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SYNTHETIC SUBSTANCES WITH MORPHINE-LIKE EFFECT *

Chemical Aspects

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SYNOPSIS

As a basis for a series of studies on the pharmacological, therapeutic, and addictive properties of synthetic drugs with morphine-like effect, this paper deals with chemical aspects of the compounds of this type so far known. Four major groups, each with a fundamentally different chemical structure, are described : pethidine, methadone, morphinan, and dithienylbutenylamine. For each substance belonging to these groups, the formula, synonyms, and methods of synthesis are indicated. A description of pethidine according to the specifications of the *Pharmacopoea Internationalis* is annexed to the paper.

As a basis for consideration of the pharmacological, therapeutic, and addictive properties of these substances (see, e.g., Wolff [35]), it was felt necessary to start with a reference to the principles of the various chemical processes leading to the final products, and an effort has been made to explain the different syntheses as simply and completely as possible. However, for obvious reasons it was not always easy to find the method of

* This is the first of a series of studies covering the scientific aspects of synthetic drugs with morphine-like effect, undertaken in accordance with resolution No. 505 (XVI)C adopted at the sixteenth session (30 June-5 August 1953) of the United Nations Economic and Social Council on the recommendation of the Commission on Narcotic Drugs (eighth session). The text of this resolution is as follows :

" *The Economic and Social Council,*

Considering the increasing importance of the therapeutic use of synthetic drugs throughout the world,

Having regard to the considerable number of aspects of the problem,

Taking into account the report . . . submitted by the Secretary-General to the Commission on Narcotic Drugs on the problem of synthetic drugs and the recommendations of the Commission,

1. *Invites* the World Health Organization to prepare, in consultation with the United Nations Secretariat, information regarding the views expressed in the technical literature on the following problems :

(*a*) The addictive properties and therapeutic advantages of synthetic narcotics as compared with natural narcotics;

(*b*) The status of scientific knowledge on the relationship between the chemical structure of a drug and its addictive properties;

(*c*) The relationship between the strongly analgesic qualities of a drug and its addiction-producing properties;

and to transmit this information to the Commission in order to enable it to give further consideration to the question of the studies required in this field and the method of carrying them out . . ."

synthesis employed. Although every available source has been called upon —publications in scientific periodicals as well as patent specifications and personal communications—the possibility of error in some of the details given is not excluded, and any suggestions for improvement will be gratefully received.

This general outline answers, at the same time, a question in which members of the Commission on Narcotic Drugs have repeatedly shown interest—namely, what starting materials are used in the various syntheses. These starting materials are quite often synthetic themselves, but for the purposes of this paper it was necessary to restrict the chemical steps shown to those reactions indispensable for a general understanding of the syntheses.

With the aim of increasing the practical value of the paper, some items not purely of a chemical nature have been added, e.g., an indication of the few pharmacopoeias which contain some of the substances mentioned, and a list of synonyms, in the compilation of which the Secretary of the Permanent Central Opium Board was most helpful.

The chemical description used is preferably that employed in WHO publications.

CLASSIFICATION OF SYNTHETIC DRUGS WITH MORPHINE-LIKE EFFECT

According to their chemical structure, the compounds of this type known up to the present fall into four major groups, each with a different basic chemical structure.

Pethidine group

Pethidine : 1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester
Bemidone : 1-methyl-4-(3-hydroxyphenyl)piperidine-4-carboxylic acid ethyl ester
Ketobemidone : 4-(3-hydroxyphenyl)-1-methyl-4-piperidyl ethyl ketone
Alphaprodine : α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine
Betaprodine : β-1,3-dimethyl-4-phenyl-4-propionoxypiperidine
Meprodine : β-1-methyl-3-ethyl-4-phenyl-4-propionoxypiperidine

Methadone group

Methadone : 4,4-diphenyl-6-dimethylaminoheptanone-3
Isomethadone : 4,4-diphenyl-5-methyl-6-dimethylaminohexanone-3
Methadol : 4,4-diphenyl-6-dimethylaminoheptanol-3
Acetylmethadol : 4,4-diphenyl-6-dimethylamino-3-acetoxyheptane
Phenadoxone : 4,4-diphenyl-6-morpholinoheptanone-3

Morphinan group

Levorphan : (—)-3-hydroxy-N-methylmorphinan
Racemorphan : (±)-3-hydroxy-N-methylmorphinan
Levomethorphan : (—)-3-methoxy-N-methylmorphinan
Racemethorphan : (±)-3-methoxy-N-methylmorphinan

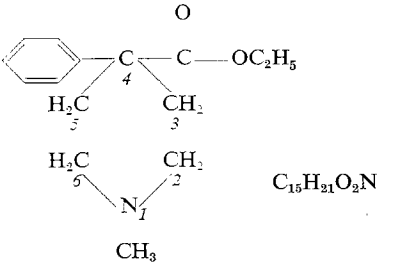
Dithienylbutenylamine group

3-dimethylamino-1,1-di-(2′-thienyl)-1-butene
3-ethylmethylamino-1,1-di-(2′-thienyl)-1-butene
3-diethylamino-1,1-di-(2′-thienyl)-1-butene

PETHIDINE GROUP

Pethidine

Formula :



$C_{15}H_{21}O_2N$

1-methyl-4-phenylpiperidine-4-carboxylic acid ethyl ester

Proposed international non-proprietary name : pethidine

Synonyms : († indicates that the name is used for the hydrochloride of the substance.) Adolens,† Alodan,† Antiduol,† Biphenal,† Centralgin,† D-140,† Demerol, Dispadol,† Dodonal,† Dolantal, Dolantin,† Dolantol,† Dolaren,† Dolarenil, Dolarin,† Dolatol,† Dolental,† Dolestine, Dolinal,† Dolisina,† Dolopetin,† Dolor, Dolosal,† Dolosil, Dolvanol,† Eudolat,† Felidin,† Gratidine,† Isonipecaine, Lydol, Meperidine, Mephedina,† Mephedine,† Operidine, Pantalgine,† Piridosal,† Precedyl,† Sauteralgyl,† Simesalgina,† Spasmedal, Suppolosal

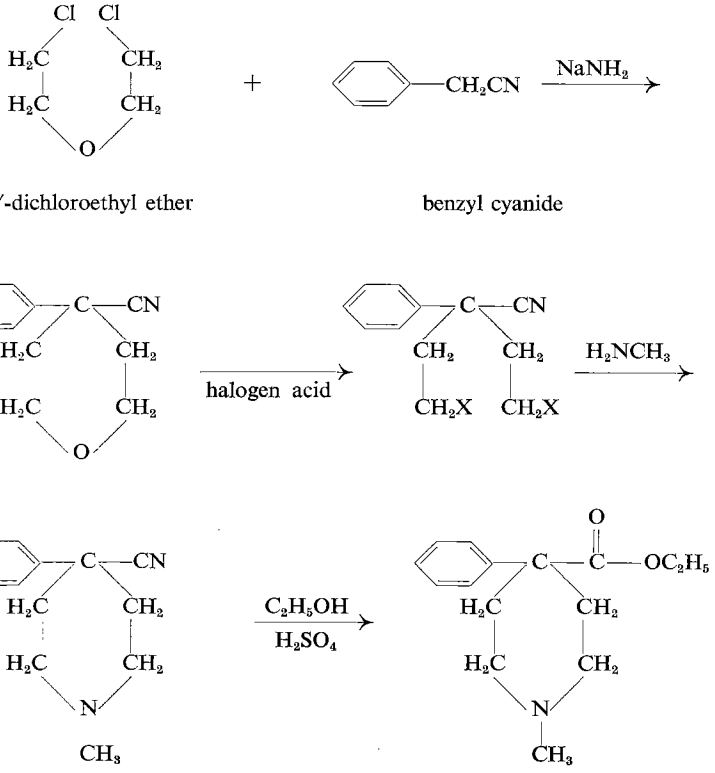
Pethidine (see Annex 1, page 1036, for description) is included in the *Pharmacopoea Internationalis* [36] and in the following national pharmacopoeias : *Pharmacopoea Danica*, 9th ed., 1948; *Codex français*, 7th ed., 1949; *British pharmacopoeia* 1953; *The pharmacopoeia of the United*

States of America, Fourteenth Revision, 1950; *Gosudarstvennaia farmakopeia Soiuza Sovetskikh Sotsialisticheskikh Respublik*, 8th ed., 1952, Addendum I.

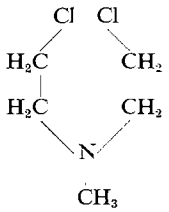
Synthesis :

(1) The first synthesis of pethidine by Eisleb [13] comprised the following steps :

First, β,β'-dichloroethyl ether was condensed with benzyl cyanide, using sodium amide as condensing agent. The resulting pyran derivative was treated with a halogen acid in order to open up the pyran ring. By treating with methylamine a new ring closure was brought about. Treatment of the resulting compound with alcohol and sulfuric acid resulted in the formation of pethidine.



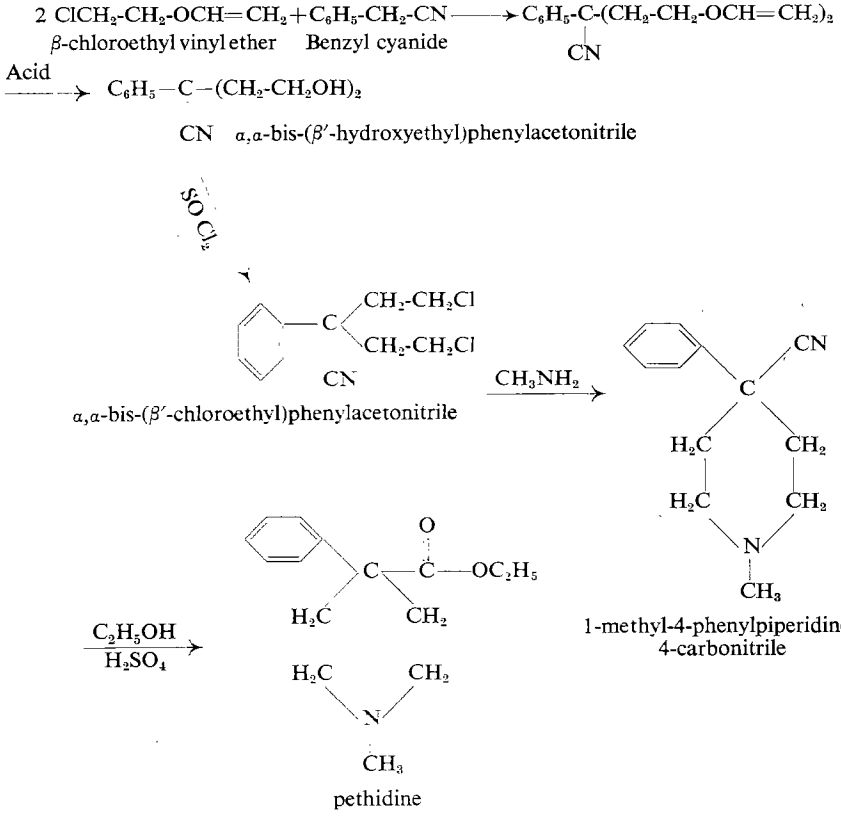
Furthermore, bis-(β-chloroethyl)methylamine was introduced instead of β,β'-dichloroethyl ether,[34] which facilitates and shortens the synthesis.



