.

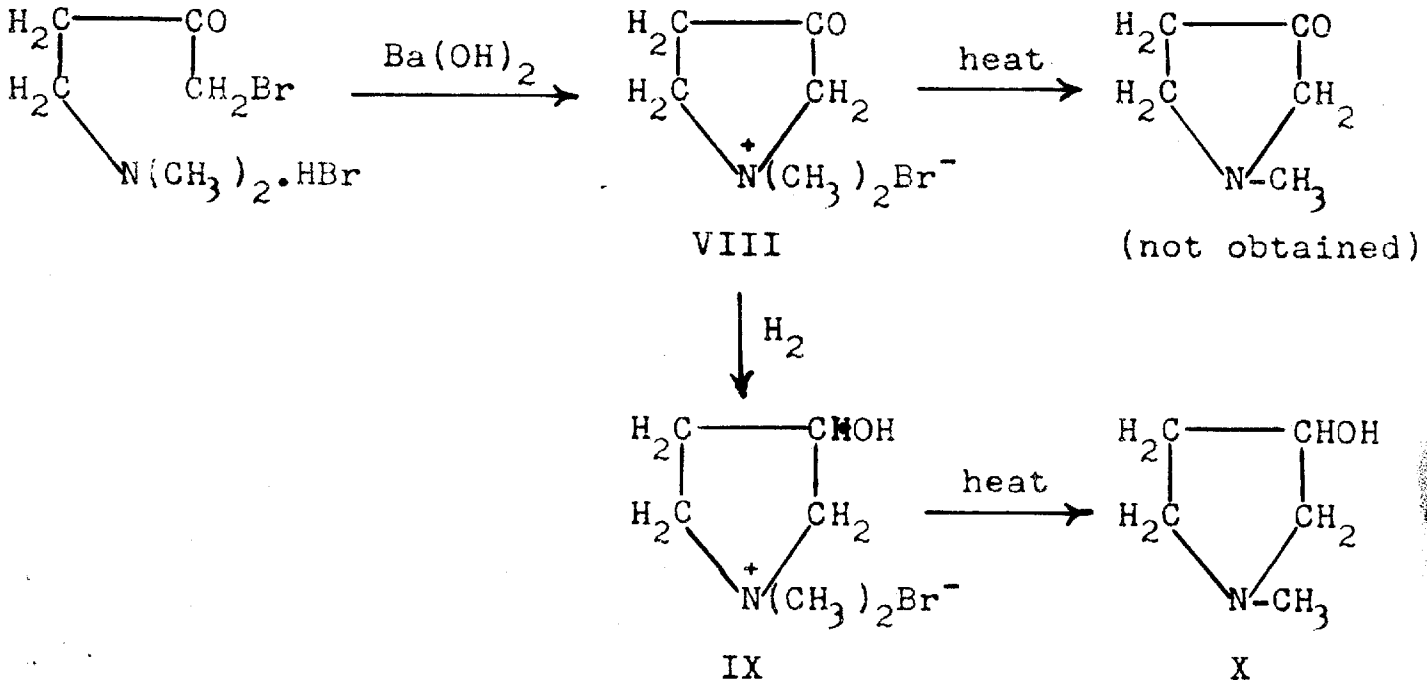
Treatment of IV with zinc and hydrochloric acid produced II in 79% yield. This compound was probably formed by



IV II

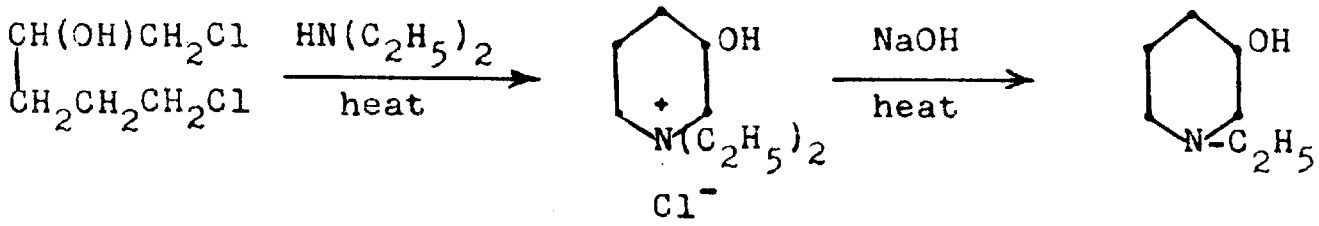
"hydramine fission" of the intermediate alcohol. Cleavage, by acids, of the nitrogen-carbon linkage in β-hydroxy amines had been observed during the study of ephedrine and quinine.(128,129)

Mannich and Gollasen(130) synthesized 1-methyl-3-pyrrolidone methobromide (VIII). In their attempt to convert this salt to the free base by heat they obtained only a tarry product, however,

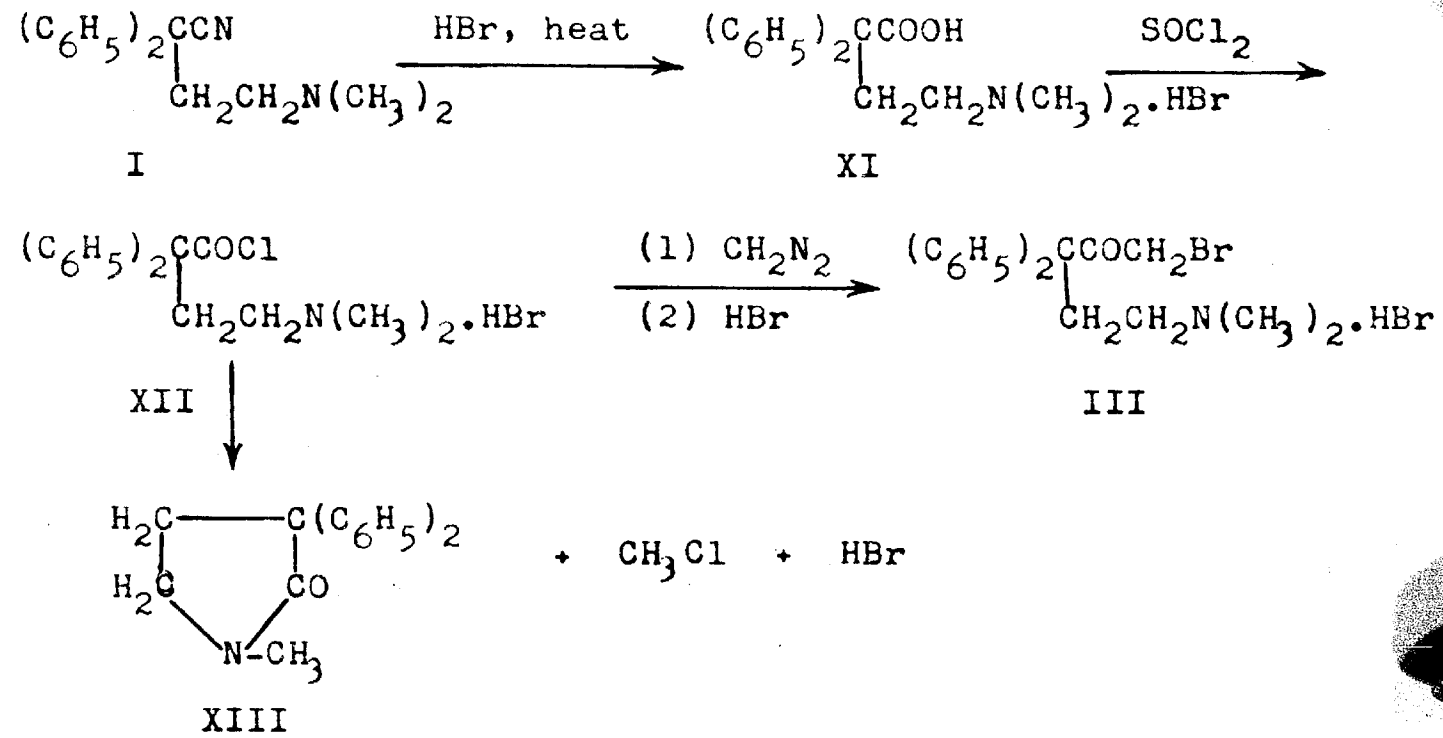


(128) Karrer, "Organic Chemistry," p. 817, 845 (1947).
(129) Rabe and Schneider, Ann., 365, 377 (1909).
(130) Mannich and Gollasen, Ber., 61, 263 (1928).

after the ketone (VIII) had been reduced to the alcohol (IX), and the latter compound heated in an atmosphere of nitrogen, 1-methyl-3-hydroxypyrrolidine (X) was produced. A British patent(131) described a simple preparation of 1-ethyl-3-hydroxy-piperidine.



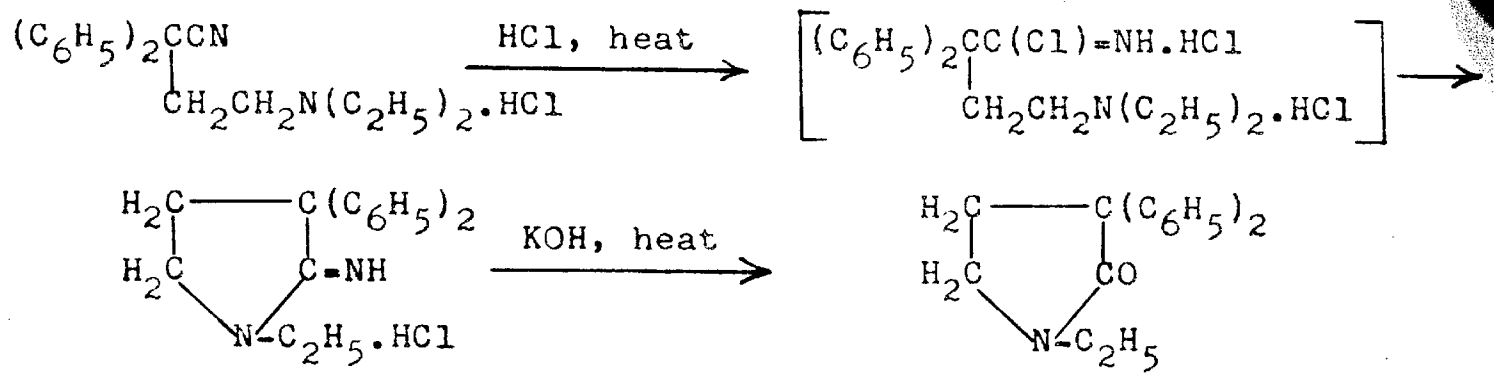
Originally we had planned to obtain the bromoketone (III), (intermediate for the preparation of V, see p. 38), according to the following reactions:



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(131) Soc. chem. Rhone-Poulenc, British Patent 598,390 (1948); Chem. Abst., 42, 7344 (1948).

The acid (XI) was treated with thionyl chloride in an attempt to obtain the acid chloride (XII). However, the reaction product which resulted proved to be the pyrrolidone (XIII). Inasmuch as the desired acid chloride was not isolated, it was impossible to treat the latter substance with diazomethane, and then with hydrogen bromide, in order to obtain III. 1-Ethyl-3,3-diphenyl-2-pyrrolidone (XIV) was produced in the same manner from the diethylamino derivative of I. This pyrrolidone (XIV) melted at the same temperature, and did not depress the melting point of the identical compound which had been prepared by Blicke and Zambito[125] according to the following reactions:



XIV

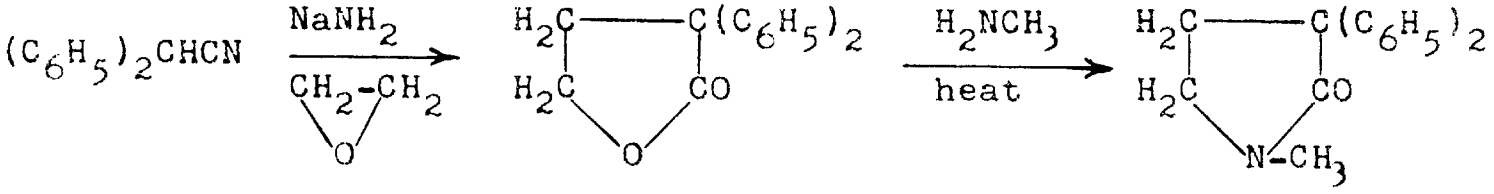
More recently Dupré and co-workers[132] reported the preparation of XIII and XIV. The former compound was obtained during an attempt to prepare the ethyl ester of the acid (XI) by means of the intermediate acid chloride (XII). The N-ethyl compound (XIV) was obtained in a similar manner. These workers prepared the intermediate acids by hydrolysis of the required

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(132) Dupré, Elks, Hems, Speyer and Evans, J. Chem. Soc., 500 (1949).

nitriles with concentrated hydrochloric acid in sealed tube at 140-150°. Our experiments showed that the use of a sealed tube could be avoided by utilizing 48% hydrobromic acid as the hydrolytic agent.

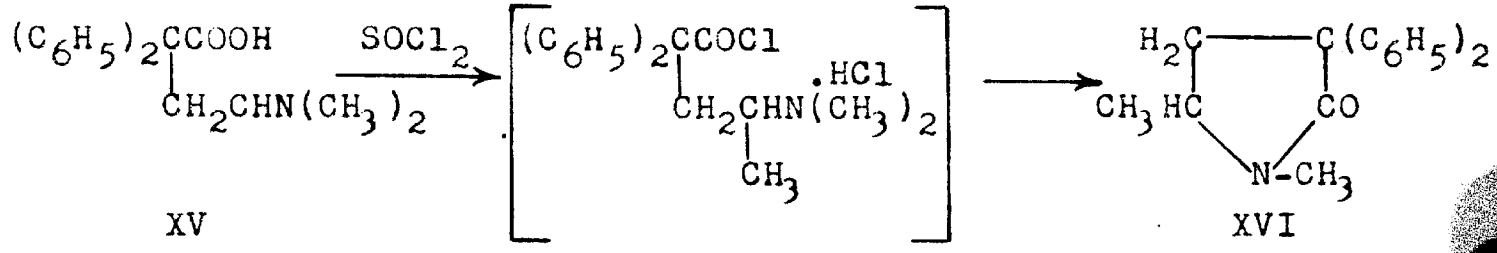
In order to prove the structure of their pyrrolidones, Dupré et al.[132] prepared them by another procedure.