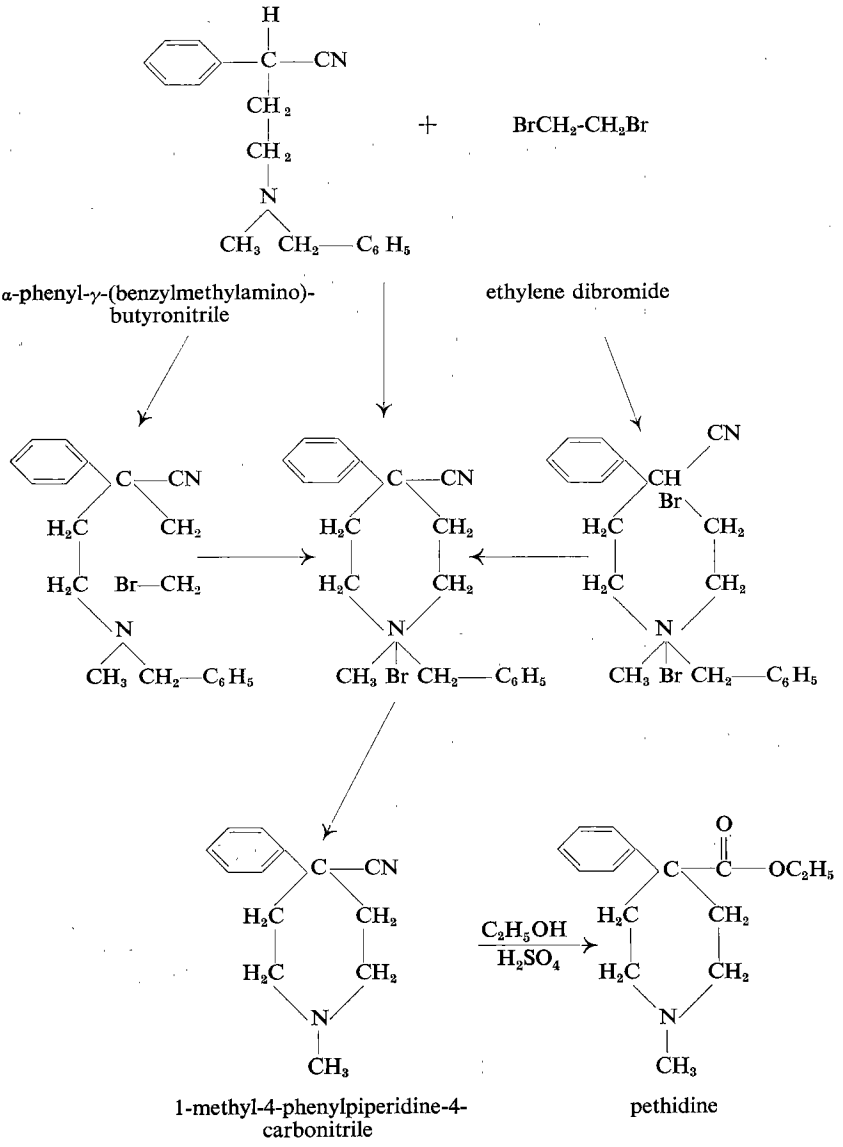
bis-(β-chloroethyl)methylamine

The use of bis-(β-chloroethyl)methylamine has, however, the disadvantage that, being a strong vesicant, it is harmful to the skin of the workers carrying out the process of manufacture.

(2) Another synthesis by Bergel, Morrison & Rinderknecht [5] starts from β-chloroethyl vinyl ether, which is condensed with benzyl cyanide. The resulting compound, when treated with acid, gives α,α-bis-(β′-hydroxyethyl)phenylacetonitrile, which when reacted with thionyl chloride gives α,α-bis-(β′-chloroethyl)phenylacetonitrile. The latter is then treated with methylamine which results in the formation of 1-methyl-4-phenylpiperidine-4-carbonitrile, from which pethidine is formed by saponification and esterification as previously described.



(3) Miescher & Kaegi [21] have developed a method starting from α-phenyl-γ-(methyl-benzylamino)butyronitrile and ethylene dibromide. These substances are allowed to react in presence of an acid-binding substance. The piperidine derivative obtained, which contains a quarternary nitrogen atom, is converted into 1-methyl-4-phenylpiperidine-4-carbonitrile by heating. This compound is then saponified and esterified into pethidine.



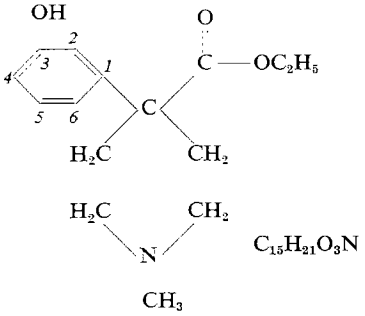
Instead of α-phenyl-γ-(methylbenzylamino)butyronitrile, the following compounds may be used : α-phenyl-γ-(dimethyl- or diethyl-amino)butyronitrile, α-(benzylhydroxy- or acylhydroxyphenyl)-γ-(methylbenzylamino)-butyronitrile, α-(*o*-anisyl)-γ-(methyldiphenylmethylamino)butyronitrile, α-(*m*-anisyl)-γ-dimethylaminobutyronitrile, α-phenyl-γ-(methylbenzylamino)-valeronitrile, α-naphthyl-γ-(dimethylamino)butyronitrile and α-phenyl-α-[*o*-(methylbenzylamino)cyclohexyl]acetonitrile.

Instead of ethylene dibromide the following compounds may be used : ethylene chlorobromide, ethylene diiodide, propylene 1, 2-dibromide, propylene 1,2-chlorobromide, butylene-1,2 or 2,3-dibromide, β-chloro-ethanol-*p*-toluenesulfonic acid ester, glycol-di-*p*-toluenesulfonic acid ester, and propane-1,2-dioldimethane sulfonic acid ester.

Any of the following acid-binding substances may be used: sodium, potassium, lithium, and calcium, in metallic form or in the form of their alcoholates, amides, hydrides, or hydrocarbon compounds (e.g., potassium tertiary butyloxide, sodium amide, sodium hydride, butyllithium, phenyl-sodium, phenyllithium).

Bemidone

Formula :



1-methyl-4-(3-hydroxyphenyl)piperidine-4-carboxylic acid ethyl ester

Proposed international non-proprietary name : bemidone

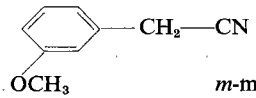
Synonym : Hydroxypethidine

Bemidone differs from pethidine by a hydroxyl group in position 3 of the benzene ring.

Synthesis :

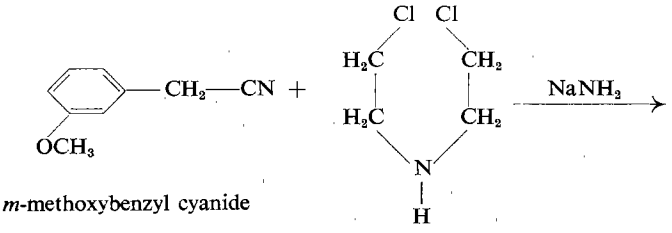
(1) Bemidone is synthesized in essentially the same way as pethidine, the sole difference being that, instead of benzyl cyanide, *m*-methoxybenzyl-cyanide[a] is used, in which one hydrogen is replaced by a methoxyl group (OCH_3),[31, 33] which, finally, is converted into an OH group.

[a] See also the general remark on this point (paragraph 2, page 1013).



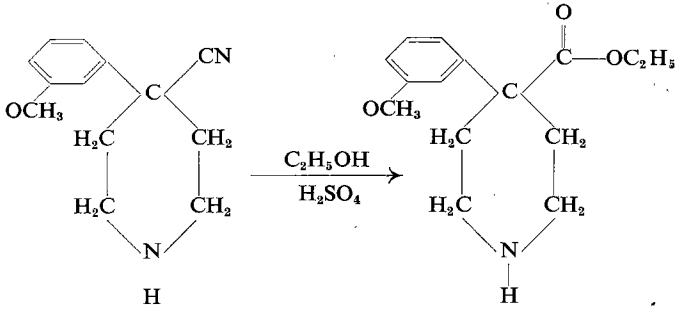
m-methoxybenzyl cyanide

(2) Bemidone can also be prepared in the following way, which differs from the earlier method in using bis-β-chloroethylamine (without the N-methyl group) and introducing the methyl group later by means of formaldehyde.[33]



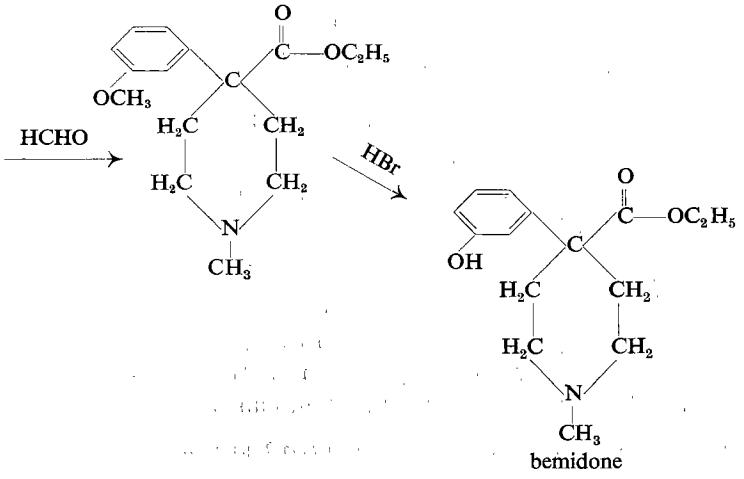
m-methoxybenzyl cyanide

bis-β-chloroethylamine



4-(*m*-methoxyphenyl)piperidine-4-carbonitrile

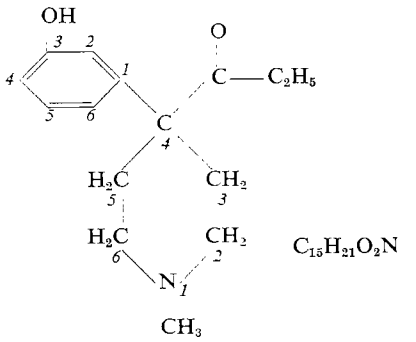
4-(*m*-methoxyphenyl)piperidine-4-carboxylic acid ethyl ester



bemidone

Ketobemidone

Formula :



4-(3-hydroxyphenyl)-1-methyl-4-piperidyl ethyl ketone

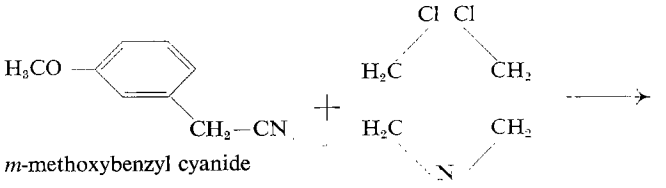
Proposed international non-proprietary name : ketobemidone

Synonyms : († indicates that the name is used for the hydrochloride of the substance.) Cliradon,† Hoechst 10720, K-4710, VIN 1539

Ketobemidone differs from bemidone by the presence of a keto group instead of a carboxyl group.