XIII

Compound XIV was obtained by treatment of the above butyrolactone with ethylamine. In contrast to the ease of cyclization of the acid chloride (XII) to yield a pyrrolidone, there was no tendency at all for the corresponding higher acid chloride to cyclize to a piperidone.[132]

The formation of 2-pyrrolidones had also been observed by Easton et al.[133] These workers obtained 1,5-dimethyl-3,3-diphenyl-2-pyrrolidone (XVI) during their attempt to prepare esters, by means of the acid chloride procedure, of the acid, XV. The latter was derived by hydrolysis of "Amidone nitrile".



XV XVI

When the corresponding acid obtained from "Isoamidone nitrile"

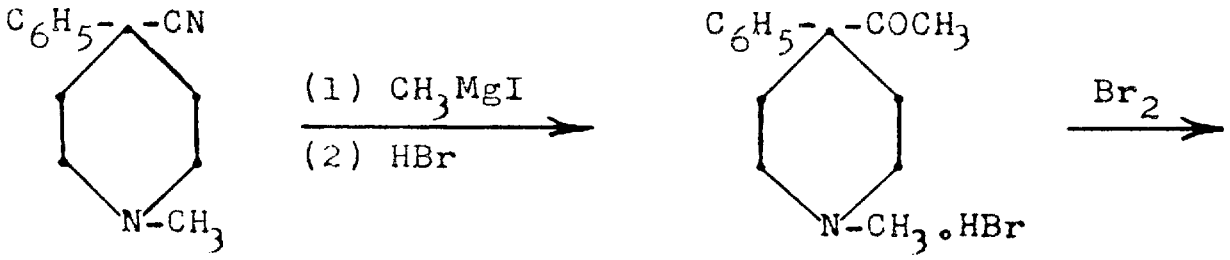
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(133) Gardner, Easton and Stevens, J. Am. Chem. Soc., 70, 2906 (1948).

was treated in the same manner, 1,4-dimethyl-3,3-diphenyl-2-pyrrolidone (XVII) was obtained. It is interesting to note that the methyl ester of XV was prepared in good yield by treatment of the bisulfate salt of XV with thionyl chloride, followed by reaction with methyl alcohol. In their attempt to obtain the isopropyl ester according to an analogous procedure, these workers obtained only XVI.

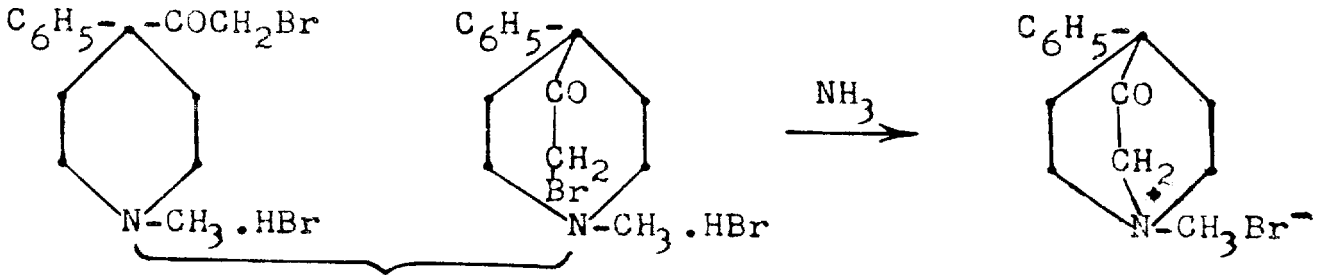
Walton et al.[100] also prepared XVI by utilization of the above equations. These workers were unable to hydrolyze the "Isoamidone nitrile" according to the same procedure employed to convert "Amidone nitrile" into the corresponding acid, however, in their attempt to hydrolyze the former compound using more drastic conditions (48% hydrobromic acid in a sealed tube at 180°), they obtained only 1,4-dimethyl-3,3-diphenyl-2-pyrrolidone (XVII). The mechanism for the formation of this compound probably corresponds to the sequence of reactions described by Blicke and Zambito (p. 45); that is, formation of the iminohydrobromide, cyclization with the loss of methyl bromide, and then hydrolysis of the resulting imino compound to the ketone.

It also appeared interesting to us to determine if a quinuclidine compound, closely related to the ketobemidone structure, would exhibit analgesic activity. The substituted 3-ketoquinuclidine, in the form of the methobromide (XX), was obtained from "Demerol nitrile" by essentially the same procedure used in the preparation of 3-piperidones. The water-soluble methobromide (XX) melted without the evolution of methyl bromide. When heated under reduced pressure, this compound sublimed unchanged. Catalytic reduction of XX yielded the corresponding alcohol. The latter substance was converted into the acetate by treatment with acetic anhydride and pyridine.



"Demerol nitrile"

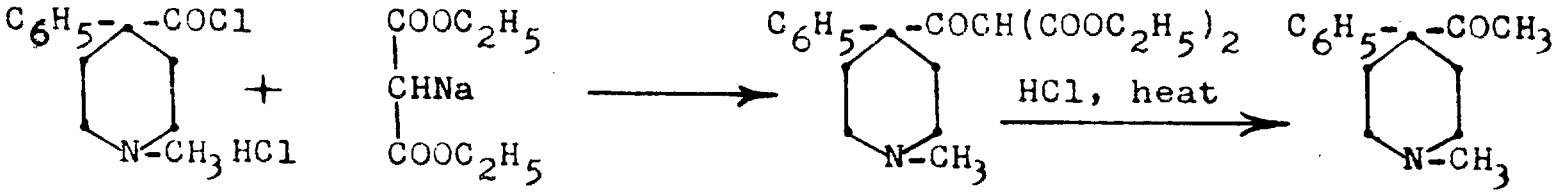
XVIII



XIX

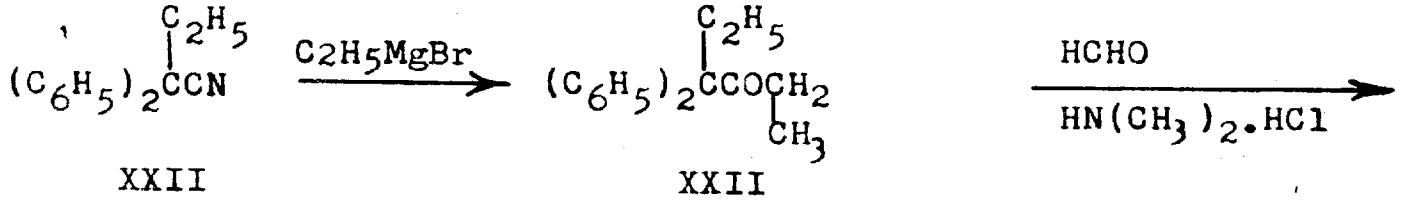
XX

A recent patent[65] described the preparation of the free base of XVIII by another method.



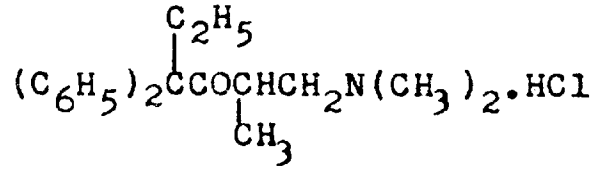
XVIII (free base

We discovered that an isomer of Isoamidone (XXIII) could be prepared readily by the use of the Mannich reaction.



XXII

XXII



XXIII

No difficulty was encountered in the preparation of the nitrile (XXI) and the ketone (XXII). The Mannich product was obtained in good yield when formalin and acetic acid were used instead of paraformaldehyde and ethyl alcohol. By interaction of the nitrile (XXI) with methylmagnesium iodide, instead of ethylmagnesium bromide, the corresponding methyl ketone (XXIV) was formed. A Mannich reaction on this ketone yielded 1-dimethylamino-4,4-diphenyl-3-hexanone hydrochloride, a lower homolog of XXIII. The ethyl ketone (XXII) did not yield a 4-nitrophenyl- or 2,4-dinitrophenylhydrazone, however, from the methyl ketone (XXIV) the latter derivative was obtained without difficulty. Compound XXIII could not be reduced catalytically by the use of platinum oxide, however, the free base of this compound was partially converted into the alcohol by treatment with lithium-aluminum hydride. Prolonged heating with this reagent probably would have resulted in complete reduction.

All of the 3-piperidone hydrochlorides, except JK-119, listed in Table V and JK-100 and JK-116, mentioned in Table IV, were tested for analgesic activity. Most of these products proved to be toxic, and none of them exhibited promising analgesic activity. The alcohols obtained from compounds JK-101, JK-102, and their acetyl derivatives, as well as the alcohol prepared from cyclic Amidone, proved to be inactive.

EXPERIMENTAL PART

The compounds described in this section are discussed in the following order:

I Preparation of Nitriles (Table I)

II Preparation of Ketones (Table II)

III Preparation of Bromoketones (Table III)

IV Preparation of Methobromides of Substituted 3-Piperidones (Cyclic Amidone and cyclic Isoamidone) (Table IV)

V Preparation of Hydrochlorides of Substituted 3-Piperidones (Cyclic Amidone and cyclic Isoamidone) (Table V)

VI Conversion of 1-Methyl-4,4-diphenyl-3-piperidone Hydrochloride into 1-Methyl-4,4-diphenyl-3-piperidone Methobromide

Conversion of 1-Methyl-4,4-diphenyl-3-piperidone Methobromide into 3,3-Diphenyl-5-dimethylamino-2-pentanone Hydrobromide

VII Preparation of 3-Piperidinols and Derivatives

VIII Preparation of Acids and Their Cyclization to 2-Pyrrolidones

IX Preparation of Substituted Quinuclidines

X Preparation of an Isomer and Lower Homolog of Isoamidone

I. Preparation of Nitriles (Table I)

2-Thienylcyclohexylacetonitrile.
2,2-Diphenyl-4-dimethylaminobutanenitrile.
2-Phenyl-2-methyl-4-dimethylaminobutanenitrile.
2-Phenyl-2-(2-cyclohexylethyl)-4-dimethylaminobutanenitrile.
2-(2-Thienyl)-2-cyclohexyl-4-dimethylaminobutanenitrile.

2-Thienylcyclohexylacetonitrile.- A suspension of 40.0 g. (1.02 moles) of finely-divided sodamide in 250 ml. of dry toluene was poured into a 2-liter, 3-necked flask equipped with a Hershberg stirrer, a dropping funnel and a condenser fitted with a soda-lime tube. The flask was immersed in an ice-salt-bath, and the mixture stirred during the dropwise addition (forty-five minutes) of a solution prepared from 123.0 g. (1.0 mole) of 2-thienylacetonitrile,[134] 163 g. (1.0 mole) of cyclohexyl bromide and 500 ml. of benzene. After two hours, the bath was removed; the nearly black mixture was stirred at room temperature for three hours, and then refluxed two hours. Water (250 ml.) was added to the cooled mixture, the aqueous layer was separated, and extracted with toluene. The organic extracts were combined, and washed with water; the solvent was removed under reduced pressure, and the residue then distilled rapidly at 125-135° (1-2 mm.). After redistillation, the product weighed 97.8 g. (47.7%); b. p. 129-132° (1-2 mm.). A considerable quantity of tar remained in the flask after the first distillation.

Anal. Calcd. for $C_{12}H_{15}NS$: N, 6.82. Found: N, 6.76.

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(134) Blicke and Leonard, J. Am. Chem. Soc., 68, 1934 (1946).

2,2-Diphenyl-4-dimethylaminobutanenitrile.- To the apparatus described above was added a suspension of 43.0 g. (1.1 moles) of finely-divided sodamide in 300 ml. of dry toluene. The mixture was immersed in an ice-salt-bath, and stirred during the dropwise addition (one hour) of 193.0 g. (1.0 mole) of diphenylacetonitrile* dissolved in 300 ml. of toluene. After the mixture had been stirred for an additional one and one-half hours, a toluene solution of 2-dimethylaminoethyl chloride was added during a fifteen-minute period. The solution of the basic alkyl chloride was prepared by addition of 100 ml. of ammonia water to 158.4 g. (1.1 moles) of 2-dimethylaminoethyl chloride hydrochloride(135) suspended in 50 ml. of cold water; the chloride was then extracted with toluene, and the solution dried with magnesium sulfate. The ice-salt-bath was replaced by a water-bath (20°). The mixture was stirred for four hours, and then refluxed for five hours. Water (300 ml.) was added to the cooled mixture; the aqueous layer was separated, and extracted with toluene. The toluene extracts were combined and washed with water. After removal of the solvent under reduced pressure, the residue was fractionated; yield, 242.3 g. (92%); b. p. 152-155° (1-2 mm.).**

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* Obtained from Winthrop-Stearns, Incorporated as a light brown solid which melted at 69-72°. After distillation under reduced pressure, the colorless distillate melted at 72-75°.

(135) Slotta and Behnish, Ber., 68, 754 (1935). This compound is now commercially available from the Michigan Chemical Corporation, Saint Louis, Michigan.

** Dupré et al. (ref. 132) obtained this compound in 70% yield; b.p. 150-152° (0.8 mm.). Their hydrochloride melted at 200-201°.

The hydrochloride was obtained by passing hydrogen chloride into an ether solution of the basic nitrile; after crystallization from isopropyl alcohol, the salt melted at 198-199°.

Anal. Calcd. for $C_{18}H_{21}ClN_2$: Cl^-, 11.79. N, 9.31.
Found: Cl^-, 11.80. N, 9.27.