Synthesis :

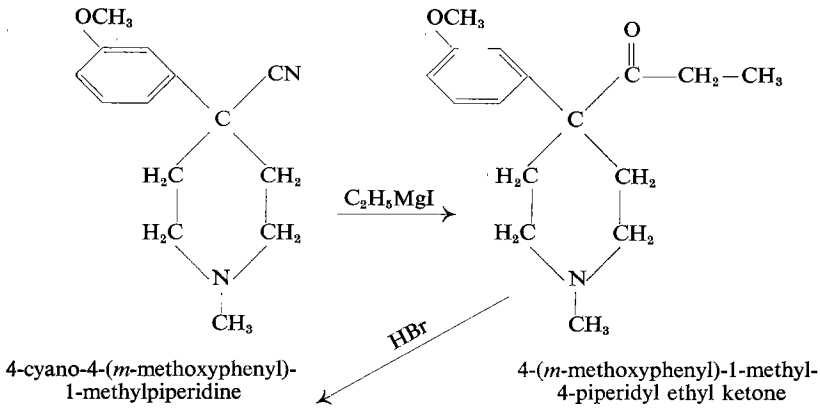
(1) Eisleb [14,34] produced ketobemidone by the following method : *m*-methoxybenzyl cyanide [b] is condensed with methyl-di-(2-chloroethyl)-amine, using an acid-binding agent. The resulting 4-cyano-4-(*m*-methoxyphenyl)-1-methylpiperidine is converted into 4-(*m*-methoxyphenyl)-1-methyl-4-piperidyl ethyl ketone by means of ethylmagnesium iodide (Grignard reaction). This ketone gives ketobemidone on treatment with hydrobromic acid.



m-methoxybenzyl cyanide

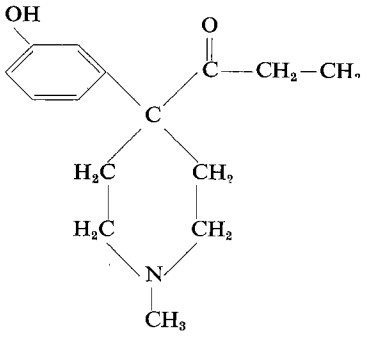
methyl-di-(2-chloroethyl)amine

[b] See also the general remark on this point (paragraph 2, page 1013).



4-cyano-4-(*m*-methoxyphenyl)-1-methylpiperidine

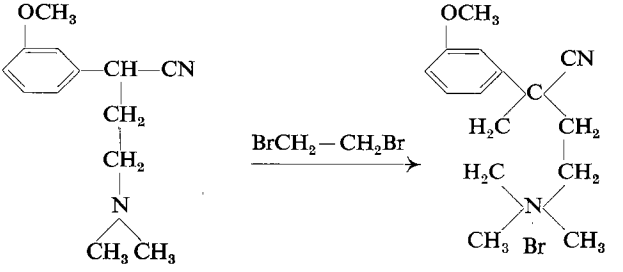
4-(*m*-methoxyphenyl)-1-methyl-4-piperidyl ethyl ketone



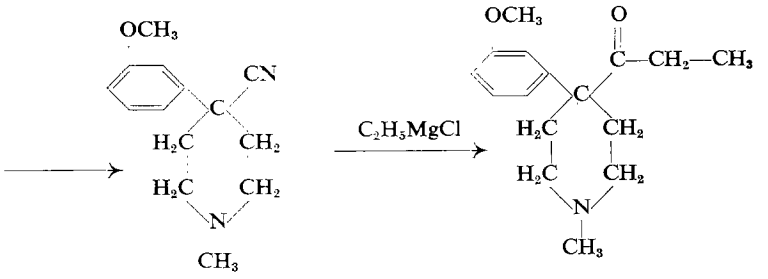
ketobemidone

(2) Miescher & Kaegi [22] have described another synthesis of ketobemidone, in which α-(*m*-methoxyphenyl)-γ-(dimethylamino)butyronitrile is reacted with ethylene dibromide to give 1,1-dimethyl-4-(*m*-methoxyphenyl)-4-cyanopiperidinium bromide.

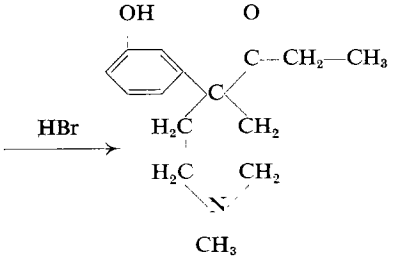
Methyl bromide is easily split off and the resulting compound is 1-methyl-4-(*m*-methoxyphenyl)-4-cyanopiperidine. By reacting with ethylmagnesiumchloride the methylated derivative of ketobemidone is formed. From this, ketobemidone is formed by treating with hydrobromic acid.



α-(*m*-methoxyphenyl)-γ-(dimethylamino)-butyronitrile

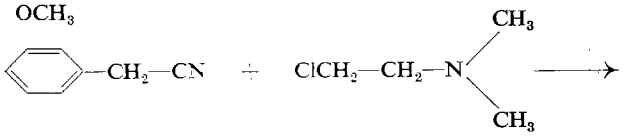


1-methyl-4-(*m*-methoxyphenyl)-4-cyanopiperidine

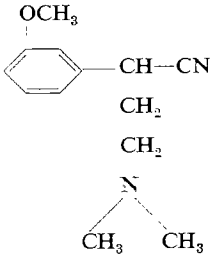


ketobemidone

The starting material α-(*m*-methoxyphenyl)-γ-(dimethylamino)butyronitrile is made by condensing *m*-methoxybenzyl cyanide with β-dimethylaminoethyl chloride.



m-methoxybenzyl cyanide β-dimethylaminoethyl chloride

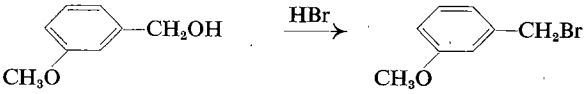


α-(*m*-methoxyphenyl)-γ-(dimethylamino)butyronitrile

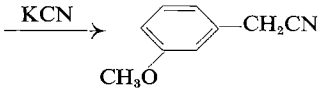
At this point a general remark might be permitted. The substances indicated as starting material for the synthesis of the final products discussed

before are frequently not easily available on the chemical market but have also to be prepared. An example might illustrate this situation. In order to obtain *m*-methoxybenzyl cyanide, the following procedures are used :

(1) Chakravarti & Rao:[8] *m*-methoxybenzyl alcohol is reacted with hydrogen bromide to *m*-methoxybenzyl bromide. Then *m*-methoxybenzyl bromide is reacted with potassium cyanide to form *m*-methoxybenzyl cyanide.

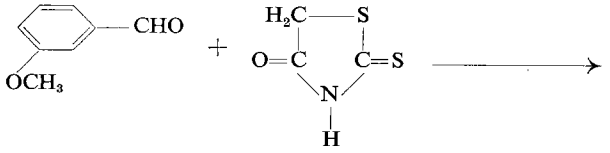


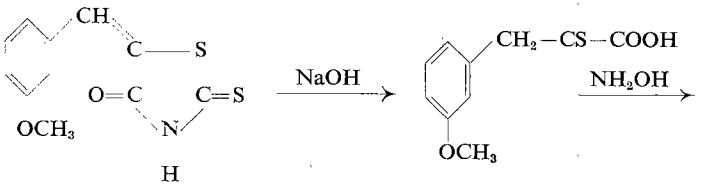
m-methoxybenzyl alcohol — *m*-methoxybenzyl bromide



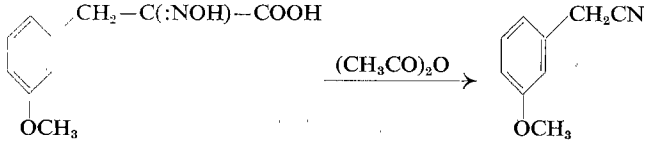
m-methoxybenzyl cyanide

(2) Another method, used by Avison & Morrison,[4] starts from *m*-methoxybenzaldehyde. When condensed with rhodanine this compound gives *m*-methoxybenzylidenerhodanine which, upon treatment with sodium hydroxide, gives *m*-methoxyphenyl-α-thiopyruvic acid. When *m*-methoxyphenyl-α-thiopyruvic acid is treated with hydroxylamine, *m*-methoxyphenyl-α-oximinopropionic acid is produced, which, upon reaction with acetic anhydride, gives *m*-methoxybenzyl cyanide.





m-methoxybenzylidenerhodanine — *m*-methoxyphenyl-α-thiopyruvic acid



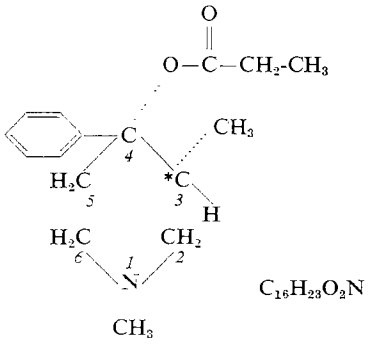
m-methoxyphenyl-α-oximinopropionic acid — *m*-methoxybenzyl cyanide

Alphaprodine, Betaprodine

These substances have the same chemical structure except for the stereoisomeric configuration at carbon-atom 3 (marked by an asterisk).

Alphaprodine is the *trans*-, and betaprodine the *cis*-isomer of these compounds.