2-Phenyl-2-methyl-4-dimethylaminobutanenitrile.- This compound was prepared, according to the procedure described above, by the interaction of 11.7 g. (0.30 mole) of finely-divided sodamide, 47.0 g. (0.25 mole) of 2-phenyl-4-dimethylaminobutanenitrile[136] and 42.6 g. (0.30 mole) of methyl iodide, each reactant suspended or dissolved in 75 ml. of toluene. The product weighed 33.3 g. (66%); b. p. 100-101° (1-2 mm.). The hydrochloride of this material, after crystallization from absolute ethanol, melted at 225-226°.

Anal. Calcd. for $C_{13}H_{19}ClN_2$: Cl^-, 14.85. N, 11.74.
Found: Cl^-, 14.86. N, 11.79.

2-Phenyl-2-(2-cyclohexylethyl)-4-dimethylaminobutanenitrile.- This nitrile was obtained by interaction of 13.7 g. (0.35 mole) of finely-divided sodamide, 56.4 g. (0.30 mole) of 2-phenyl-4-dimethylaminobutanenitrile[136] and 66.8 g. (0.35 mole) of freshly distilled 2-cyclohexylethyl bromide, each reactant suspended or dissolved in 100 ml. of toluene. The product weighed 72.0 g. (80.7%); b. p. 180-182° (1-2 mm.). The hydrochloride,

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(136) Kwartler and Lucas, J. Am. Chem. Soc., 68, 2395 (1946). The experimental details for the preparation of this compound are reported by Zambito, ref. 124.

after crystallization from isopropyl alcohol, melted at 236-237°.

Anal. Calcd. for $C_{20}H_{31}ClN_2$: Cl^-, 10.59. N, 8.37.

Cl^-, 10.63. N, 8.37.

2-(2-Thienyl)-2-cyclohexyl-4-dimethylaminobutanenitrile.- By interaction of 15.2 g. (0.39 mole) of finely-divided sodamide, 66.3 g. (0.323 mole) of 2-thienylcyclohexylacetonitrile and 2-dimethylaminoethyl chloride (obtained by liberation of the free base from 50.5 g. (0.35 mole) of the hydrochloride), each reactant dissolved or suspended in 100 ml. of toluene, we obtained 80.8 g. (90.5%) of the nitrile; b. p. 145-148° (1-2 mm.).* The hydrochloride of this base, after crystallization from isopropyl alcohol, melted at 202-203°.

TABLE I

NITRILES, $RR'C(CN)CH_2CH_2N(CH_3)_2$

Cpd.	R	R'	B. p., °C. (1-2 mm.).	Yield, %	Hydrochloride M. p., °C.
1.	C_6H_5	C_6H_5	152-155	92	198-199
2.	C_6H_5	CH_3	100-101	66	225-226
3.	C_6H_5	$C_6H_{11}CH_2CH_2$	180-182	81	236-237
4.(a)	C_4H_3S(b)	C_6H_{11}	145-148	90.5	202-203

(a) Previously prepared by Zambito by another method (ref. 124).

(b) C_4H_3S = 2-Thienyl.

* Zambito (ref. 124) obtained this compound in 47% yield by the interaction of cyclohexyl bromide and 2-(2-thienyl)-4-dimethylaminobutanenitrile, in the presence of sodamide. The hydrochloride of this material melted at 201-203°.

II. Preparation of Ketones (Table II)

3,3-Diphenyl-5-dimethylamino-2-pentanone hydrobromide.
3-Phenyl-3-methyl-5-dimethylamino-2-pentanone hydrobromide.
3-Phenyl-3-n-hexyl-5-dimethylamino-2-pentanone hydrobromide.
3-Phenyl-3-(2-cyclohexylethyl)-5-dimethylamino-2-pentanone hydrobromide.
3-Phenyl-3-cyclohexyl-5-dimethylamino-2-pentanone hydrobromide.
4-(2-Thienyl)-4-cyclohexyl-6-dimethylamino-3-hexanone hydrobromide.
4,4-Diphenyl-6-dimethylamino-3-hexanone hydrobromide.
1,4,4-Triphenyl-6-dimethylamino-3-hexanone.
3-Phenyl-5-dimethylamino-2-pentanone hydrobromide.

3,3-Diphenyl-5-dimethylamino-2-pentanone Hydrobromide.- To a solution of methylmagnesium iodide, prepared from 28.0 g. (1.15 gram atoms) of magnesium turnings, 75 ml. (1.20 moles) of methyl iodide and 300 ml. of ether in a 2-liter flask, was added, in one portion, a solution of 96.0 g. (0.364 mole) of 2,2-diphenyl-4-dimethylaminobutanenitrile and 500 ml. of dry benzene. The mixture was refluxed for forty-eight hours; a precipitate began to separate after the first hour. The cold mixture was poured cautiously into 700 ml. of ice-cold, concentrated hydrochloric acid; the organic solvents were distilled from the mixture, and the residue then refluxed for twelve hours. The mixture was cooled, and the aqueous layer decanted from the red oil. The latter was refluxed with 300 ml. of concentrated hydrochloric acid for nine hours; an additional 200 ml. of hydrochloric acid was added, and the mixture heated for another nine hours. The cooled mixture was made alkaline with strong sodium hydroxide

solution, and then extracted with ether; the ether extracts were combined and dried over magnesium sulfate, filtered, and hydrogen bromide passed into the filtrate. The hydrobromide, after trituration with fresh ether and then with isopropyl alcohol, weighed 118.3 g. (89.5%); m.p. 171-173°. The melting point of this material was not changed after crystallization from isopropyl alcohol.

Anal. Calcd. for $C_{19}H_{24}BrNO$: Br^-, 22.06. N, 3.87.

Found: Br^-, 22.17. N, 4.05.

The free base of this compound distilled at 156-158° (1-2 mm.).*

3-Phenyl-3-methyl-5-dimethylamino-2-pentanone Hydrobromide.- A solution of 28.8 g. (0.143 mole) of 2-phenyl-2-methyl-4-dimethylaminobutanenitrile in 200 ml. of benzene was added to methylmagnesium iodide, prepared from 14.5 g. (0.60 gram atom) of magnesium turnings, 37.5 ml. (0.60 mole) of methyl iodide and 150 ml. of dry ether. The mixture was refluxed for forty-eight hours; a precipitate began to separate after two hours. The reaction mixture was decomposed with 350 ml. of cold concentrated hydrochloric acid, and the basic ketone was isolated in the manner described in the above experiment. The crude ketone was distilled prior to conversion into the hydrobromide; yield, 20.1 g. (64.5%); b. p. 95-98° (1-2 mm.). The hydrobromide melted at 157-163°. The sample employed for analysis, after

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* Dupré et al. (ref. 132) reported a 83% yield. They characterized this compound as the hydrochloride, m.p. 186-187.5°.

crystallization from absolute ethanol, melted at 163-165°.

Anal. Calcd. for $C_{14}H_{22}BrNO$: Br^-, 26.62. N, 4.67.

Found: Br^-, 26.69. N, 4.67.

3-Phenyl-3-n-hexyl-5-dimethylamino-2-pentanone Hydrobromide.- This compound was prepared in 70% yield, in a manner similar to that described above, by the interaction of 29.0 g. (0.107 mole) of 2-phenyl-2-n-hexyl-4-dimethylaminobutanenitrile* in benzene with an ether solution of approximately 0.4 mole of methylmagnesium iodide. In this case, the crude ketone was not treated with fresh concentrated hydrochloric acid. The free base distilled at 140-143° (1-2 mm.); the crude hydrobromide melted at 125-127°. After crystallization from isopropyl alcohol, the salt melted at 129-130°.

Anal. Calcd. for $C_{19}H_{32}BrNO$: Br^-, 21.58. N, 3.78.

Found: Br^-, 21.67. N, 3.83.

3-Phenyl-3-(2-cyclohexylethyl)-5-dimethylamino-2-pentanone Hydrobromide.- To the Grignard reagent, prepared from 24.3 g. (1.0 gram atom) of magnesium turnings, 62.5 ml. (1.0 mole) of methyl iodide and 200 ml. of ether, was added a solution of 68.5 g. (0.23 mole) of 2-phenyl-2-(2-cyclohexylethyl)-4-dimethylaminobutanenitrile in 350 ml. of benzene. The mixture, from which a gray precipitate separated, was refluxed for twenty-four hours. The cold mixture was poured cautiously into 600 ml. of ice-cold, concentrated hydrochloric acid; the organic solvents were distilled from the mixture, and the residue then refluxed for

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* Zambito, ref. 124.

fourteen hours. The cooled mixture was made alkaline with strong sodium hydroxide solution, and then extracted with ether. The ether extracts were combined, dried over magnesium sulfate, filtered, and the ether evaporated from the filtrate. The residue distilled as a pale yellow, thick oil; b. p. 169-172° (1-2 mm.); yield, 51.0 g. (70.3%). The basic ketone was dissolved in dry ether, and treated with hydrogen bromide. The salt melted at 176-177°. An analytical sample was prepared by crystallization from isopropyl alcohol; m.p. 178-179°.

Anal. Calcd. for $C_{21}H_{34}BrNO$: Br^-, 20.16. N, 3.53.

Found: Br^-, 20.14. N, 3.60.

3-Phenyl-3-cyclohexyl-5-dimethylamino-3-pentanone Hydrobromide.- A solution of 2-phenyl-2-cyclohexyl-4-dimethylaminobutanenitrile* (54.0 g., 0.20 mole) in 350 ml. of benzene was refluxed for forty-eight hours with methylmagnesium iodide, prepared from 19.0 g. (0.78 gram atom) of magnesium turnings, 50 ml. (0.80 mole) of methyl iodide and 200 ml. of ether. The mixture was cooled and poured into 400 ml. of cold concentrated hydrochloric acid. The basic ketone hydrobromide was isolated in the manner described in the above experiment; yield, 50.9 g. (69.0%); m.p. 223-224°. The analytical sample was prepared by crystallization from isopropyl alcohol; m. p. 226-228°.

Anal. Calcd. for $C_{19}H_{30}BrNO$: Br^-, 21.70. N, 3.80.

Found: Br^-, 21.53. N, 3.90.

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* Zambito, ref. 124.

4-(2-Thienyl)-4-cyclohexyl-6-dimethylamino-3-hexanone Hydrobromide.- A mixture of 55.2 g. (0.20 mole) of 2-(2-thienyl)-2-cyclohexyl-4-dimethylaminobutanenitrile, dissolved in benzene, and an ether solution of approximately 0.80 mole of ethylmagnesium bromide was refluxed for thirty-one hours. The product was isolated in the manner described above; yield, 54.5 g. (88.7%); b. p. 151-153° (1-2 mm.). The hydrobromide, after crystallization from isopropyl alcohol, melted at 186-187°.*

Anal. Calcd. for $C_{18}H_{30}BrNOS$: Br^-, 20.58. N, 3.61.
Found: Br^-, 20.61. N, 3.64.

4,4-Diphenyl-6-dimethylamino-3-hexanone Hydrobromide.- This compound was prepared in 95% yield by interaction of 53.0 g. (0.20 mole) of 2,2-diphenyl-4-dimethylaminobutanenitrile, dissolved in benzene, and an ether solution of approximately 0.80 mole of ethylmagnesium bromide for a period of thirty-six hours. The hydrobromide, subsequent to several crystallizations from isopropyl alcohol, melted at 142-143°.**

Anal. Calcd. for $C_{20}H_{26}BrNO$: Br^-, 21.24. N, 3.72.
Found: Br^-, 21.32. N, 3.83.

1,4,4-Triphenyl-6-dimethylamino-3-hexanone.- To the Grignard reagent, prepared from 9.7 g. (0.40 gram atom) of magnesium turnings, 26.4 g. (0.40 mole) of 2-phenylethyl bromide and 200 ml. of ether, was added 26.4 g. (0.10 mole) of 2,2-diphenyl-4-dimethylaminobutanenitrile, dissolved in 300 ml. of benzene. After the

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* Zambito (ref. 124) reported the hydrochloride.

** Dupré et al. (ref. 132) obtained a 78% yield of the free base; the hydrochloride melted at 173.5-175°.

mixture had been refluxed for forty-eight hours; the basic ketone was isolated in the usual manner. The ketone distilled as a pale yellow, viscous oil; b. p. 206-208° (1-2 mm.); yield, 26.0 g. (70%).

Anal. Calcd. for $C_{26}H_{29}NO$: N, 3.77.

Found: N, 3.78.

The hydrobromide separated from an ether solution as an oil, and could not be crystallized. The hydrochloride, after crystallization from water, was isolated as a monohydrate; m.p. 109-113°.

Anal. Calcd. for $C_{26}H_{30}ClNO.H_2O$: Cl^-, 8.32.

Found: Cl^-, 8.34.

It was heated in an oven for several hours in order to remove the water of crystallization; m. p., about 60°.

Anal. Calcd. for $C_{26}H_{30}ClNO$: Cl^-, 8.85.

Found: Cl^-, 8.70.

To an ether solution of 1.0 g. of the free base was added 1.0 ml. of methyl iodide; the precipitated methiodide, after it had been washed with ether, melted at 179-181° (previous softening). The product crystallized from water as colorless, plate-like crystals; m. p. 187-188°. This material softened at 94°, which indicated presence of water of crystallization.

3-Phenyl-5-dimethylamino-2-pentanone Hydrobromide.- This ketone was prepared in 49% yield by the interaction of 2-phenyl-4-dimethylaminobutanenitrile and four equivalents of methylmagnesium iodide. The free base distilled at 82-85° (1-2 mm.);

the hydrobromide, after crystallization from isopropyl alcohol, melted at 123-124°.

Anal. Calcd. for $C_{13}H_{20}BrNO$: Br^-, 27.92.

Found: Br^-, 27.88.

TABLE II

KETONES, $RR'C(CH_2CH_2NMe_2)COR''$

Cpd.	R	R'	R''	B. p., °C. (1-2 mm.)	Yield %	Hydrobromide M. p., °C.
1.(a)	C_6H_5	C_6H_5	CH_3	156-158	89.5	171-173
2.	C_6H_5	CH_3	CH_3	95-98	64.5	163-165
3.	C_6H_5	C_6H_{13}	CH_3	140-143	70	129-130
4.	C_6H_5	$C_6H_{11}CH_2CH_2$	CH_3	169-172	70	178-179
5.	C_6H_5	C_6H_{11}	CH_3	(b)	69	226-228
6.(c)	C_4H_3S	C_6H_{11}	C_2H_5	151-153	89	186-187
7.	C_6H_5	C_6H_5	C_2H_5	(b)	95	142-143
8.	C_6H_5	C_6H_5	$CH_2CH_2C_6H_5$	206-208	70	(d)

(a) The hydrochloride was reported by Dupré et al., ref. 132.
(b) The ketone was not distilled.
(c) The hydrochloride was reported by Zambito, ref. 124.
(d) The base did not yield a crystalline hydrobromide. It was characterized as the hydrochloride, see experimental part.

III. Preparation of Bromoketones (Table III)

1-Bromo-3,3-diphenyl-5-dimethylamino-2-pentanone hydrobromide.
1,1-Dibromo-3,3-diphenyl-5-dimethylamino-2-pentanone hydrobromide.
1-Bromo-3-phenyl-3-methyl-5-dimethylamino-2-pentanone hydrobromide.
1-Bromo-3-phenyl-3-n-hexyl-5-dimethylamino-2-pentanone hydrobromide.
1-Bromo-3-phenyl-3-(2-cyclohexylethyl)-5-dimethylamino-2-pentanone hydrobromide.
1-Bromo-3-phenyl-3-cyclohexyl-5-dimethylamino-2-pentanone hydrobromide.
2-Bromo-4-(5-bromo-2-thienyl)-4-cyclohexyl-6-dimethylamino-3-hexanone hydrobromide.
2-Bromo-4,4-diphenyl-6-dimethylamino-3-hexanone hydrobromide.
2-Bromo-1,4,4-triphenyl-6-dimethylamino-3-hexanone hydrobromide.
2-Bromo-4,4-diphenyl-6-dimethylamino-3-heptanone hydrobromide. (Brominated Amidone).
2-Bromo-4,4-diphenyl-5-methyl-6-dimethylamino-3-hexanone hydrobromide. (Brominated Isoamidone)
1-Bromo-3-phenyl-5-dimethylamino-2-pentanone hydrobromide (?)

1-Bromo-3,3-diphenyl-5-dimethylamino-2-pentanone Hydrobromide.- A mixture of 25.0 g. (0.069 mole) of 3,3-diphenyl-5-dimethylamino-2-pentanone hydrobromide and 70 ml. of acetic acid was refluxed, and to the solution was added, dropwise, during a fifteen minute period, a mixture of 11.05 g. (0.069 mole) of bromine and 30 ml. of glacial acetic acid. After the material had been refluxed for an additional fifteen minutes, about half of the solvent was distilled, and 200 ml. of ether was added to the cooled residue. The product, which first separated as an oil, crystallized after some time. The crude product was crystallized from 30 ml. of isopropyl alcohol;

yield, 27.0 g. (89%); m. p. 158-159° (dec.).

Anal. Calcd. for $C_{19}H_{23}Br_2NO$: Br, 36.23. N, 3.17.

Found: Br, 36.48. N, 3.13.

1,1-Dibromo-3,3-diphenyl-5-dimethylamino-2-pentanone Hydrobromide.- A mixture of 14.5 g. (0.04 mole) of 3,3-diphenyl-5-dimethylamino-2-pentanone hydrobromide and 40 ml. of glacial acetic acid was treated with 12.8 g. (0.08 mole) of bromine, dissolved in 25 ml. of glacial acetic acid, in the manner described above. The reaction mixture was cooled, and diluted with ether. The precipitate, after crystallization from 15 ml. of glacial acetic acid, weighed 17.4 g. (83%); m. p. 188-189° (dec.). An analytical sample was prepared by recrystallization from glacial acetic acid; m. p. 193-194° (dec.).

Anal. Calcd. for $C_{19}H_{22}Br_3NO$: Br, 46.10. N, 2.69.

Found: Br, 45.89. N, 2.72.

1-Bromo-3-phenyl-3-methyl-5-dimethylamino-2-pentanone Hydrobromide.- To a hot solution of 5.96 g. (0.02 mole) of 3-phenyl-3-methyl-5-dimethylamino-2-pentanone hydrobromide in 15 ml. of glacial acetic acid was added, over a period of ten minutes, a mixture of 3.18 g. (0.02 mole) of bromine and 10 ml. of glacial acetic acid. After the solution had been refluxed for an additional twenty minutes, it was cooled and diluted with about 150 ml. of ether. The product weighed 7.16 g. (95%); 141-143° (dec.). This material was used without further purification in a later reaction. An analytical sample, after two

crystallizations from isopropyl alcohol, melted at 151-152° (dec.).

Anal. Calcd. for $C_{14}H_{21}Br_2NO$: Br, 42.15. N, 3.70.
Found: Br, 42.58. N, 3.70.

1-Bromo-3-phenyl-3-n-hexyl-5-dimethylamino-2-pentanone Hydrobromide.- 3-Phenyl-3-n-hexyl-5-dimethylamino-2-pentanone hydrobromide (17.81 g., 0.0482 mole) and 100 ml. of carbon tetrachloride were heated to reflux. To this solution was added, over a period of thirty minutes, a mixture of 7.70 g. (0.0482 mole) of bromine and 50 ml. of carbon tetrachloride. After the material had been refluxed for an additional fifteen minutes, the solution was cooled. The oily surface layer slowly turned into flat, plate-like crystals. The product was filtered, washed with carbon tetrachloride, and then with ether. After crystallization from isopropyl alcohol, the bromoketone weighed 17.2 g. (80%); m. p. 134-135°. The sample employed for analysis was obtained by recrystallization from isopropyl alcohol; m. p. 138-139°.

Anal. Calcd. for $C_{19}H_{31}Br_2NO$: Br, 35.57. N, 3.12.
Found: Br, 35.12. N, 3.12.

1-Bromo-3-phenyl-3-(2-cyclohexylethyl)-5-dimethylamino-2-pentanone Hydrobromide.- A mixture of 19.8 g. (0.05 mole) of 3-phenyl-3-(2-cyclohexylethyl)-5-dimethylamino-2-pentanone hydrobromide and 25 ml. of glacial acetic acid was refluxed, and then treated with 8.0 g. (0.05 mole) of bromine, dissolved

in 25 ml. of glacial acetic acid. The reaction mixture was cooled, and diluted with ether. The crystalline precipitate weighed 19.9 g. (83.8%); m. p. 154-155° (dec.). The analytical sample, after crystallization from isopropyl alcohol, melted at 158-159° (dec.).

Anal. Calcd. for $C_{21}H_{33}Br_2NO$: Br, 33.63. N, 2.95.
Found: Br, 33.67. N, 2.92.

1-Bromo-3-phenyl-3-cyclohexyl-5-dimethylamino-2-pentanone Hydrobromide.- A mixture of 15.0 g. (0.0407 mole) of 3-phenyl-3-cyclohexyl-5-dimethylamino-2-pentanone hydrobromide and 80 ml. of glacial acetic acid was refluxed, and to the solution was added, dropwise, a mixture of 6.51 g. (0.0407 mole) of bromine and 20 ml. of glacial acetic acid. The product crystallized from the cooled reaction mixture; yield, 15.7 g. (86.3%); m. p. 182-184° (dec.). An analytical sample, after crystallization from glacial acetic acid, melted at 182-184° (dec.).

Anal. Calcd. for $C_{19}H_{29}Br_2NO$: Br, 35.74. N, 3.13.
Found: Br, 35.74. N, 3.15.

2-Bromo-4-(5-bromo-2-thienyl)-4-cyclohexyl-6-dimethylamino-3-hexanone Hydrobromide.- 4-(2-Thienyl)-4-cyclohexyl-6-dimethylamino-3-hexanone hydrobromide (15.5 g., 0.04 mole), dissolved in 20 ml. of hot glacial acetic acid, was treated with a mixture of 12.8 g. (0.08 mole) of bromine and 25 ml. of glacial acetic acid. Dilution of the reaction mixture with ether yielded a precipitate; weight, 21.5 g. (98.6%); m. p. 179-180° (dec.). The analytical sample was prepared by

crystallization from isopropyl alcohol; m. p. 179-180° (dec.).

Anal. Calcd. for $C_{18}H_{28}Br_3NOS$: Br, 43.89. N, 2.57.

Found: Br, 43.41. N, 2.58.

Monobromination of the above starting material yielded a mixture of 2-bromo-4-(2-thienyl)-4-cyclohexyl-6-dimethylamino-3-hexanone hydrobromide (about 85%), 4-(5-bromo-2-thienyl)-4-cyclohexyl-6-dimethylamino-3-hexanone hydrobromide, the above dibromo compound and unreacted starting material.

2-Bromo-4,4-diphenyl-6-dimethylamino-3-hexanone Hydrobromide.- A mixture of 10.0 g. (0.0266 mole) of 4,4-diphenyl-6-dimethylamino-3-hexanone hydrobromide and 40 ml. of glacial acetic acid was heated, and then treated with 4.25 g. (0.0266 mole) of bromine, dissolved in 15 ml. of acetic acid. The product was isolated by dilution of the reaction mixture with ether; yield, 11.2 g. (92.5%); m. p. 173-174° (dec.). The melting point was not changed by crystallization from isopropyl alcohol.

Anal. Calcd. for $C_{20}H_{25}Br_2NO$: Br, 35.11. N, 3.08.

Found: Br, 35.18. N, 3.12.

2-Bromo-1,4,4-triphenyl-6-dimethylamino-3-hexanone Hydrobromide.- Hydrogen bromide was passed into a mixture of 4.43 g. (0.0119 mole) of 1,4,4-triphenyl-6-dimethylamino-3-hexanone and 20 ml. of glacial acetic acid. The red solution of the hydrobromide salt was heated to reflux, and treated with 1.91 g. (0.0119 mole) of bromine, dissolved in 5 ml. of glacial acetic acid. Dilution of the reaction mixture yielded an oil which could not be crystallized.

2-Bromo-4,4-diphenyl-6-dimethylamino-3-heptanone Hydrobromide. (Brominated Amidone).- A mixture of 38.85 g. (0.0965 mole) of 4,4-diphenyl-6-dimethylamino-3-heptanone hydrobromide (Amidone hydrobromide)* and 60 ml. of glacial acetic acid was refluxed, and to the solution was added, dropwise, during a twenty-four minute period, a mixture of 16.0 g. (0.10 mole) of bromine and 40 ml. of glacial acetic acid. After the material had been refluxed for an additional fifteen minutes, about half of the solvent was distilled, and 50 ml. of ether was added to the cooled residue. The precipitate weighed 45.27 g. (96.7%); m. p. 185° (dec.). An analytical sample, after crystallization from glacial acetic acid, melted at 190° (dec.).

Anal. Calcd. for $C_{21}H_{27}Br_2NO$: Br, 34.06. N, 2.99.

Found: Br, 34.13. N, 2.99.

2-Bromo-4,4-diphenyl-5-methyl-6-dimethylamino-3-hexanone Hydrobromide. (Brominated Isoamidone).- This compound was obtained in 97% yield by the bromination of 4,4-diphenyl-5-methyl-6-dimethylamino-3-hexanone hydrobromide (Isoamidone hydrobromide), according to the procedure employed in the above experiment. The product separated with one molecular equivalent of acetic acid. An analytical sample was prepared

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* The free base was prepared according to the procedure of Schultz et al. (ref. 90). The hydrobromide melted at 224-225°. Thorp et al. (ref. 113) reported 224°.

by crystallization from glacial acetic acid; m. p. 123-125° (dec.).

Anal. Calcd. for $C_{21}H_{27}Br_2NO.CH_3COOH$: Br, 30.20. N, 2.65.
Found: Br, 30.56. N, 2.65.

In order to remove the solvent from the above sample, it was dissolved in chloroform, and then precipitated with ether; m. p. 195° (dec.).

Anal. Calcd. for $C_{21}H_{27}Br_2NO$: Br, 34.06. N, 2.99.
Found: Br, 34.19. N, 2.99.

1-Bromo-3-phenyl-5-dimethylamino-2-pentanone Hydrobromide (?).- This bromoketone was isolated in 57% yield by the bromination of 3-phenyl-5-dimethylamino-2-pentanone, with the use of carbon tetrachloride as a solvent. The product was purified by crystallization from isopropyl alcohol; m. p. 144-145°.

Anal. Calcd. for $C_{13}H_{19}Br_2NO$: Br, 43.77. N, 3.84.
Found: Br, 43.82. N, 3.84.

The position of the bromine atom was not established; it is possible that 3-bromo-3-phenyl-5-dimethylamino-2-pentanone hydrobromide was formed.

TABLE III

BROMOKETONES, $RR'C(CH_2CH_2NMe_2)COR''$

Cpd.	R	R'	R''	Hydrobromide[a] M. p., °C.	Yield, %
1.	C_6H_5	C_6H_5	CH_2Br	158-159	89
2.	C_6H_5	CH_3	CH_2Br	151-152	95
3.	C_6H_5	C_6H_{13}	CH_2Br	138-139	80
4.	C_6H_5	$C_6H_{11}CH_2CH_2$	CH_2Br	158-159	84
5.	C_6H_5	C_6H_{11}	CH_2Br	182-184	86
6.	C_4H_2BrS[b]	C_6H_{11}	$CHBrCH_3$	179-180	99
7.	C_6H_5	C_6H_5	$CHBrCH_3$	173-174	92.5
8.[c]	C_6H_5	C_6H_5	$CHBrCH_2C_6H_5$		
*	*	*	*	*	*
9.	2-Bromo-4,4-diphenyl-6-dimethylamino-3-heptanone hydrobromide (Brominated Amidone).			190	97
10.	2-Bromo-4,4-diphenyl-5-methyl-6-dimethylamino-3-hexanone hydrobromide (Brominated Isoamidone).			195	97

(a) All of the hydrobromides, except 3, melted with decomposition.
(b) C_4H_2BrS = 5-Bromo-2-thienyl.
(c) This hydrobromide could not be crystallized.