Formula (alphaprodine) :

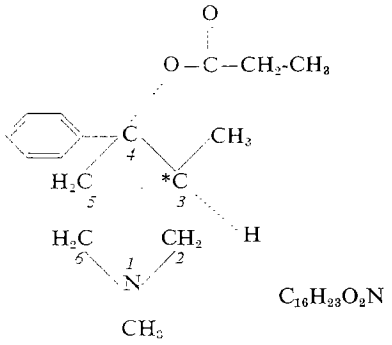


α-1,3-dimethyl-4-phenyl-4-propionoxypiperidine

Proposed international non-proprietary name : alphaprodine

Synonyms and trade names : Nisentil, Nisintil, NU-1196, Prisilidine

Formula (betaprodine) :

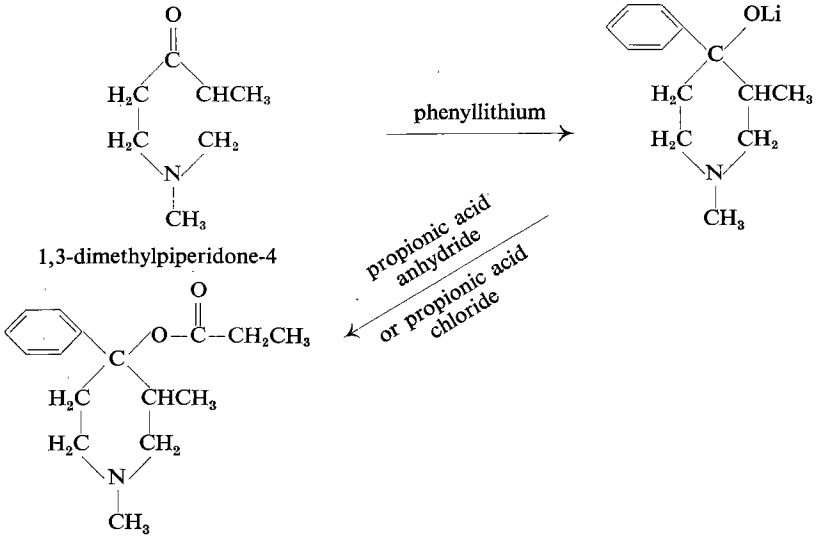


β-1,3-dimethyl-4-phenyl-4-propionoxypiperidine

Synonym : NU-1779

Synthesis :

Both alphaprodine and betaprodine are obtained in one and the same synthesis. In the method developed by Lee, Ziering & Berger,[6, 18] the synthesis comprises the following steps : 1,3-dimethylpiperidone-4 is reacted with phenyllithium to form the lithium derivative of 1,3-dimethyl-4-phenyl-4-hydroxypiperidine which, upon treatment with propionic acid chloride or propionic acid anhydride, yields a mixture of alphaprodine and betaprodine.



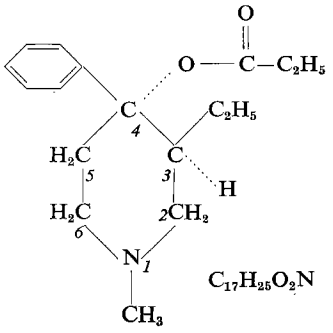
1,3-dimethylpiperidone-4

mixture of alphaprodine and betaprodine

The separation of the two stereoisomers is carried out by making use of their different solubilities in organic solvents.[37]

Formula :

Meprodine [c]



β-1-methyl-3-ethyl-4-phenyl-4-propionoxypiperidine

[c] Name used in the United Kingdom of Great Britain and Northern Ireland

Proposed international non-proprietary name : betameprodine

Synonym : NU-1932

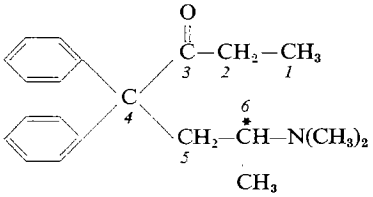
Synthesis :

Meprodine is synthesized in the same way as alphaprodine and betaprodine, using 1-methyl-3-ethylpiperidone-4 as starting material instead of 1,3-dimethylpiperidone-4.

METHADONE GROUP

Methadone

Formula :



$C_{21}H_{27}ON$

4,4-diphenyl-6-dimethylaminoheptanone-3

(also described as 6-dimethylamino-4,4-diphenyl-3-heptanone; furthermore, according to another numbering system, as 2-dimethylamino-4,4-diphenylheptanone-(5))

Proposed international non-proprietary name : methadone

Synonyms (racemic form) : († indicates that the name is used for the hydrochloride of the substance.) Adanon, Algidon,† Algil, Algolysin,† Algoxale,† Amidone, Amidosan, Butalgin, Depridol, Diaminon, Dianone, Dolafin, Dolamid, Dolcsona, Dolophine, Dorexol, Fenadone,† Heptadon, Heptanal, Hoechst 10820, Ketalgin, Mecodin, Mepecton, Mephenon, Miadone, Moheptan, Phenadon,† Physeptone,† Polamidon, Sin-Algin, Symoron, Turanone, Vermonyl †

Synonym (laevorotatory form) : Levadone (bitartrate)

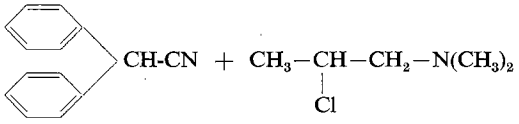
Methadone is included in the *Pharmacopoea Internationalis* [36] and in the following national pharmacopoeias : *Pharmacopoea Danica*, 9th ed., 1948, Addendum 1951 ; *British pharmacopoeia 1953* ; *Gosudarstvennaia farmakopeia Soiuza Sovetskikh Sotsialisticheskikh Respublik*, 8th ed., 1952, Addendum I.

Synthesis :

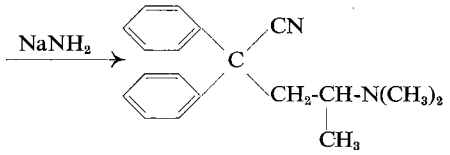
(1) According to the synthesis by Bockmühl & Ehrhart,[7,25] diphenylacetonitrile is condensed with 1-dimethylamino-2-chloropropane, using

sodium amide as condensing agent. In this way two isomeric aminonitriles are formed, 2,2-diphenyl-4-dimethylaminovaleronitrile and 2,2-diphenyl-3-methyl-4-dimethylaminobutyronitrile.

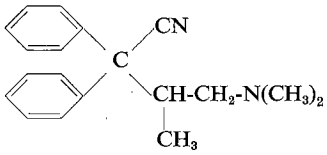
2,2-diphenyl-4-dimethylaminovaleronitrile yields methadone by the Grignard reaction; whereas 2,2-diphenyl-3-methyl-4-dimethylaminobutyronitrile yields isomethadone by the same reaction.



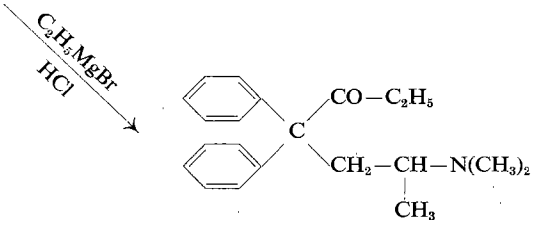
diphenylacetonitrile 1-dimethylamino-2-chloropropane



2,2-diphenyl-4-dimethylaminovaleronitrile

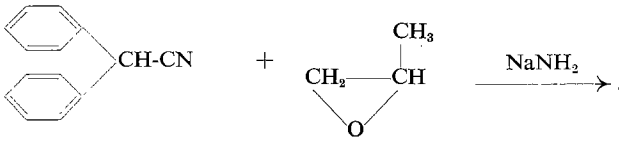


2,2-diphenyl-3-methyl-4-dimethylaminobutyronitrile

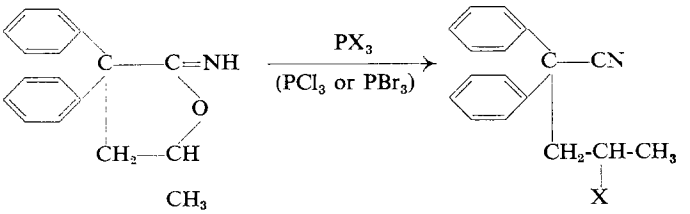


methadone

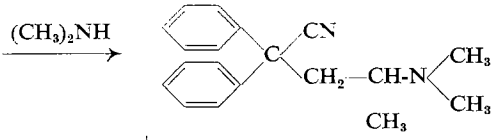
(2) Easton, Gardner & Stevens [11] have developed another synthesis for methadone in which diphenylacetonitrile is condensed with propylene oxide. Sodium amide is used as condensing agent. The resulting compound is treated with phosphorus trichloride or phosphorus tribromide to form 2,2-diphenyl-4-halogen-valeronitrile. On treating this compound with dimethylamine, the product is 2,2-diphenyl-4-dimethylaminovaleronitrile, which yields methadone on treatment with ethylmagnesium bromide.



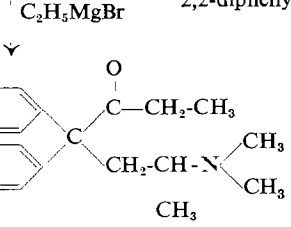
diphenylacetonitrile propylene oxide



2,2-diphenyl-4-halogen-valeronitrile

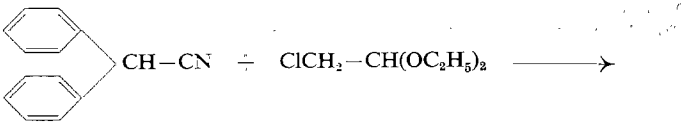


2,2-diphenyl-4-dimethylaminovaleronitrile

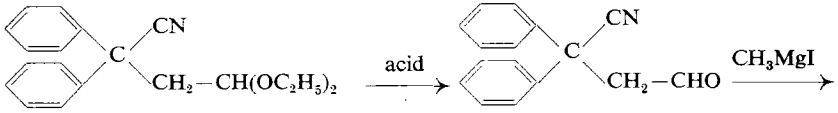


methadone

(3) Morrison & Rinderknecht [23] introduced a third synthesis. In this synthesis, diphenylacetonitrile is condensed with 1-chloro-2,2-diethoxyethane producing 3-cyano-3,3-diphenylpropionic aldehyde diethyl acetal, which on acid hydrolysis gives 3-cyano-3,3-diphenylpropionic aldehyde. This aldehyde on treatment with methylmagnesium iodide produces a secondary alcohol. When this alcohol is treated with thionyl chloride in the presence of dimethylaniline, a chloro compound is obtained which, on condensation with dimethylamine, gives 2,2-diphenyl-4-dimethylaminovaleronitrile. This is the precursor of methadone, which is then obtained by the Grignard reaction, as previously described.