IV. Preparation of Methobromides of Substituted 3-Piperidones (Cyclic Amidone and cyclic Isoamidone) (Table IV)

1-Methyl-4,4-diphenyl-3-piperidone methobromide.
1,4-Dimethyl-4-phenyl-3-piperidone methobromide.
1-Methyl-4-phenyl-4-n-hexyl-3-piperidone methobromide.
1-Methyl-4-phenyl-4-(2-cyclohexylethyl)-3-piperidone methobromide.
1-Methyl-4-phenyl-4-cyclohexyl-3-piperidone methobromide.
1,2-Dimethyl-4-(5-bromo-2-thienyl)-4-cyclohexyl-3-piperidone methobromide.
1,2-Dimethyl-4,4-diphenyl-3-piperidone methobromide.
1-Methyl-2-benzyl-4,4-diphenyl-3-piperidone methobromide.
1,2,6-Trimethyl-4,4-diphenyl-3-piperidone methobromide. (Cyclic Amidone methobromide).
1,2,5-Trimethyl-4,4-diphenyl-3-piperidone methobromide. (Cyclic Isoamidone methobromide).

1-Methyl-4,4-diphenyl-3-piperidone Methobromide.- To a cooled, stirred suspension of 26.4 g. (0.06 mole) of 1-bromo-3,3-diphenyl-5-dimethylamino-2-pentanone hydrobromide in 120 ml. of water was added 9 ml. of concentrated ammonia water. A heavy precipitate formed immediately. After four hours, the product was filtered, and washed with a small quantity of cold water. This material was purified by crystallization from absolute ethanol; m. p. 231-233° (dec.); 82.5% yield.

Anal. Calcd. for $C_{19}H_{22}BrNO$: Br^-, 22.18. N, 3.89.
Found: Br^-, 21.97. N, 3.83.

1,4-Dimethyl-4-phenyl-3-piperidone Methobromide.- To a mixture of 15.2 g. (0.04 mole) of 1-bromo-3-phenyl-3-methyl-5-dimethylamino-2-pentanone hydrobromide and 15 ml. of water was added 5 ml. of concentrated ammonia water. After several

hours, the solution was evaporated to dryness on a steam-bath. The light brown solid was pulverized and dried. It was refluxed with about 75 ml. of isopropyl alcohol, the insoluble ammonium bromide was filtered, and the methobromide crystallized from the filtrate. The product was filtered, and then recrystallized from isopropyl alcohol; yield, 8.0 g. (80.3%); m. p. 207-208° (dec.).

Anal. Calcd. for $C_{14}H_{20}BrNO$: Br^-, 26.80. N, 4.70.
Found: Br^-, 26.82. N, 4.75.

1-Methyl-4-phenyl-4-n-hexyl-3-piperidone Methobromide.- A mixture of 8.75 g. (0.0195 mole) of 1-bromo-3-phenyl-3-n-hexyl-5-dimethylamino-2-pentanone hydrobromide and 9 ml. of water was treated with 3 ml. of concentrated ammonia water. The product was isolated according to the procedure described in the above experiment; yield, 6.2 g. (85%); m. p. 163-165° (dec.). An analytical sample, after crystallization from isopropyl alcohol, melted at 165-167° (dec.).

Anal. Calcd. for $C_{19}H_{30}BrNO$: Br^-, 21.70. N, 3.80.
Found: Br^-, 21.70. N, 3.84.

1-Methyl-4-phenyl-4-(2-cyclohexylethyl)-3-piperidone Methobromide.- To a suspension of 18.75 g. (0.0394 mole) of 1-bromo-3-phenyl-3-(2-cyclohexylethyl)-5-dimethylamino-2-pentanone hydrobromide in 20 ml. of water was added 5 ml. of concentrated ammonia water. The methobromide was isolated in the manner described above; yield, 12.5 g. (80.5%); m. p. 175-178° (dec.).

The analytical sample was prepared by recrystallization from isopropyl alcohol; m. p. 185-187° (dec.).

Anal. Calcd. for $C_{21}H_{32}BrNO$: Br^-, 20.26. N, 3.55.
Found: Br^-, 20.19. N, 3.52.

1-Methyl-4-phenyl-4-cyclohexyl-3-piperidone Methobromide.- To a stirred suspension of 17.56 g. (0.0392 mole) of 1-bromo-3-phenyl-3-cyclohexyl-5-dimethylamino-2-pentanone hydrobromide in 150 ml. of cold water was added 5 ml. of concentrated ammonia water. A heavy precipitate formed immediately. After several hours, the material was filtered and washed with a small quantity of cold, dilute ammonia water; yield, 13.7 g. (95%); m. p. 247-248° (dec.). The melting point was not changed by crystallization from absolute ethanol.

Anal. Calcd. for $C_{19}H_{28}BrNO$: Br^-, 21.82. N, 3.82.
Found: Br^-, 21.83. N, 3.84.

1,2-Dimethyl-4-(5-bromo-2-thienyl)-4-cyclohexyl-3-piperidone Methobromide.- Concentrated ammonia water (4 ml.) was added to a suspension of 18.34 g. (0.0336 mole) of 2-bromo-4-(5-bromo-2-thienyl)-4-cyclohexyl-6-dimethylamino-3-hexanone hydrobromide in 100 ml. of water. After several hours, the crystalline precipitate was filtered and washed with cold water; yield, 15.52 (99%); m. p. 226-228° (dec.). An analytical sample, after crystallization from glacial acetic acid, melted at 235-237° (dec.).

Anal. Calcd. for $C_{18}H_{27}Br_2NOS$: Br, 34.35. N, 3.01.
Found: Br, 34.82. N, 3.02.

1,2-Dimethyl-4,4-diphenyl-3-piperidone Methobromide.- This compound was obtained in 95% yield by treatment of a suspension of 9.22 g. (0.0203 mole) of 2-bromo-4,4-diphenyl-6-dimethylamino-3-hexanone hydrobromide in 20 ml. of water with 4 ml. of concentrated ammonia water. The analytical sample was prepared by crystallization from water; m. p. 208-210° (dec.).

Anal. Calcd. for $C_{20}H_{24}BrNO$: Br^-, 21.35. N, 3.74.
Found: Br^-, 21.54. N, 3.69.

1-Methyl-2-benzyl-4,4-diphenyl-3-piperidone Methobromide.- To approximately 0.0119 mole of crude 2-bromo-1,4,4-triphenyl-6-dimethylamino-3-hexanone hydrobromide, described in previous section, was added 20 ml. of water. The mixture was then made alkaline by the addition of ammonia water. The oil solidified after an hour. The product was filtered and crystallized from 10 ml. of isopropyl alcohol; yield, 4.5 g. (74%, based on 1,4,4-triphenyl-6-dimethylamino-3-hexanone); m. p. 128-133° (dec.). This compound crystallized with one molecule of solvent. After recrystallization from isopropyl alcohol, it melted at 130-131° (dec.).

Anal. Calcd. for $C_{26}H_{28}BrNO \cdot C_3H_7OH$: Br^-, 15.65. N, 2.74.
Found: Br^-, 15.58. N, 2.81.

1,2,6-Trimethyl-4,4-diphenyl-3-piperidone Methobromide, (Cyclic Amidone methobromide).- To a suspension of 31.65 g. (0.0675 mole) of 2-bromo-4,4-diphenyl-6-dimethylamino-3-heptanone hydrobromide in 45 ml. of water was added 9 ml. of

concentrated ammonia water. The gummy material soon dissolved. After about one-half hour, the methobromide began to crystallize from the solution. This product weighed 25.16 g. (96%); m. p. 228-229° (dec.). The analytical sample was prepared by crystallization from absolute ethanol; m. p. 228-229° (dec.).

Anal. Calcd. for $C_{21}H_{26}BrNO$: Br^-, 20.58. N, 3.61.
Found: Br^-, 20.68. N, 3.56.

1,2,5-Trimethyl-4,4-diphenyl-3-piperidone Methobromide. (Cyclic Isoamidone methobromide).- Concentrated ammonia water (8 ml.) was added gradually to a suspension of 2-brom-4,4-diphenyl-5-methyl-6-dimethylamino-3-hexanone hydrobromide (18.2 g., 0.0344 mole) in 25 ml. of water. A crystalline product separated from the solution. The methobromide was filtered and crystallized from isopropyl alcohol; m. p. 205-208° (dec.); yield, 12.9 g. (97%). An analytical sample, after crystallization from isopropyl alcohol, melted at 209-210° (dec.).

Anal. Calcd. for $C_{21}H_{26}BrNO$: Br^-, 20.58. N, 3.61.
Found: Br^-, 20.53. N, 3.44.

The starting material used in this cyclization contained one molecular equivalent of acetic acid.

TABLE IV

SUBSTITUTED 1-METHYL-3-PIPERIDONE METHOBROMIDES

Cpd.	Substituents 2	4	4	5	6	M. p., (a) °C.	Yield, %
1. (b)	H	C_6H_5	C_6H_5	H	H	231-233	82.5
2.	H	C_6H_5	CH_3	H	H	207-208	80
3.	H	C_6H_5	C_6H_{13}	H	H	165-167	85
4.	H	C_6H_5	$CH_2CH_2C_6H_{11}$	H	H	185-187	80.5
5.	H	C_6H_5	C_6H_{11}	H	H	247-248	95
6.	CH_3	C_4H_2BrS (c)	C_6H_{11}	H	H	235-237	99
7.	CH_3	C_6H_5	C_6H_5	H	H	208-210	95
8. (d)	$CH_2C_6H_5$	C_6H_5	C_6H_5	H	H	130-131	74
9. (e)	CH_3	C_6H_5	C_6H_5	H	CH_3	228-229	96
10.	CH_3	C_6H_5	C_6H_5	CH_3	H	209-210	97

(a) At the melting point, these compounds decomposed with the evolution of a gas.
(b) Code No., JK-100.
(c) C_4H_2BrS = 5-Bromo-2-thienyl.
(d) Code No., JK-116.
(e) The compound contained one molecular equivalent of isopropyl alcohol.

V. Preparation of Hydrochlorides of Substituted 3-Piperidones (Cyclic Amidone and cyclic Isoamidone) (Table V)

1-Methyl-4,4-diphenyl-3-piperidone hydrochloride.
1,4-Dimethyl-4-phenyl-3-piperidone hydrochloride.
1-Methyl-4-phenyl-4-n-hexyl-3-piperidone hydrochloride.
1-Methyl-4-phenyl-4-(2-cyclohexylethyl)-3-piperidone hydrochloride.
1-Methyl-4-phenyl-4-cyclohexyl-3-piperidone hydrochloride.
1,2-Dimethyl-4-(5-bromo-2-thienyl)-4-cyclohexyl-3-piperidone hydrochloride.
1,2-Dimethyl-4,4-diphenyl-3-piperidone hydrochloride.
1-Methyl-2-benzyl-4,4-diphenyl-3-piperidone hydrochloride.
1,2,6-Trimethyl-4,4-diphenyl-3-piperidone hydrochloride. (Cyclic Amidone hydrochloride).
1,2,5-Trimethyl-4,4-diphenyl-3-piperidone hydrochloride. (Cyclic Isoamidone hydrochloride).

1-Methyl-4,4-diphenyl-3-piperidone Hydrochloride.- To a 25 ml. distillation flask, connected to a high-vacuum pump with a liquid-air trap in the system, was added 6.5 g. (0.0185 mole) of 1-methyl-4,4-diphenyl-3-piperidone methobromide. The system was evacuated to a pressure of 0.02 mm., and the flask heated gently with a free flame; the solid melted with the evolution of methyl bromide. The light red oil which formed was then distilled rapidly at the above pressure. The pale yellow distillate, which solidified in the receiver, was dissolved in ether and treated with hydrogen chloride. The nearly colorless precipitate was purified by crystallization from absolute ethanol; m. p. 235-236° (dec., with previous softening); yield, 80%.

Anal. Calcd. for $C_{18}H_{20}ClNO$: Cl^-, 11.75. N, 4.64.

Found: Cl^-, 11.64. N, 4.61.

1,4-Dimethyl-4-phenyl-3-piperidone Hydrochloride.- This compound was obtained from 7.2 g. (0.0242 mole) of 1,4-dimethyl-4-phenyl-3-piperidone methobromide, according to the procedure described above. The crude hydrochloride (4.8 g.) was crystallized from about 20 ml. of absolute ethanol; yield, 4.2 g. (72.7%); m. p. 193-195° (dec.). The analytical sample was prepared by crystallization from absolute ethanol; m. p. 194-195° (dec.).

Anal. Calcd. for $C_{13}H_{18}ClNO$: Cl^-, 14.79. N, 5.84.
Found: Cl^-, 14.85. N, 5.83.

1-Methyl-4-phenyl-4-n-hexyl-3-piperidone Hydrochloride.- A 2.0 g. and a 3.2 g. portion of 1-methyl-4-phenyl-4-n-hexyl-3-piperidone methobromide was decomposed in the manner described above. The colorless distillates were combined, dissolved in ether, and treated with hydrogen chloride. The crude salt (3.68 g.) was crystallized from absolute ethanol; yield, 3.15 g. (71.5%); m. p. 177-178° (dec.).

Anal. Calcd. for $C_{18}H_{28}ClNO$: Cl^-, 11.44. N, 4.52.
Found: Cl^-, 11.51. N, 4.57.

1-Methyl-4-phenyl-4-(2-cyclohexylethyl)-3-piperidone Hydrochloride.- This compound was obtained by thermal decomposition of 1-methyl-4-phenyl-(2-cyclohexylethyl)-3-piperidone methobromide, followed by treatment of an ether solution of the distilled base with hydrogen chloride. The salt was purified by crystallization from isopropyl alcohol; yield, 65.2%;

m.p. 206-207° (dec.). An analytical sample, after recrystallization from isopropyl alcohol, melted at 209-210° (dec.).

Anal. Calcd. for $C_{20}H_{30}ClNO$: Cl^-, 10.56. N, 4.17.
Found: Cl^-, 10.63. N, 4.26.