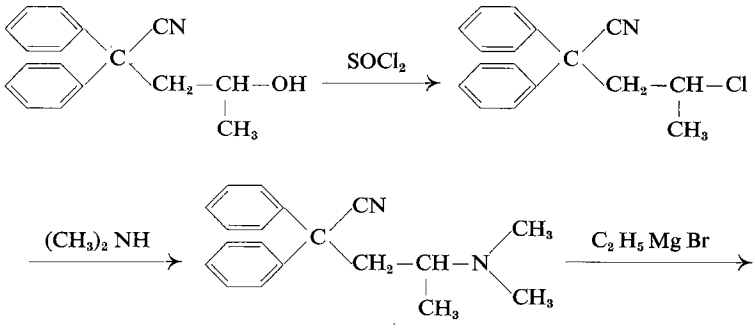


diphenylacetonitrile 1-chloro-2,2-diethoxyethane

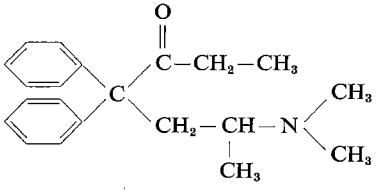


3-cyano-3,3-diphenylpropionic aldehyde diethyl acetal

3-cyano-3,3-diphenyl-propionic aldehyde



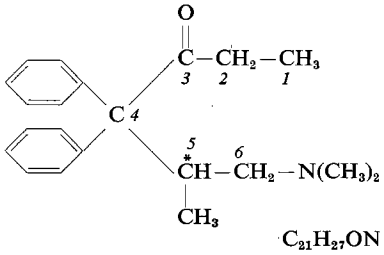
2,2-diphenyl-4-dimethylaminovaleronitrile



methadone

Isomethadone

Formula :



$C_{21}H_{27}ON$

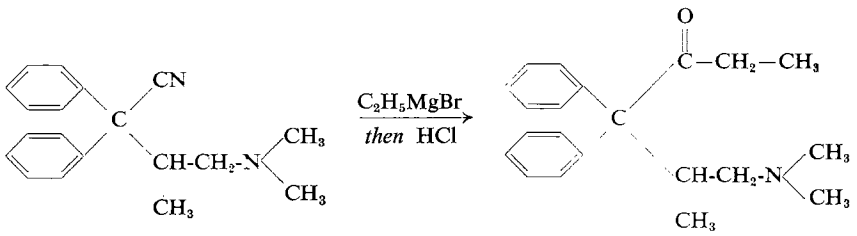
4,4-diphenyl-5-methyl-6-dimethylaminohexanone-3
(also described as 6-dimethylamino-5-methyl-4,4-diphenyl-3-hexanone; furthermore, according to another numbering system, as 1-dimethylamino-2-methyl-3,3-diphenyl-hexanone-4)

Proposed international non-proprietary name : isomethadone.

Synonyms : Isoadanon, Isoamidone

Synthesis :

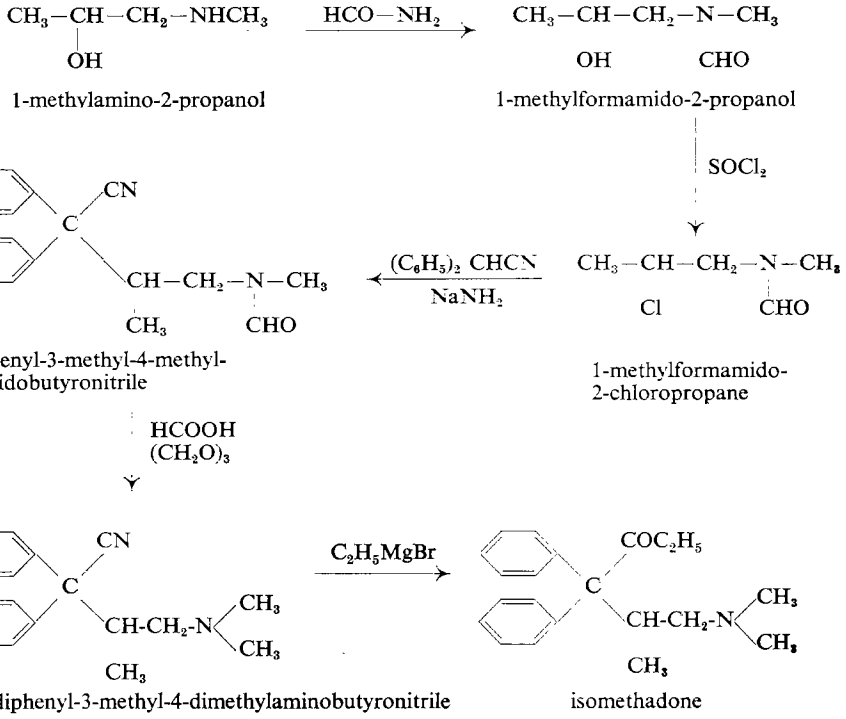
(1) According to the synthesis by Bockmühl & Ehrhart,[7] for making methadone, 2,2-diphenyl-3-methyl-4-dimethylaminobutyronitrile was formed. This substance, on treatment with ethylmagnesium bromide, yields isomethadone (see page 1018).



2,2-diphenyl-3-methyl-4-dimethylamino-butyronitrile

isomethadone

(2) Sletzinger & Tishler[30] have devised the following method which enables isomethadone to be produced without simultaneous production of methadone : 1-methylamino-2-propanol is reacted with formamide to produce 1-methylformamido-2-propanol, which is then treated with thionyl chloride to form 1-methylformamido-2-chloropropane. This compound is treated with the reaction product of diphenylacetonitrile and sodamide to produce 2,2-diphenyl-3-methyl-4-methylformamidobutyronitrile. The latter is reduced by treatment with formic acid and trioxane (or paraformaldehyde) to form 2,2-diphenyl-3-methyl-4-dimethylamino-butyronitrile, which on treatment with ethylmagnesium bromide forms isomethadone.



1-methylamino-2-propanol

1-methylformamido-2-propanol

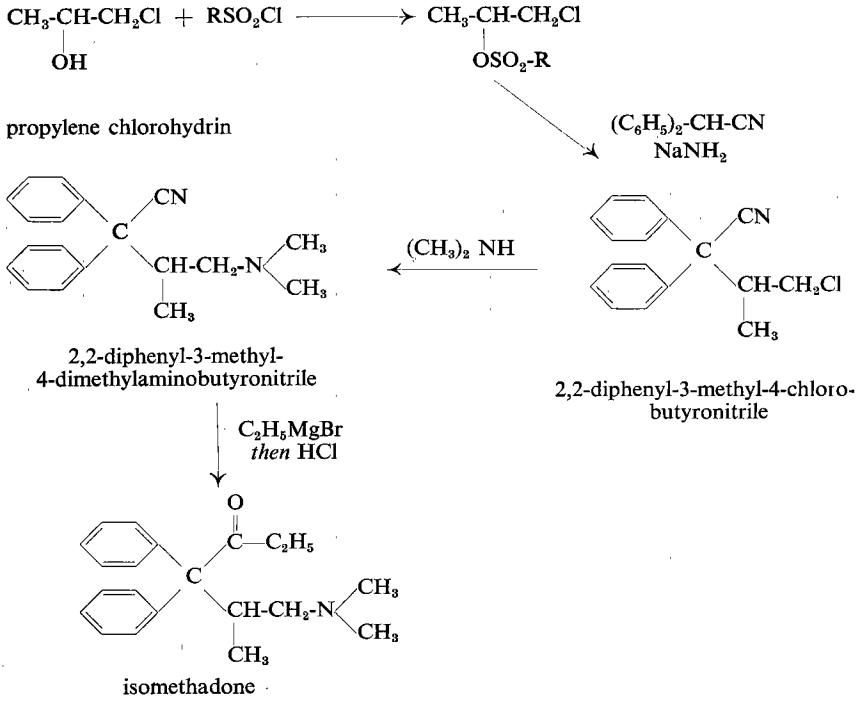
2,2-diphenyl-3-methyl-4-methyl-formamidobutyronitrile

1-methylformamido-2-chloropropane

2,2-diphenyl-3-methyl-4-dimethylaminobutyronitrile

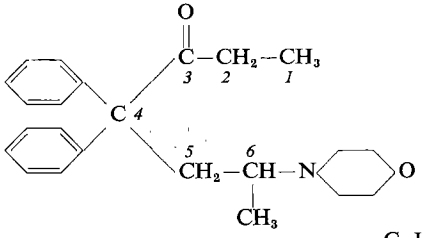
isomethadone

(3) An improved method has recently been introduced by Chamberlin & Tishler.[9] Propylene chlorohydrin is reacted with an organic sulfonyl chloride to produce the corresponding 1-methyl-2-chloroethylsulfonate compound, which is then treated with the reaction product of diphenylacetonitrile and sodamide. This produces 2,2-diphenyl-3-methyl-4-chlorobutyronitrile which upon treatment with dimethylamine forms 2,2-diphenyl-3-methyl-4-dimethylaminobutyronitrile. From this compound isomethadone is obtained by treatment with ethylmagnesium bromide, as previously described.



Phenadoxone

Formula :



$C_{23}H_{29}O_2N$

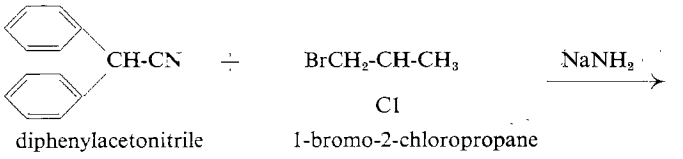
4,4-diphenyl-6-morpholinoheptanone-3

Proposed international non-proprietary name : phenadoxone

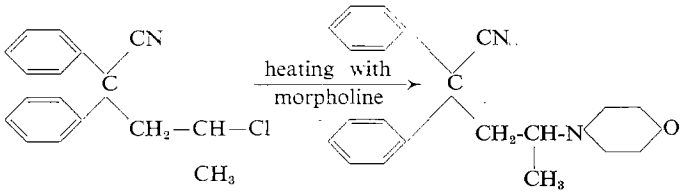
Synonyms : (†indicates that the name is used for the hydrochloride of the substance.) C.B. 11, Heptalgin,† Heptalin†

Synthesis :

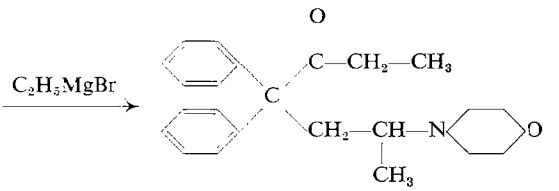
(1) According to the method of Hems & Elks,[16] this compound is prepared by condensing diphenylacetonitrile with 1-bromo-2-chloropropane under the influence of sodium amide. The resulting product, 2,2-diphenyl-4-chlorovaleronitrile, is heated with morpholine which gives 4-morpholino-2,2-diphenylvaleronitrile. The latter, on treatment with ethylmagnesium bromide, gives phenadoxone.