1-Methyl-4-phenyl-4-cyclohexyl-3-piperidone Hydrochloride.- This material was prepared from the corresponding methobromide, in the usual manner. The salt was purified by crystallization from a mixture of absolute thanol and ether; yield, 74.4%; m.p. 208-210° (dec.).

Anal. Calcd. for $C_{18}H_{26}ClNO$: Cl^-, 11.52. N, 4.55.
Found: Cl^-, 11.62. N, 4.52.

1,2-Dimethyl-4-(5-bromo-2-thienyl)-4-cyclohexyl-3-piperidone Hydrochloride.- Pyrolysis of 6.13 g. (0.0132 mole) of the methobromide yielded the free base, which distilled as a pale yellow liquid. It was dissolved in ether, and treated with hydrogen chloride; yield, 4.6 g. (86%); m. p. 200-203° (dec.). The salt was purified, in low recovery, by crystallization from absolute ethanol; m. p. 216-218° (dec.).

Anal. Calcd. for $C_{17}H_{25}BrClNOS$: Br + Cl, 28.36. N, 3.44.
Found: Br + Cl, 28.05. N, 3.44.

1,2-Dimethyl-4,4-diphenyl-3-piperidone Hydrochloride.- Thermal decomposition, under reduced pressure, of 1,2-dimethyl-4,4-diphenyl-3-piperidone methobromide yielded the free base. In this case, the base was not distilled; the flask was cooled, and the residue dissolved in ether. The unchanged methobromide

was filtered, and the filtrate treated with hydrogen chloride. The salt was crystallized from absolute ethanol; 71% yield. After recrystallization from absolute ethanol, the material melted at 211-213° (dec.).

Anal. Calcd. for $C_{19}H_{22}ClNO$: Cl^-, 11.23. N, 4.44.
Found: Cl^-, 11.21. N, 4.44.

1-Methyl-2-benzyl-4,4-diphenyl-3-piperidone Hydrochloride.- The hydrochloride was obtained from the corresponding methobromide, according to the procedure described above. After crystallization of the crude salt from absolute ethanol, it contained one molecular equivalent of ethanol; m. p. 202-204° (dec.); yield, 90.5%.

Anal. Calcd. for $C_{25}H_{26}ClNO.C_2H_5OH$: Cl^-, 8.10. N, 3.20.
Found: Cl^-, 8.09. N, 3.19.

1,2,6-Trimethyl-4,4-diphenyl-3-piperidone Hydrochloride, (Cyclic Amidone hydrochloride).- Thermal decomposition of the methobromide yielded the free base, which distilled as a pale yellow liquid. It was dissolved in ether, and treated with hydrogen chloride. The salt was purified by crystallization from absolute ethanol; m. p. 219-220° (dec.); yield, 86%. After several weeks, this material became red in color.

Anal. Calcd. for $C_{20}H_{24}ClNO$: Cl^-, 10.75. N, 4.25.
Found: Cl^-, 10.73. N, 4.01.

1,2,5-Trimethyl-4,4-diphenyl-3-piperidone Hydrochloride. (Cyclic Isoamidone hydrochloride).- This compound was obtained from the corresponding methobromide. Although the crude salt (80% yield) melted over a wide range, beginning at 115°, it gave a satisfactory analysis.

Anal. Calcd. for $C_{20}H_{24}ClNO$: Cl^-, 10.75. N, 4.25.
Found: Cl^-, 10.78. N, 4.12.

After crystallization from isopropyl alcohol, the product contained one-half of a molecular equivalent of solvent; m. p. 140-142° (dec.). The colorless salt became light brown in color after several weeks.

Anal. Calcd. for $C_{20}H_{24}ClNO \cdot 1/2C_3H_7OH$: Cl^-, 9.85. N, 3.90.
Found: Cl^-, 9.98. N, 3.86.

The picrate was prepared by addition of an alcoholic solution of picric acid to an ether solution of the free base. After crystallization from acetone, it melted at 177° (dec.).

Anal. Calcd. for $C_{26}H_{26}N_4O_8$: N, 10.72.
Found: N, 10.78.

TABLE V

SUBSTITUTED 1-METHYL-3-PIPERIDONE HYDROCHLORIDES

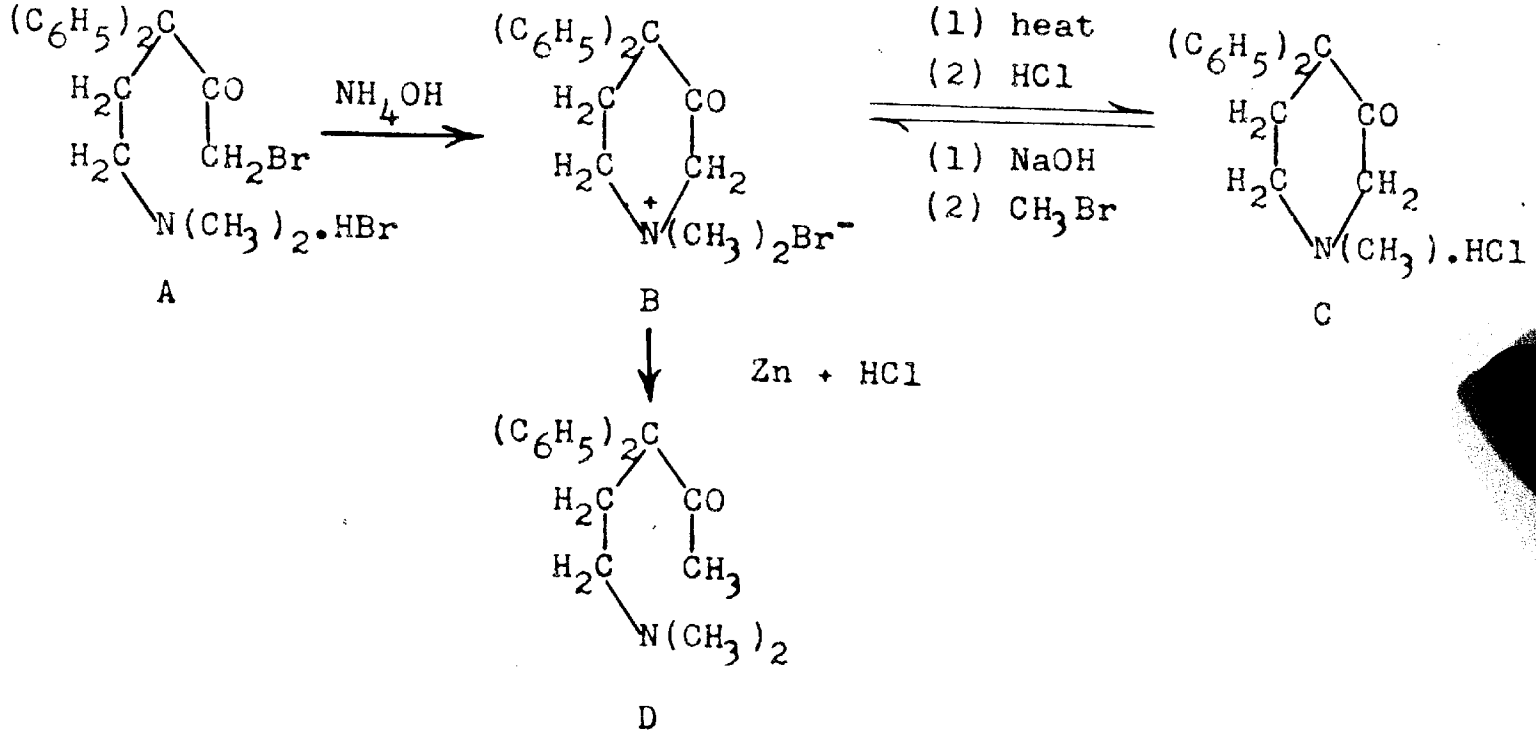
Cpd.	Code No.	Substituents 2	4	4	5	6	M. p., °C.[a]	Yield, %
1.	JK-101	H	C_6H_5	C_6H_5	H	H	235-236	80
2.	JK-109	H	C_6H_5	CH_3	H	H	194-195	73
3.	JK-108	H	C_6H_5	C_6H_{13}	H	H	177-178	71.5
4.	JK-113	H	C_6H_5	$CH_2CH_2C_6H_{11}$	H	H	209-210	65
5.	JK-102	H	C_6H_5	C_6H_{11}	H	H	208-210	74
6.	JK-114	CH_3	C_4H_2BrS[b]	C_6H_{11}	H	H	216-218	86
7.	JK-103	CH_3	C_6H_5	C_6H_5	H	H	211-213	71
8.[c]	JK-107	$CH_2C_6H_5$	C_6H_5	C_6H_5	H	H	202-204	90.5
9.	JK-106	CH_3	C_6H_5	C_6H_5	H	CH_3	219-220	86
10.[d]	JK-119	CH_3	C_6H_5	C_6H_5	CH_3	H	140-142	80

(a) The compounds melt to a red liquid.
(b) C_4H_2BrS = 5-Bromo-2-thienyl.
(c) The compound contains a molecular equivalent of ethyl alcohol.
(d) The compound contains one-half of a molecular equivalent of isopropyl alcohol.

VI. Conversion of 1-Methyl-4,4-diphenyl-3-piperidone Hydrochloride into 1-Methyl-4,4-diphenyl-3-piperidone Methobromide

Conversion of 1-Methyl-4,4-diphenyl-3-piperidone Methobromide into 3,3-Diphenyl-5-dimethylamino-2-pentanone Hydrobromide.

Although the purpose of the following two experiments has been mentioned in the Theoretical Part, their significance may be made somewhat clearer by the following discussion.



(Isolated as the hydrobromide)

When compound A was treated with ammonia water, at a temperature below that of the laboratory, very rapid cyclization of the free base took place with the formation of the methobromide of the piperidone B. In view of the very mild reaction conditions, there is little doubt that the six membered ring (B) was formed. When B was heated to its melting point (231°), under

reduced pressure, methyl bromide was evolved, and B was transformed into C. Since a high temperature was employed, there was a possibility that B might have been converted into a pyrrolidone instead of the piperidine C. The fact that C, when treated with methyl bromide in the manner described below, yielded the methobromide B proved that no change in ring size took place during the evolution of methyl bromide from B.

Experimental evidence which indicated that compound B actually was a piperidone was obtained by treatment of B with zinc and concentrated hydrochloric acid. The reaction product was 3,3-diphenyl-5-dimethylamino-2-pentanone (D), a product which would be expected from the hydramine cleavage of B. Such a cleavage is possible since, during the reaction of the basic keto compound (B) undoubtedly is reduced to the corresponding basic secondary alcohol prior to the cleavage.

Conversion of 1-Methyl-4,4-diphenyl-3-piperidone Hydrochloride into 1-Methyl-4,4-diphenyl-3-piperidone Methobromide (C into B).- A suspension of 3.55 g. (0.0117 mole) of 1-methyl-4,4-diphenyl-3-piperidone hydrochloride in about 10 ml. of water was treated with excess sodium hydroxide solution, and the resulting free base was extracted with ether. After the extract had been dried over magnesium sulfate, the ether solution was filtered, and treated with about 10 g. of methyl bromide. The precipitated methobromide, after several days, was filtered and washed with ether; yield, 3.46 g. (82%); m. p. 231-233° (dec.). This material,

subsequent to crystallization from absolute ethanol, melted at 231-233° and did not depress the melting points of the methobromide B.

Conversion of 1-Methyl-4,4-diphenyl-3-piperidone Methobromide into 3,3-Diphenyl-5-dimethylamino-2-pentanone Hydrobromide (B into D).- To a warm solution of 4.0 g. (0.0111 mole) of 1-methyl-4,4-diphenyl-3-piperidone methobromide, in a mixture of 100 ml. of concentrated hydrochloric acid and 50 ml. of water, was added 15.0 g. of zinc dust over a period of one hour. The mixture was heated on a steam-bath until all the zinc dissolved, cooled, treated with excess ammonia water, and the free base extracted with several portions of ether. After the extracts had been dried over magnesium sulfate, the ether solution was filtered, and the filtrate treated with hydrogen bromide. The oily product was converted into the crystalline salt by trituration with ether, and then with isopropyl alcohol; yield, 3.15 g. (79%); m. p. 171-173°. This material gave a satisfactory analysis for 3,3-diphenyl-5-dimethylamino-2-pentanone hydrobromide, and did not depress the melting point of an authentic sample of this material (p. 55).

Anal. Calcd. for $C_{19}H_{24}BrNO$: Br^-, 22.06.

Found: Br^-, 22.02.

In another experiment the hydrochloride of D was isolated; m. p. 185-186°. This material did not depress the melting point of an authentic sample of 3,3-diphenyl-5-dimethylamino-2-pentanone hydrochloride, and also gave a satisfactory analysis

for the latter compound.

Anal. Calcd. for $C_{19}H_{24}ClNO$: Cl^-, 11.16. N, 4.41.
Found: Cl^-, 11.21. N, 4.35.

VII. Preparation of 3-Piperidinols and Derivatives

1-Methyl-4,4-diphenyl-3-piperidinol methobromide.
1-Methyl-4,4-diphenyl-3-piperidinol.
1-Methyl-4,4-diphenyl-3-piperidinol hydrochloride.
1-Methyl-3-acetoxy-4,4-diphenylpiperidine hydrochloride.
1-Methyl-3-(4-nitrobenzoyloxy)-4,4-diphenylpiperidine hydrochloride.
1-Methyl-3-(4-aminobenzoyloxy)-4,4-diphenylpiperidine hydrochloride.
1-Methyl-4-phenyl-4-cyclohexyl-3-piperidinol hydrochloride.
1-Methyl-3-acetoxy-4-phenyl-4-cyclohexylpiperidine hydrochloride.
1,2,6-Trimethyl-4,4-diphenyl-3-piperidinol hydrochloride.
1,2,5-Trimethyl-4,4-diphenyl-3-piperidinol hydrochloride.

1-Methyl-4,4-diphenyl-3-piperidinol Methobromide.- To a suspension of 4.5 g. (0.0125 mole) of 1-methyl-4,4-diphenyl-3-piperidone methobromide in 100 ml. of 90% ethanol was added 0.5 g. of platinum oxide catalyst and the mixture hydrogenated under an initial pressure of 45 pounds. After two hours, the catalyst was filtered, and the filtrate evaporated to dryness under reduced pressure. The residue was crystallized from about 10 ml. of absolute ethanol; yield, 3.9 g. (86%); m. p. 215-217° (dec.). An analytical sample was prepared by recrystallization from absolute ethanol; m. p. 216-217° (dec.).

Anal. Calcd. for $C_{19}H_{24}BrNO$: Br^-, 22.06. N, 3.87.
Found: Br^-, 21.73. N, 3.76.

1-Methyl-4,4-diphenyl-3-piperidinol.- 1-Methyl-4,4-diphenyl-3-piperidinol methobromide (1.72 g., 0.00474 mole) was heated in a small distillation flask under reduced pressure. The solid melted with the liberation of methyl bromide, and the free base sublimed on the walls of the flask. The sublimate, m. p. 156-158°, was dissolved in dilute hydrochloric acid and then precipitated by the addition of excess ammonia water. This product, after crystallization from isopropyl alcohol, melted at 158-159°, and did not depress the melting point of the free base of the product described in the experiment below.

1-Methyl-4,4-diphenyl-3-piperidinol Hydrochloride.- To a suspension of 10.8 g. (0.036 mole) of 1-methyl-4,4-diphenyl-3-piperidone hydrochloride in 100 ml. of 90% ethanol was added 0.3 g. of platinum oxide catalyst and the ketone hydrogenated under an initial pressure of 45 pounds; reduction was essentially completed in twenty minutes. After fifty minutes, the catalyst was filtered, and the filtrate evaporated to dryness under reduced pressure. The nearly colorless, practically pure compound weighed 10.9 g. (100%); m. p. 254-256° (dec.). An analytical sample was prepared by crystallization from absolute ethanol; m. p. 257-258° (dec.).

Anal. Calcd. for $C_{18}H_{22}ClNO$: Cl^-, 11.67. N, 4.61.

Found: Cl^-, 11.68. N, 4.69.

The free base was prepared by the addition of excess ammonia water to an aqueous suspension of the salt. The product, after crystallization from isopropyl alcohol, melted at 158-159°.

1-Methyl-3-acetoxy-4,4-diphenylpiperidine Hydrochloride.- A mixture of 2.0 g. (0.0066 mole) of 1-methyl-4,4-diphenyl-3-piperidinol hydrochloride and 10 ml. of acetic anhydride was refluxed for one minute, cooled, and diluted with ether. This product, after crystallization from absolute ethanol-ether, weighed 1.96 g. (84%); m. p. 226.5-227.5° (dec.).

Anal. Calcd. for $C_{20}H_{24}ClNO_2$: Cl^-, 10.26. N, 4.05.

Found: Cl^-, 10.21. N, 4.05.

1-Methyl-3-(4-nitrobenzoyloxy)-4,4-diphenylpiperidine Hydrochloride.- A mixture of 3.95 g. (0.013 mole) of 1-methyl-4,4-diphenyl-3-piperidinol hydrochloride, 4.0 g. (0.021 mole) of 4-nitrobenzoyl chloride and 25 ml. of dry pyridine was heated on a steam-bath for three and one-half hours. After removal of the pyridine, the residue was triturated with ether, and suspended in 20 ml. of water. This mixture was made alkaline with sodium hydroxide solution and then extracted with ether. The dried extract was treated with hydrogen chloride, the precipitate triturated with ether, and then with absolute ethanol-ether. The product weighed 4.05 g. (67%). The melting point of this material, 256-257° (dec.), was not changed by crystallization from absolute ethanol.

Anal. Calcd. for $C_{25}H_{25}ClN_2O_4$: Cl^-, 7.83.

Found: Cl^-, 7.87.

1-Methyl-3-(4-aminobenzoyloxy)-4,4-diphenylpiperidine Hydrochloride.- A mixture of 2.55 g. (0.00563 mole) of 1-methyl-3-(4-nitrobenzoyloxy)-4,4-diphenylpiperidine hydrochloride, 0.15 g. of platinum oxide catalyst and 40 ml. of 90% ethanol was treated with hydrogen, under 45 pounds pressure, for a period of two hours. The catalyst was filtered, and the colorless filtrate was evaporated to dryness under an atmosphere of nitrogen. The residue was heated with 30 ml. of absolute ethanol, cooled, and filtered; yield, 2.0 g. (76%); m. p. 212-215° (dec., softening at 200°). This material crystallized as a solvate.

Anal. Calcd. for $C_{25}H_{27}ClN_2O_2.C_2H_5OH$: Cl^-, 7.54.
Found: Cl^-, 7.52.

The dihydrochloride was obtained by treatment of the above material with hydrochloric acid, followed by evaporation of the solution to dryness in a desiccator. This salt also crystallized from absolute ethanol as a solvate; m. p. 219-222° (dec., softening at 200°).

Anal. Calcd. for $C_{25}H_{28}Cl_2N_2O_2.C_2H_2OH$: Cl^-, 14.03. N, 5.54.
Found: Cl^-, 14.16. N, 5.48.

1-Methyl-4-phenyl-4-cyclohexyl-3-piperidinol Hydrochloride.- Catalytic reduction, in the presence of platinum oxide, of 8.1 g. (0.0262 mole) of 1-methyl-4-phenyl-4-cyclohexyl-3-piperidone hydrochloride yielded 8.15 g. (100%) of the alcohol; m. p. 264-266° (dec.). The analytical sample was prepared by

crystallization from isopropyl alcohol; m. p. 271-272° (dec.).

Anal. Calcd. for $C_{18}H_{28}ClNO$: Cl^-, 11.44. N, 4.52

Found: Cl^-, 11.44. N, 4.55.

1-Methyl-3-acetoxy-4-phenyl-4-cyclohexylpiperidine Hydrochloride.- A mixture of 3.25 g. (0.0105 mole) of 1-methyl-4-phenyl-4-cyclohexylpiperidinol hydrochloride and 10 ml. of acetic anhydride was refluxed for several minutes, cooled, and diluted with ether. This product, after two crystallizations from isopropyl alcohol, weighed 2.7 g. (73%); m. p. 199-201°.

Anal. Calcd. for $C_{20}H_{30}ClNO_2$: Cl^-, 10.07. N, 3.98.

Found: Cl^-, 9.89. N, 3.88.

1,2,6-Trimethyl-4,4-diphenyl-3-piperidinol Hydrochloride.- This compound was obtained in quantitative yield by catalytic reduction, in the presence of platinum oxide catalyst, of 1,2,6-trimethyl-4,4-diphenyl-3-piperidone hydrochloride. After crystallization from absolute ethanol, this product melted at 293° (dec.).

Anal. Calcd. for $C_{20}H_{26}ClNO$: Cl^-, 10.68. N, 4.22.

Found: Cl^-, 10.67. N, 4.24.

1,2,5-Trimethyl-4,4-diphenyl-3-piperidinol Hydrochloride.- This alcohol was prepared by catalytic reduction, in the presence of platinum oxide catalyst, of 1,2,5-trimethyl-4,4-diphenyl-3-piperidone hydrochloride. After crystallization from absolute ethanol, this compound melted at 284-285° (dec.).

Anal. Calcd. for $C_{20}H_{26}ClNO$: Cl^-, 10.68. N, 4.22.

Found: Cl^-, 10.77. N, 4.37.

VIII. Preparation of Acids and Their Cyclization to 2-Pyrrolidones

2,2-Diphenyl-4-dimethylaminobutyric acid hydrobromide.
2,2-Diphenyl-4-diethylaminobutyric acid hydrobromide.
1-Methyl-3,3-diphenyl-2-pyrrolidone.
1-Ethyl-3,3-diphenyl-2-pyrrolidone.

2,2-Diphenyl-4-dimethylaminobutyric Acid Hydrobromide.- A mixture of 13.2 g. (0.05 mole) of 2,2-diphenyl-4-dimethylaminobutanenitrile and 100 ml. of 48% hydrobromic acid was refluxed for seventeen hours. After distillation of about half of the hydrobromic acid, the product was allowed to separate from the residue. The colorless, crystalline precipitate was filtered, washed with 48% hydrobromic acid and then with acetone; yield, 15.4 g. (84.5%); m. p. 237-239° (dec.). The melting point was not changed by crystallization from absolute ethanol.

Anal. Calcd. for $C_{18}H_{22}BrNO_2$: Br^-, 21.94.

Found: Br^-, 21.95.

2,2-Diphenyl-4-diethylaminobutyric Acid Hydrobromide.- A mixture of 9.52 g. (0.0326 mole) of 2,2-diphenyl-4-diethylaminobutanenitrile and 70 ml. of 48% hydrobromic acid was refluxed for seventeen hours. The hydrobromic acid was removed under reduced pressure. The residue, after it had been dried in a desiccator over sodium hydroxide, was heated with about 80 ml. of absolute ethanol, and the undissolved ammonium bromide was filtered. The filtrate was diluted with dry ether. After several days the precipitate was filtered and washed with ether; yield, 10.85 g. (85%); m. p. 183-185°. An analytical

sample was prepared by crystallization from isopropyl alcohol; m. p. 185-186°.

Anal. Calcd. for $C_{20}H_{26}BrNO_2$: Br^-, 20.37.

Found: Br^-, 20.26.

1-Methyl-3,3-diphenyl-2-pyrrolidone.- A mixture of 3.64 g. (0.01 mole) of 2,2-diphenyl-4-dimethylaminobutyric acid hydrobromide, 1.5 g. (0.012 mole) of thionyl chloride and 15 ml. of chloroform was refluxed for three hours on a steam-bath. The solvent was removed under reduced pressure; the residue, after crystallization from absolute ethanol, weighed 2.2 g. (87.5%); m. p. 143-145°.*

Anal. Calcd. for $C_{17}H_{17}NO$: N, 5.57.

Found: N, 5.60.

1-Ethyl-3,3-diphenyl-2-pyrrolidone.- This compound was prepared by treatment of 2,2-diphenyl-4-diethylaminobutyric acid with thionyl chloride in the manner described above. After crystallization from petroleum ether (60-75°), this product melted at 109-111°** and did not depress the melting point of an authentic sample, m. p. 109-111°, which had been prepared by Blicke and Zambito (ref. 125).

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* Dupré et al. (ref. 132) obtained this product in 96% yield by treatment of 2,2-diphenyl-4-dimethylaminobutyric acid with fifteen equivalents of thionyl chloride for a period of one hour; m. p. 146.5-147°.

** Dupré et al. (ref. 132) reported 111.5-113°.

IX. Preparation of Substituted Quinuclidines

1-Methyl-4-acetyl-4-phenylpiperidine hydrobromide.
1-Methyl-4-bromoacetyl-4-phenylpiperidine hydrobromide.
3-Keto-4-phenylquinuclidine methobromide.
3-Hydroxy-4-phenylquinuclidine methobromide.
3-Acetoxy-4-phenylquinuclidine methobromide.

1-Methyl-4-acetyl-4-phenylpiperidine Hydrobromide.- To a Grignard solution, prepared from 19.0 g. (0.78 gram atom) of magnesium turnings, 50 ml. (0.80 mole) of methyl iodide and 200 ml. of dry ether in a 1-liter flask, was added a solution of 40.0 g. (0.20 mole) of 1-methyl-4-cyano-4-phenylpiperidine dissolved in 300 ml. of toluene. The mixture was refluxed for forty hours. About half of the solvent was removed by distillation through a fractionating column; the residue was refluxed for an additional eight hours, cooled, and poured carefully into 400 ml. of cold concentrated hydrochloric acid. The organic solvent was removed by distillation, and the residue refluxed for twelve hours. The cooled mixture was made alkaline with concentrated sodium hydroxide solution, extracted several times with ether, and the extracts dried over magnesium sulfate. After filtration, the ether was evaporated, and the residue fractionated; wt., 29.0 g.; b. p. 109-116° (1-2 mm.).[137] This material was dissolved in dry ether and converted into the salt by passing in hydrogen bromide. After filtration and washing with ether, the crude hydrobromide (40.0 g.) was crystallized from about 250 ml. of isopropyl alcohol; yield, 34.0 g. (57%); m. p. 221-223°. The analytical sample melted at 223-224°.

(137) Eisleb (U. S. Patent 2,248,018; Chem. Abst., 35, 6394 (1941)) reported 143° (3.5 mm.).

Anal. Calcd. for $C_{14}H_{20}BrNO$: Br^-, 26.80.

Found: Br^-, 26.82.

The free base, obtained by treatment of the hydrobromide with excess sodium hydroxide solution, was converted into the hydrochloride. This salt, after crystallization from isopropyl alcohol, melted at 248° (dark red melt).*

1-Methyl-4-bromoacetyl-4-phenylpiperidine Hydrobromide.- To a refluxing solution of 14.61 g. (0.049 mole) of 1-methyl-4-acetyl-4-phenylpiperidine hydrobromide in 30 ml. of glacial acetic acid, a solution of 7.84 g. (0.049 mole) of bromine in 20 ml. of glacial acetic acid was added, dropwise, during a twenty-minute period. After the material had been refluxed for an additional twenty minutes, about half of the solvent was distilled, and to the cooled residue was added about 250 ml. of ether. The oily product solidified after several hours. After filtration, the material was washed with ether and dried; yield, 18.12 g. (98%); m. p. 193-195° (dec.). The product was used, without purification, in the following reaction. The sample employed for analysis was obtained by two crystallizations from small quantities of glacial acetic acid; m. p. 201° (dec.).

Anal. Calcd. for $C_{14}H_{19}Br_2NO$: Br, 42.38.

Found: Br, 41.23.