diphenylacetonitrile 1-bromo-2-chloropropane

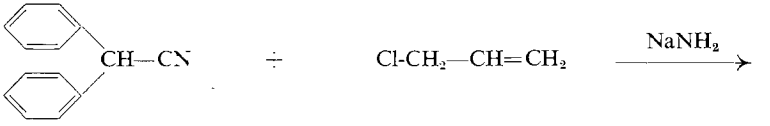


2,2-diphenyl-4-chlorovaleronitrile 2,2-diphenyl-4-morpholinovaleronitrile

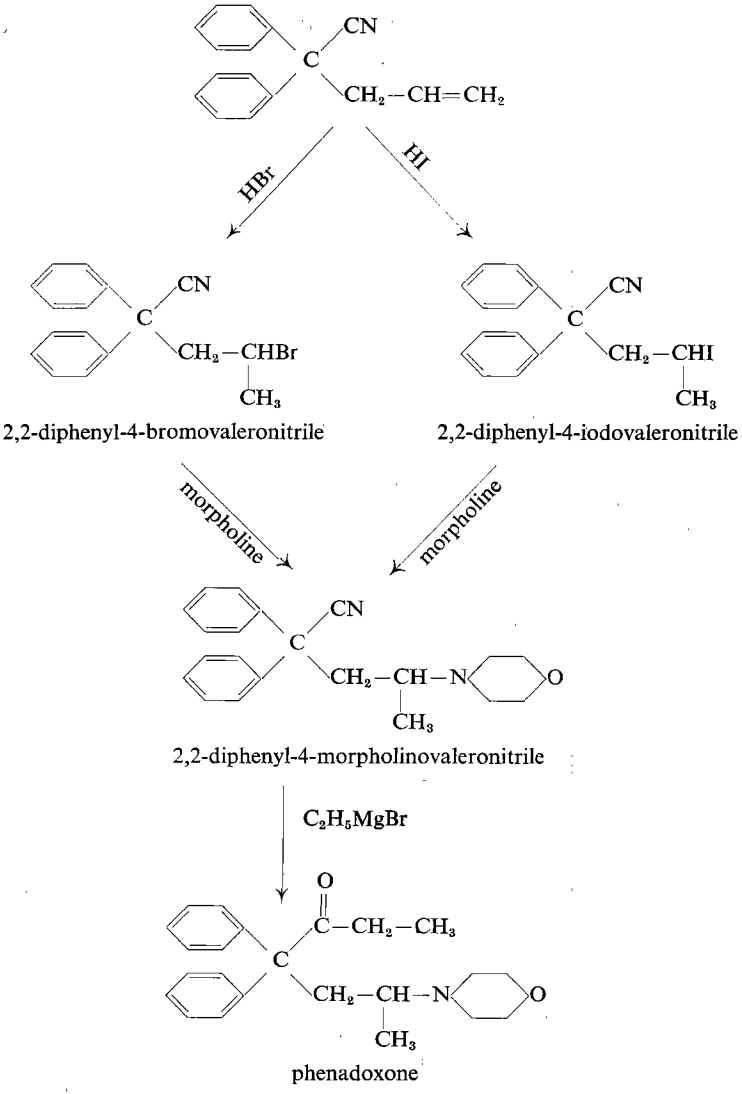


phenadoxone

(2) In another synthesis, developed by Attenburrow, Elks, Hems & Speyer,[3] diphenylacetonitrile is condensed with allyl chloride. By adding hydrogen bromide or hydrogen iodide to the resulting olefin, 2,2-diphenyl-4-halogen-valeronitrile is formed; heating with morpholine and treating with ethylmagnesium bromide results in phenadoxone.



diphenylacetonitrile allyl chloride



2,2-diphenyl-4-bromovaleronitrile

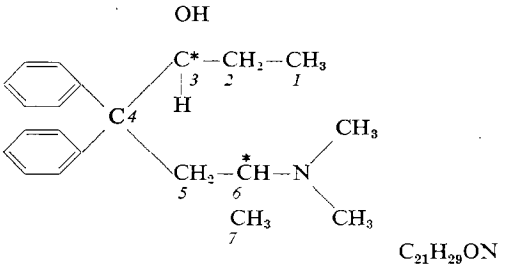
2,2-diphenyl-4-iodovaleronitrile

2,2-diphenyl-4-morpholinovaleronitrile

phenadoxone

Methadols

The methadols are reduction products of methadone. They all have the following fundamental structure :



4,4-diphenyl-6-dimethylamino-3-heptanol

Because of the two asymmetric carbon atoms (marked by an asterisk) six methadols are theoretically possible. These compounds are the following:

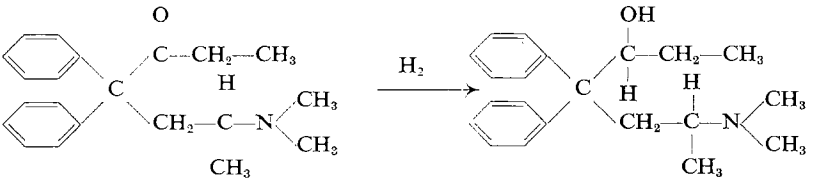
α-(±)-methadol	β-(±)-methadol
α-(−)-methadol	β-(−)-methadol
α-(+)-methadol	β-(+)-methadol

The α- and β- refer to the stereometric configuration, while (+)- and (—)- refer to optical isomerism.

Synonyms : Amidol, N.I.H.-2933

Synthesis :

The α-methadols are made by the reduction of the keto group of methadone by platinum oxide hydrogenation or lithium aluminium hydride reduction : [20, 32]

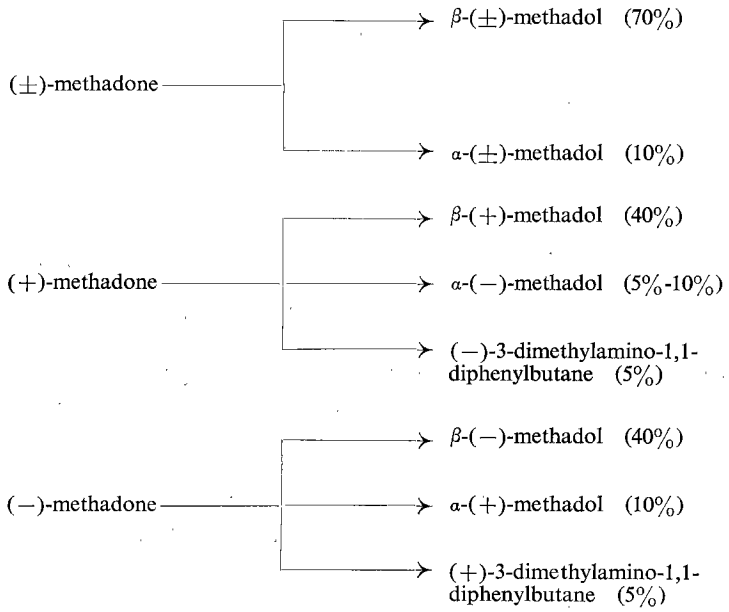


Pohland, Marshall & Carney [21] have reported a certain peculiarity concerning the optical isomerism of the α-methadols, their optical rotation being opposite to that of the parent ketone :

(—)-methadone ⟶ α-(+)-methadol

(+)-methadone ⟶ α-(−)-methadol

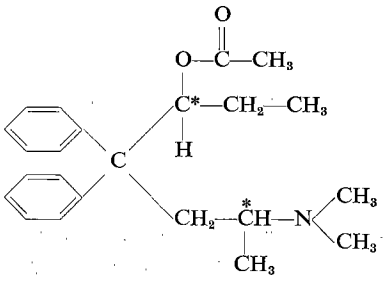
The β-methadols are formed when sodium propanol reduction is employed instead of platinum oxide. Contrary to the α-methadols, the β-methadols retain the optical rotation of their parent ketone.[12]



As may be seen from this tabulation, the β-forms are produced in much greater quantity than the α-forms by this type of reduction.

Acetylmethadols

General fundamental structure :



4,4-diphenyl-6-dimethylamino-3-acetoxyheptane (also described as 6-dimethylamino-4,4-diphenyl-3-acetoxyheptane)

Synonyms : Amidol acetate, Methadyl acetate, N.I.H.-2953

Owing to the presence of two asymmetric carbons (marked by an asterisk) six compounds corresponding to the various methadols exist.

Synthesis :

The acetylmethadols are synthesized by heating the corresponding methadol with acetic anhydride.[10, 12, 20, 24, 32]

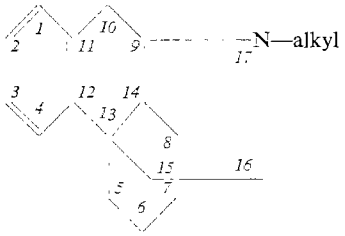
Isomethadols and Acetylisomethadols

In a corresponding way, isomethadols and acetylisomethadols can be synthesized starting from isomethadone.[19]

MORPHINAN GROUP

In 1946 Grewe & Mondon [15] described a relatively simple synthesis of morphinan, which can be regarded as the basic compound of the morphine series.

General formula :

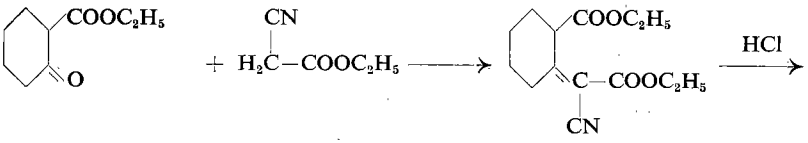


By inserting different radicals in position 2, 3, or on nitrogen, different morphinan derivatives are obtained. The first compound in this series was N-methylmorphinan.

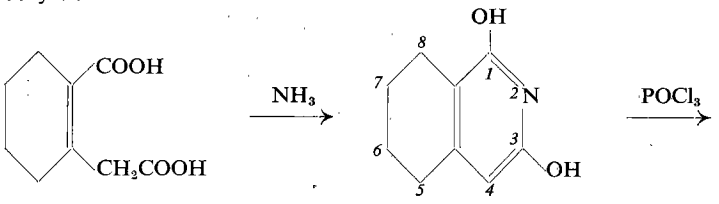
N-methylmorphinan

Synthesis :

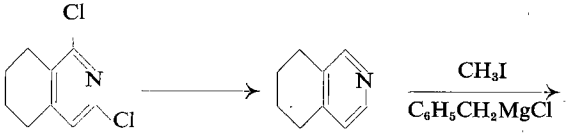
Grewe's synthesis of N-methylmorphinan starts from ethyl cyclohexanone-*o*-carboxylate which is condensed with ethyl cyanoacetate. The reaction product is hydrolysed to 3,4,5,6-tetrahydrohomophthalic acid, which, upon treatment with ammonia, yields 1,3-dihydroxy-5,6,7,8-tetrahydroisoquinoline. Removal of the hydroxyl group through chlorination and reduction leads to 5,6,7,8-tetrahydroisoquinoline. Treatment of the latter compound with methyl iodide and benzylmagnesium chloride gives 1-benzyl-N-methyl-1,2,5,6,7,8-hexahydroisoquinoline. Hydrogenation yields 1-benzyl-N-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline which, on treatment with phosphoric acid, gives N-methylmorphinan.