3-Keto-4-phenylquinuclidine Methobromide.- To a solution of 7 ml. of ammonia water and 50 ml. of water was added, in

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* Ciba, Ltd. (ref. 65) reported 240-242°. They prepared this compound by another method (see p. 48).

portions, 17.0 g. (0.045 mole) of 1-methyl-4-acetyl-4-phenylpiperidine hydrobromide. The material first separated as an oil which completely dissolved in a few minutes to form a pale yellow solution. After several hours, the solution was evaporated to dryness under reduced pressure. The residual solid was heated with about 80 ml. of absolute ethanol, and the undissolved ammonium bromide was filtered; the filtrate was evaporated to dryness under reduced pressure, and the resulting material was heated with about 80 ml. of isopropyl alcohol. After filtration of the ammonium bromide, the filtrate was diluted with about 300 ml. of dry ether. The crude hydroscopic methobromide was filtered, washed with ether, and dried in a desiccator. After crystallization from about 400 ml. of pyridine, followed by drying in an oven at 100° for several hours, the pure, colorless product weighed 10.25 g. (76.5%); m. p. 207-209°. This substance melted without the evolution of a gas; most methobromides melt with decomposition (evolution of methyl bromide) at their melting point.

Anal. Calcd. for $C_{14}H_{14}BrNO$: Br^-, 27.35. N, 4.79.

Found: Br^-, 27.08. N, 4.89.

The above product was neutral to alkacid paper, indicating that any linear compounds which may have formed were removed during the course of crystallization.

3-Hydroxy-4-phenylquinuclidine Methobromide.- To a solution of 9.9 g. (0.0455 mole) of 3-keto-4-phenylquinuclidine methobromide

in 100 ml. of 90% ethanol was added 0.5 g. of platinum oxide catalyst. Hydrogenation, under an initial pressure of 45 pounds, was essentially completed in five minutes. After four hours, the catalyst was filtered, and the filtrate evaporated to dryness under reduced pressure. The dry solid was crystallized from 100 ml. of isopropyl alcohol; wt., 9.3 g. (93%); m. p. 203-205°.

Anal. Calcd. for $C_{14}H_{16}BrNO$: Br^-, 27.17. N, 4.76.
Found: Br^-, 26.84. N, 4.75.

3-Acetoxy-4-phenylquinuclidine Methobromide.- A mixture of 2.0 g. (0.068 mole) of 3-hydroxy-4-phenylquinuclidine methobromide, 10 ml. of acetic anhydride and 20 ml. of pyridine was refluxed. As soon as all of the material had dissolved, the crystalline product began to precipitate. The mixture was refluxed for five minutes, cooled, and diluted with ether. The product was filtered, and washed with ether; wt., 2.28 g.; m. p. 281-283°. After crystallization from absolute ethanol, the pure product weighed 2.04 g. (89.5%); m. p. 283-285°.

Anal. Calcd. for $C_{16}H_{18}BrNO$: Br^-, 23.77. N, 4.17.
Found: Br^-, 23.53. N, 3.81.

X. Preparation of an Isomer and Lower Homolog of Isoamidone

2,2-Diphenylbutanenitrile.
4,4-Diphenyl-3-hexanone.
3,3-Diphenyl-2-pentanone.
1-Dimethylamino-2-methyl-4,4-diphenyl-3-hexanone hydrochloride.
1-Dimethylamino-4,4-diphenyl-3-hexanone hydrochloride.

2,2-Diphenylbutanenitrile.- A suspension of 21.5 g. (0.55 mole) of finely-divided sodamide in 100 ml. of toluene was placed in a 1-liter, 3-necked flask equipped with a Hershberg stirrer, a dropping funnel, and a condenser fitted with a soda-lime tube. The mixture was stirred, and maintained below 10° during the dropwise addition (thirty minutes) of 96.5 g. (0.5 mole) of diphenylacetonitrile, dissolved in 200 ml. of toluene. After the mixture had been stirred for an additional sixty minutes, 60.0 g. (0.55 mole) of ethyl bromide, dissolved in 100 ml. of toluene, was added over a period of thirty minutes. The temperature was maintained below 20° during the addition of the ethyl bromide solution. After the mixture had been stirred at room temperature for sixty minutes, it was then refluxed for three hours. Water (75 ml.) was added to the cooled mixture, the aqueous layer was separated, and then extracted with toluene. The toluene extracts were combined and washed with water, the solvent removed under reduced pressure, and the residue fractionated. The product weighed 103.5 g. (93.8%); b. p. 130-133° (1-2 mm.).[138]

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(138) Larsen, Ruddy, Elpern and MacMullin (J. Am. Chem. Soc., 71, 532 (1949)) reported 145-147° (0.3 mm.).

4,4-Diphenyl-3-hexanone.- To a Grignard solution, prepared from 38.9 g. (1.6 gram atoms) of magnesium, 175 g. (1.6 moles) of ethyl bromide and 400 ml. of dry ether in a 2-liter flask, was added a solution of 87.6 g. (0.396 mole) of 2,2-diphenylbutanenitrile in 600 ml. of dry benzene. The mixture was refluxed for twenty-four hours, cooled, and poured carefully into 600 ml. of cold concentrated hydrochloric acid. The solvent was distilled until the temperature reached 85°, and the residue refluxed for twelve hours. The cooled mixture was neutralized with strong sodium hydroxide solution, and extracted several times with ether. After the combined extracts had been dried over magnesium sulfate, the ether was evaporated, and the residue fractionated; wt., 89.5 g. (89%); b. p. 124-130° (1-2 mm.). This nitrogen-free material did not yield a 4-nitrophenyl- or 2,4-dinitrophenylhydrazone.

3,3-Diphenyl-2-pentanone.- This ketone was prepared, according to the procedure described above, by interaction of 55.0 g. (0.249 mole) of 2,2-diphenylbutanenitrile and approximately 1.0 mole of methylmagnesium iodide. The product weighed 50.0 g. (84.5%); b. p. 130-133° (1-2 mm.).(139)

The 2,4-dinitrophenylhydrazone of this ketone, after crystallization from 95% ethanol, melted at 134-136°.

Anal. Calcd. for $C_{23}H_{22}N_4O_4$: N, 13.39.

Found: N, 13.44.

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(139) Meerwein (Ann., 419, 121 (1919)) reported 179° (11 mm.). He obtained this compound by rearrangement, in sulfuric acid, of 1,1-diphenyl-2-methyl-2-ethylglycol.

1-Dimethylamino-2-methyl-4,4-diphenyl-3-hexanone Hydrochloride.- A mixture of 63.0 g. (0.25 mole) of 4,4-diphenyl-3-hexanone, 37.5 ml. (0.5 mole) of 37% formaldehyde, 40.8 g. (0.5 mole) of dimethylamine hydrochloride and 200 ml. of glacial acetic acid was refluxed for fifty-five hours; additional 10-ml. portions of 37% formaldehyde were added after twenty-four and fifty-two hours. The solvent was removed until the temperature of the vapor reached 120°. The cooled residue was made alkaline with sodium hydroxide solution, and the residual oil extracted with ether. After evaporation of the ether from the dried extract, the product distilled as a pale yellow, thick oil, b. p. 155-165° (about 5 mm.). This material (60 g.) was dissolved in dry ether, and converted into the salt by the use of hydrogen chloride. The colorless precipitate, after it had been washed with ether and dried, weighed 35.8 g.; m. p. 185-187°. The hydrochloride was purified by crystallization from 100 ml. of isopropyl alcohol; wt., 32.0 g. (37.2%); m. p. 189-190°.

Anal. Calcd. for $C_{21}H_{28}ClNO$: Cl^-, 10.25. N, 4.05.

Found: Cl^-, 10.26. N, 4.13.

Evaporation of the ether, from which the crude hydrochloride had been precipitated, yielded 32.0 g. of slightly impure starting material, b. p. 122-130° (1-2 mm.). This material slowly decolorized bromine and permanganate solutions, which indicated the presence of a small quantity of unsaturated compound which had been formed probably during the distillation of the basic product.(140)

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(140) Blicke, "Organic Reactions", Vol. I, p. 318. John Wiley and Sons, Inc., New York, N. Y. (1942).

1-Dimethylamino-4,4-diphenyl-3-hexanone Hydrochloride.- This product was obtained in approximately 22% yield by the interaction of 3,3-diphenyl-2-pentanone, 37% formaldehyde and dimethylamine hydrochloride, in acetic acid solution, according to a procedure analogous to that described above. This compound, after crystallization from isopropyl alcohol, melted at 200-201°.

Anal. Calcd. for $C_{20}H_{26}ClNO$: Cl^-, 10.68. N, 4.22.

Found: Cl^-, 10.35. N, 4.07.

SUMMARY

The object of this investigation was the preparation of cyclic analogs of the analgesic Amidone, 4,4-diphenyl-6-dimethylamino-3-heptanone.

The piperidine ring in morphine, and in Demerol, is an essential part of the molecule since, if this ring is ruptured, analgesic activity is lost. In view of this fact it seemed that cyclic analogs of Amidone - compounds which contain a piperidine ring such as 1,2,6-trimethyl-4,4-diphenyl-3-piperidone - might be expected to exhibit high analgesic activity.

It was discovered that cyclic compounds, which possessed the desired structure, could be obtained by a simple general process, the first step of which was the bromination of the hydrobromide of a ketone of the Amidone type. The free base of the bromo derivative cyclized very rapidly to form the methobromide of a 3-piperidone. When the latter substance was heated, methyl bromide was evolved, and the piperidone itself was produced.

The entire synthesis of a 3-piperidone is illustrated in the case of 1-methyl-4,4-diphenyl-3-piperidone. Interaction of 2-dimethylaminoethyl chloride and diphenylacetonitrile, in the presence of sodamide, yielded 2,2-diphenyl-4-dimethylaminobutanenitrile. Treatment of the latter nitrile with methylmagnesium iodide produced 3,3-diphenyl-5-dimethylamino-2-pentanone. The hydrobromide of the ketone was brominated with

the formation of 1-bromo-3,3-diphenyl-5-dimethylamino-2-pentanone hydrobromide. After treatment of the hydrobromide with ammonia water, the free base cyclized rapidly to 1-methyl-4,4-diphenyl-3-piperidone methobromide. When the methobromide was heated under reduced pressure, methyl bromide was evolved, and 1-methyl-4,4-diphenyl-3-piperidone was obtained. The compound was purified as the hydrochloride.

By the use of the proper disubstituted acetonitrile, basic alkyl halide and Grignard reagent, it should be possible to prepare 1-methyl-3-piperidones with substituents in any or all of the 2, 4, 5 and 6 nuclear positions. The substituted 3-piperidones which were synthesized are listed below:

1-Methyl-4,4-diphenyl-3-piperidone Hydrochloride
1,4-Dimethyl-4-phenyl-3-piperidone Hydrochloride
1-Methyl-4-phenyl-4-n-hexyl-3-piperidone Hydrochloride
1-Methyl-4-phenyl-4-(2-cyclohexylethyl)-3-piperidone Hydrochloride
1-Methyl-4-phenyl-4-cyclohexyl-3-piperidone Hydrochloride
1,2-Dimethyl-4-(5-bromo-2-thienyl)-4-cyclohexyl-3-piperidone Hydrochloride
1,2-Dimethyl-4,4-diphenyl-3-piperidone Hydrochloride
1-Methyl-2-benzyl-4,4-diphenyl-3-piperidone Hydrochloride
1,2,6-Trimethyl-4,4-diphenyl-3-piperidone Hydrochloride (Cyclic Amidone Hydrochloride)
1,2,5-Trimethyl-4,4-diphenyl-3-piperidone Hydrochloride (Cyclic Isoamidone Hydrochloride)

Four of the above ketones were reduced to their respective alcohols:

1-Methyl-4,4-diphenyl-3-piperidinol Hydrochloride
1-Methyl-4-phenyl-4-cyclohexyl-3-piperidinol Hydrochloride
1,2,6-Trimethyl-4,4-diphenyl-3-piperidinol Hydrochloride
1,2,5-Trimethyl-4,4-diphenyl-3-piperidinol Hydrochloride

The first two alcohols were converted into acetates by treatment with acetic anhydride. The p-aminobenzoate of the first alcohol was also synthesized. Most of the 3-piperidones and their derivatives were tested pharmacologically. None of them exhibited high analgesic activity, and several were quite toxic to mice.

1-Methyl-4-cyano-4-phenylpiperidine reacted with methylmagnesium iodide to yield 1-methyl-4-acetyl-4-phenylpiperidine. Bromination of the hydrobromide of the latter substance converted it into the hydrobromide of the corresponding 4-bromoacetyl derivative. When the base of this substance was liberated, it cyclized rapidly to 3-keto-4-phenylquinuclidine methobromide, a substance which is closely related to the methobromide of the potent analgesic Ketobemidone. Unfortunately, it was not possible to remove methyl bromide from the quaternary compound by the application of heat. The methobromide ketone was reduced to the alcohol, and the latter substance converted into the acetate by treatment with acetic anhydride and pyridine.

It was found that an isomer of Isoamidone, 1-dimethylamino-2-methyl-4,4-diphenyl-3-hexanone hydrochloride, was obtained by interaction of 4,4-diphenyl-3-hexanone, formalin and dimethylamine hydrochloride, in the presence of acetic acid. Utilization of 3,3-diphenyl-2-pentanone, as a starting material in the Mannich reaction, produced 1-dimethylamino-4,4-diphenyl-3-hexanone hydrochloride.

It was discovered that nitriles, such as 2,2-diphenyl-4-dimethylaminobutanenitrile, could be hydrolyzed readily to their respective acids when they were refluxed with 48% hydrobromic acid. This procedure made it unnecessary to employ hydrochloric acid in a sealed tube at an elevated temperature. During an attempt to convert 2,2-diphenyl-4-dimethylaminobutyric acid into the acid chloride, by treatment with thionyl chloride, 1-methyl-3,3-diphenyl-2-pyrrolidone was obtained in good yield. The ease of preparation of the necessary acids from the nitriles, and also the rapid cyclization of the acid chloride makes this procedure an advantageous one for the preparation of substituted 2-pyrrolidones.