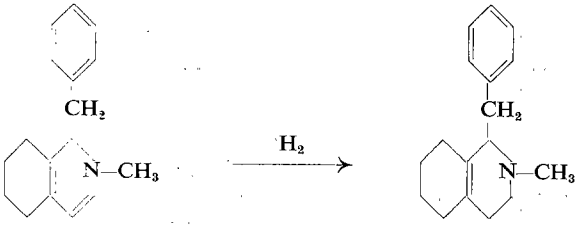
ethyl cyclohexanone-*o*-carboxylate ethyl cyanoacetate



3,4,5,6,-tetrahydrohomophthalic acid 1,3-dihydroxy-5,6,7,8-tetrahydroisoquinoline

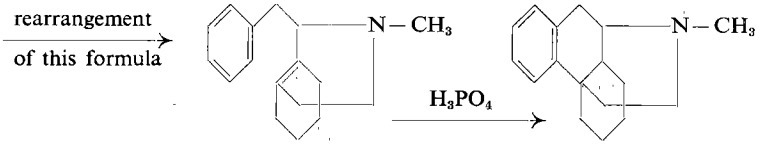


5,6,7,8-tetrahydro-isoquinoline



1-benzyl-N-methyl-1,2,5,6,7,8-hexahydroisoquinoline

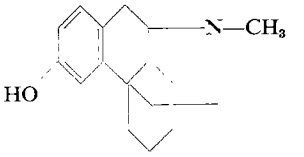
1-benzyl-N-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline



N-methylmorphinan

3-hydroxy-N-methylmorphinan

Formula :



3-hydroxy-N-methylmorphinan

The drugs of this group under international narcotics control are :

Levorphan : [d] (—)-3-hydroxy-N-methylmorphinan, also described as *l*-3-hydroxy-N-methylmorphinan

Synonyms : Dromoran, Laevo-Dromoran tartrate

Racemorphan : [d] (±)-3-hydroxy-N-methylmorphinan, also described as rac. 3-hydroxy-N-methylmorphinan

Synonym : Cetarin

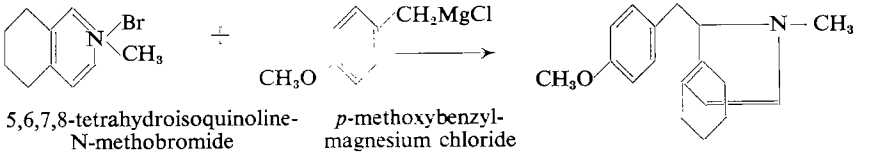
(The name Dromoran was previously given to Racemorphan but is now used for Levorphan.)

Synthesis :

(1) 3-Hydroxy-N-methylmorphinan was first made by Schnider & Grüssner [26] in the following way : 5,6,7,8-tetrahydroisoquinoline is treated with methyl bromide to form 5,6,7,8-tetrahydroisoquinoline-N-methobromide. This compound is condensed with *p*-methoxybenzylmagnesium chloride. In this way 1-(*p*-methoxybenzyl)-N-methyl-1,2,5,6,7,8-hexahydroisoquinoline is formed. By reduction with hydrogen (palladium-black as catalyst) 1-(*p*-methoxybenzyl)-N-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline results, which, on heating with phosphoric acid, gives 3-hydroxy-N-methylmorphinan.

5,6,7,8-tetrahydroisoquinoline

5,6,7,8-tetrahydroisoquinoline-N-methobromide

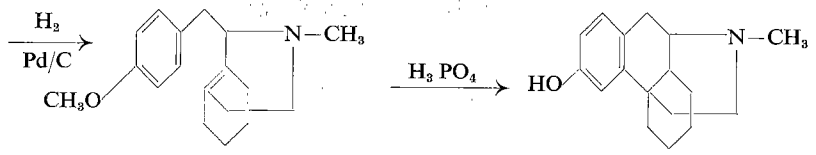


5,6,7,8-tetrahydroisoquinoline-N-methobromide

p-methoxybenzylmagnesium chloride

1-(*p*-methoxybenzyl)-N-methyl-1,2,5,6,7,8-hexahydroisoquinoline

[d] Proposed international non-proprietary name



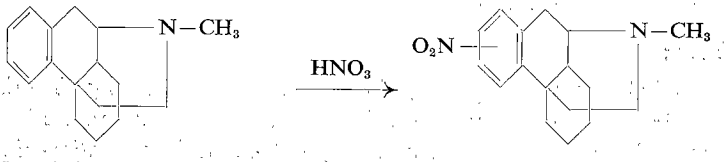
1-(*p*-methoxybenzyl)-N-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline

3-hydroxy-N-methylmorphinan

3-Hydroxy-N-methylmorphinan is also prepared, by the same authors,[26] with a better yield from N-methylmorphinan or from 1-benzyl-N-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline.

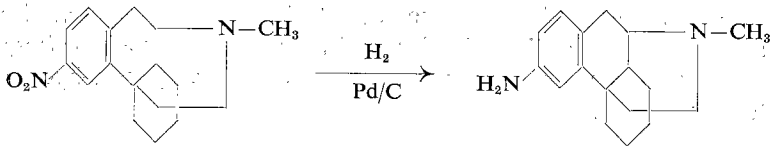
(2) The synthesis of 3-hydroxy-N-methylmorphinan from N-methylmorphinan comprises the following steps :

N-methylmorphinan is treated with nitric acid to form two isomeric nitro compounds, one of them being 3-nitro-N-methylmorphinan. This compound is reduced to 3-amino-N-methylmorphinan, which, upon diazotization and heating, gives 3-hydroxy-N-methylmorphinan.



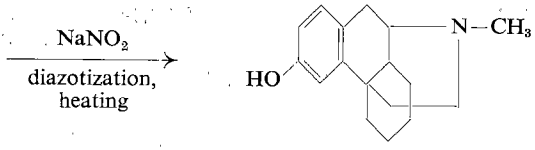
N-methylmorphinan

mixture of 2- and 3-nitro-N-methylmorphinan



3-nitro-N-methylmorphinan

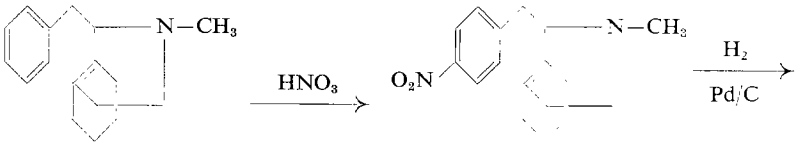
3-amino-N-methylmorphinan



3-hydroxy-N-methylmorphinan

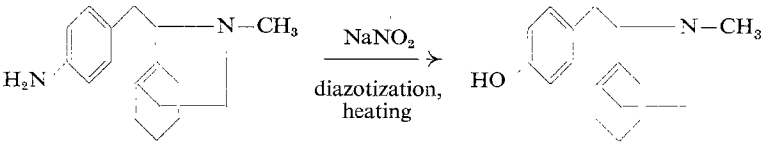
(3) The synthesis of 3-hydroxy-N-methylmorphinan from 1-benzyl-N-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline is as follows :[26] 1-benzyl-

N-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline is nitrated to 1-(*p*-nitrobenzyl)-N-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline, which is reduced to 1-(*p*-aminobenzyl)-N-methyloctahydroisoquinoline. This compound gives, by diazotization and heating, 1-(*p*-hydroxybenzyl)-N-methyloctahydroisoquinoline which, upon heating with phosphoric acid, gives 3-hydroxy-N-methylmorphinan.



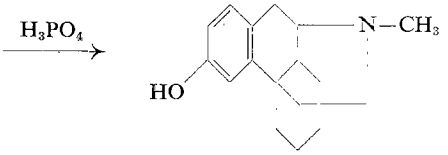
1-benzyl-N-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline

1-(*p*-nitrobenzyl)-N-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline



1-(*p*-aminobenzyl)-N-methyl-octahydroisoquinoline

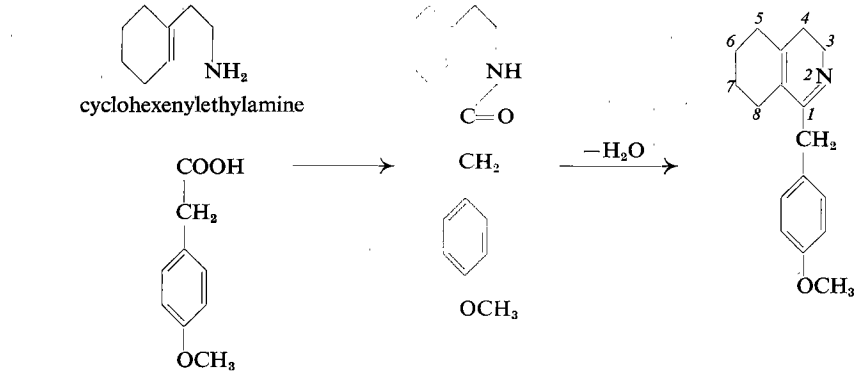
1-(*p*-hydroxybenzyl)-N-methyl-octahydroisoquinoline



3-hydroxy-N-methylmorphinan

(4) Another method for the synthesis of 3-hydroxy-N-methylmorphinan (Schnider & Hellerbach[28, 29]) starts from cyclohexenylethylamine or cyclohexenylethylmethylamine which is condensed with *p*-methoxyphenylacetic acid[e] to *p*-methoxyphenylacetic acid cyclohexenylethylamide. This compound, on treatment with phosphorus oxychloride or phosphorus pentoxide (removal of 1 molecule of water), yields 1-(*p*-methoxybenzyl)-3,4,5,6,7,8-hexahydroisoquinoline which, on reduction (with Raney nickel), yields 1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline. This substance, on methylation and cyclization, yields 3-hydroxy-N-methylmorphinan.

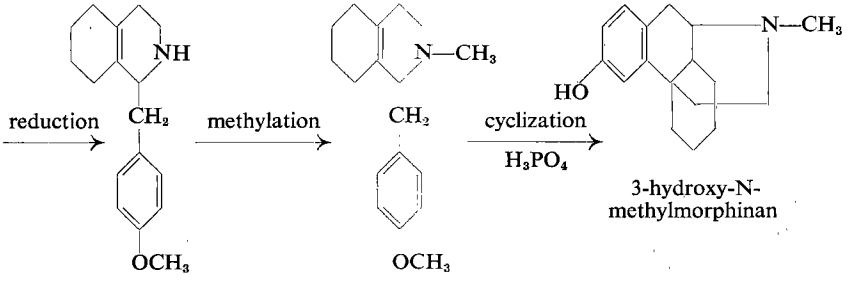
[e] *p*-Methoxyphenylacetic acid chloride can also be used.



p-methoxyphenylacetic acid

p-methoxyphenylacetic acid cyclohexenylethylamide

1-(*p*-methoxybenzyl)-3,4,5,6,7,8-hexahydroisoquinoline

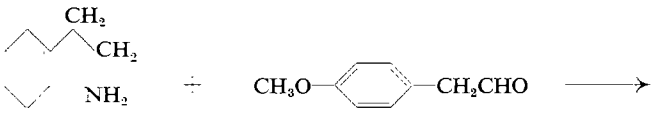


1-(*p*-methoxybenzyl)-1,2,3,4,5,6,7,8-octahydroisoquinoline

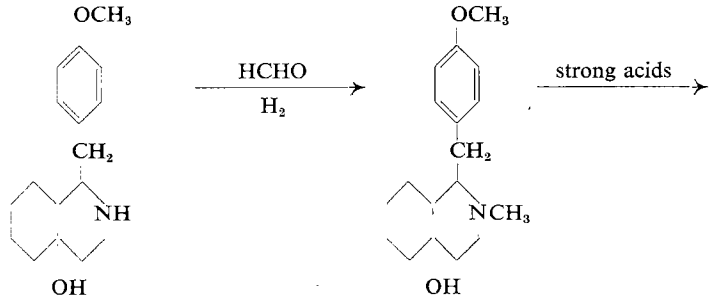
1-(*p*-methoxybenzyl)-N-methyl-1,2,3,4,5,6,7,8-octahydroisoquinoline

3-hydroxy-N-methylmorphinan

(5) The most recent synthesis by Henecka, aimed at reducing the number of steps, includes the following reactions:[17] cyclohexenylethylamine is condensed with *p*-methoxyphenylacetaldehyde bisulfite. The reaction product, 1-(*p*-methoxybenzyl)-10-hydroxydecahydroisoquinoline, is then methylated, e.g., by formaldehyde and Raney nickel, to N-methyl-1-(*p*-methoxybenzyl)-10-hydroxydecahydroisoquinoline. This compound, when heated with concentrated acids, gives directly 3-hydroxy-N-methylmorphinan.

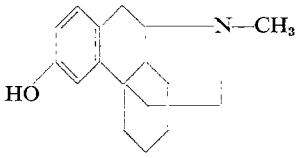


cyclohexenylethylamine + *p*-methoxyphenylacetaldehyde →



1-(*p*-methoxybenzyl)-10-hydroxy-decahydroisoquinoline

N-methyl-1-(*p*-methoxybenzyl)-10-hydroxydecahydroisoquinoline



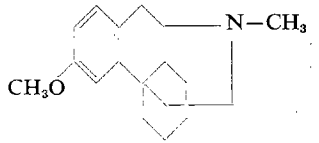
3-hydroxy-N-methylmorphinan

The best way to split 3-hydroxy-N-methylmorphinan into its optical antipodes is by means of D-tartaric acid.[27]

The addiction liability, and consequently the need of control, is confined to the laevogyre compound. The dextro-isomer has antitussive but no significant analgesic or other morphine-like effect. The production of the dextro-isomer by the synthesis described would necessitate the accumulation of an excess of the laevo-isomer. It can be avoided by resolution before the final stage completing the synthesis on the dextro-isomer only.[25a]

3-methoxy-N-methylmorphinan

Formula :



3-methoxy-N-methylmorphinan

The drugs of this group under international narcotics control are :

Levomethorphan : *f* (—)-3-methoxy-N-methylmorphinan, also described as *l*-3-methoxy-N-methylmorphinan

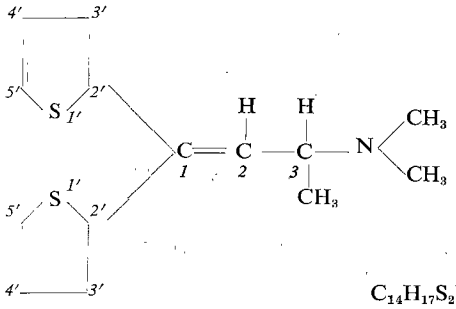
Racemethorphan : *f* (±)-3-methoxy-N-methylmorphinan, also described as rac. 3-methoxy-N-methylmorphinan

Levomethorphan and racemethorphan are methyl ethers of the corresponding hydroxy-N-methylmorphinan compounds. They are prepared by methylation of hydroxy-N-methylmorphinan, in the same way as the methylation of morphine to codeine, e.g., by using phenyltrimethylammonium hydroxide (personal communication from O. Schnider).

DITHIENYLBUTENYLAMINE GROUP

3-dimethylamino-1,1-di-(2′-thienyl)-1-butene

Formula :



$C_{14}H_{17}S_2N$

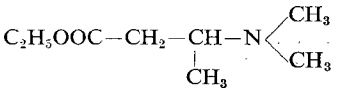
Synthesis :

According to Adamson[1,2] (and personal communication), this compound is synthesized in the following way : β-methylacrylic acid ethyl ester is condensed with dimethylamine to yield β-dimethylaminobutyric acid ethyl ester, which, on treatment with 2′-thienyllithium, gives 3-dimethylamino-1,1-di-(2′-thienyl)butan-1-ol. On heating with hydrochloric acid, this compound is dehydrated to 3-dimethylamino-1,1-di-(2′-thienyl)-1-butene.

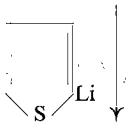
$$C_2H_5OOC-CH=\underset{\displaystyle CH_3}{\underset{|}{CH}} + NH(CH_3)_2 \longrightarrow$$

β-methylacrylic acid ethyl ester dimethylamine

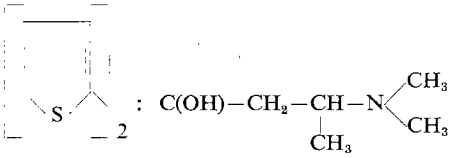
f Proposed international non-proprietary name



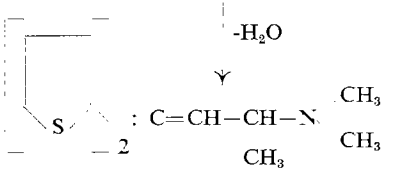
β-dimethylaminobutyric acid ethyl ester



2-thienyllithium



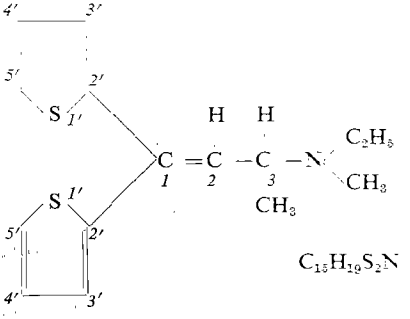
3-dimethylamino-1,1-di-(2′-thienyl)butan-1-ol



3-dimethylamino-1,1-di-(2′-thienyl)-1-butene

3-ethylmethylamino-1,1-di-(2′-thienyl)-1-butene

Formula :

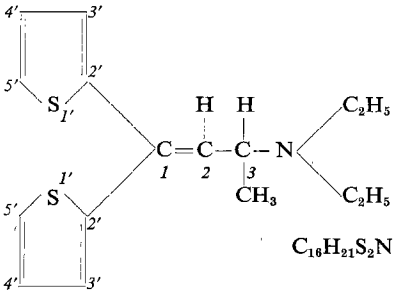


Synthesis :

This compound is synthesized in the same way as 3-dimethylamino-1,1-di-(2′-thienyl)-1-butene (see page 1034), the sole difference being that methylethylamine is used as starting material in place of dimethylamine.

3-diethylamino-1,1-di-(2′-thienyl)-1-butene

Formula :



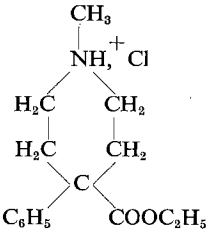
$C_{16}H_{21}S_2N$

Synthesis :

This compound is synthesized in the same way as 3-dimethylamino-1, 1-di-(2′-thienyl)-1-butene (see page 1034), the sole difference being that diethylamine is used as starting material in place of dimethylamine.

Annex 1 [g]

PETHIDINI HYDROCHLORIDUM



$C_{15}H_{21}O_2N,HCl$ Mol. Wt. 283.8

Pethidine hydrochloride is the hydrochloride of ethyl 1-methyl-4-phenyl-piperidyl-4-carboxylate. It contains not less than 99.0% of $C_{15}H_{21}O_2N,HCl$.

[g] Reproduced from the *Pharmacopoea Internationalis* [86]

Description

A white, crystalline powder; odourless; taste, acid and bitter.

Solubility

Very soluble in water; freely soluble in ethanol (90%) reagent (R) and in chloroform R; practically insoluble in ether R.

Identification

(1) To 5 ml of a 2.0% w/v solution in water add 15 ml of a saturated solution of trinitrophenol R in water; a yellow crystalline precipitate of pethidine picrate is produced. Drain the precipitate, wash with water, and dry; melting-range of the pethidine picrate, 188° to 191° C.

(2) Yields the reactions characteristic of chlorides.

Melting-range

187° to 189° C

Reaction

A 5.0% w/v solution in water is neutral to methyl red test solution (TS).

Loss on drying

When dried to constant weight at 110°, loses not more than 0.5% of its weight.

Residue on ignition

Not more than 0.1%

Assay

Place about 0.3 g, accurately weighed, in a separator, dissolve in 25 ml of water and add 5 ml of sodium hydroxide TS. Extract the solution with five successive quantities of 25 ml, 20 ml, 20 ml, 10 ml, and 10 ml of ether R. Wash the combined ethereal solutions with 10 ml of water, add 20 ml of 0.1 N hydrochloric acid, and shake. Evaporate the ether on a water bath and titrate the excess of acid with 0.1 N sodium hydroxide, using methyl red TS as indicator. Each ml of 0.1 N hydrochloric acid is equivalent to 0.02838 g of $C_{15}H_{21}O_2N,HCl$.

Storage

Pethidine hydrochloride should be kept in a well-closed container, protected from light.

ACKNOWLEDGEMENTS

The authors are indebted to Dr. O. Schnider of Basle, Switzerland, and Drs. N. B. Eddy and L. F. Small of Bethesda, USA, for useful advice in the final preparation of the paper.

RÉSUMÉ

Cet article est le premier d'une série qui traitera de la chimie, de la pharmacologie, de la valeur thérapeutique et de l'effet toxicomanogène de substances synthétiques à effet morphinique.

Quatre groupes principaux sont décrits, ayant chacun une structure fondamentale particulière : péthidine, méthadone, morphinane et dithiénylbutylamine. Pour chaque

substance appartenant à l'un de ces groupes, les auteurs donnent la formule, les synonymes et les méthodes de synthèse. Une description de la péthidine, conforme aux spécifications de la *Pharmacopoea Internationalis* figure en annexe.

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