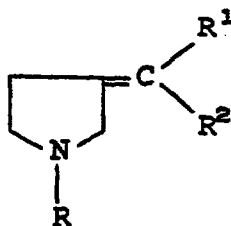


PRODUCTION OF METHYLENE-CYCLOAMINES

The present invention relates to novel methods for the production of methylene-cycloamines.

Prior art technology of general interest in connection with the present invention are the procedures for producing compounds such as α -(1-R-3-pyrrolidinyl)- α , α -diphenyl-acetamides (and-acetonitriles) and α -(1-R-3-pyrrolidinyl)- α -phenyl- α -(2-pyridyl)acetamides (and-acetonitriles) which are disclosed in U.S. Patents 3,192,206; 3,192,210; 3,192,221; 3,102,230; and 4,002,766.

Also of interest are the synthesis methods for producing antidepressant 3-disubstituted methylene-pyrrolidines which are described in U.S. Patent 3,732,247. The methylenepyrrolidines disclosed therein correspond to the formula:

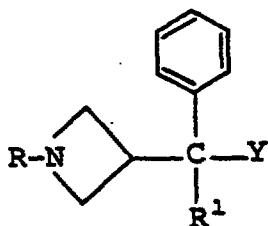


I

wherein R represents a hydrogen atom, a lower-alkyl, phenyl-lower-alkyl, substituted phenyl-lower-alkyl, cycloalkyl, phenoxy-lower-alkyl, phenylamino-lower-alkyl or substituted phenyl group, the said lower-alkyl group being limited to contain 2 to 8 carbon atoms when R¹ and R² both represent phenyl groups; R¹ represents a lower-alkyl, phenyl-lower-alkyl, cycloalkyl, phenyl or substituted phenyl group; and R² represents a phenyl or substituted phenyl group.

United States Patent 4,133,881 describes the

production of a class of α -(1-R-3-azetidiny)- α -phenyl
- α -substituted-acetamides and -acetonitriles correspond-
5 ing to the following formula:



II

wherein R represents a hydrogen atom or a lower alkyl,
lower cycloalkyl or phenyl-lower-alkyl group, R¹
15 represents a phenyl or 2-pyridyl group, and Y represents
a carbamoyl or cyano group, which compounds exhibit
anti-arrhythmic activity.

It is a main object of the present invention to
provide an improved process for producing methylene-
20 cycloamine compounds such as 3-methyleneazetidine
compounds which are characterized by one or more pharm-
acological properties useful for counteracting specific
physiological abnormalities in humans and other mammals.

It is another object of this invention to provide
25 a new and efficient method for converting a compound
such as α , α -diphenyl- α -(1-ethyl-3-pyrrolidinyl) aceta-
mide to a methyleneacycloamine compound such as 1-ethyl
-3-diphenyl-methylenepyrrolidine.

According to the present invention a process for
30 producing methylene-cycloamines involves reacting a

5

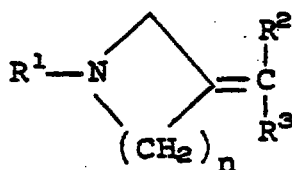
15



25

30

mediate in an acidic medium to yield a methylene-
5 cycloamine product corresponding to the formula:



10

IV

where R¹, R², R³ and n are as previously defined. R²
and R³ can be the same or different.

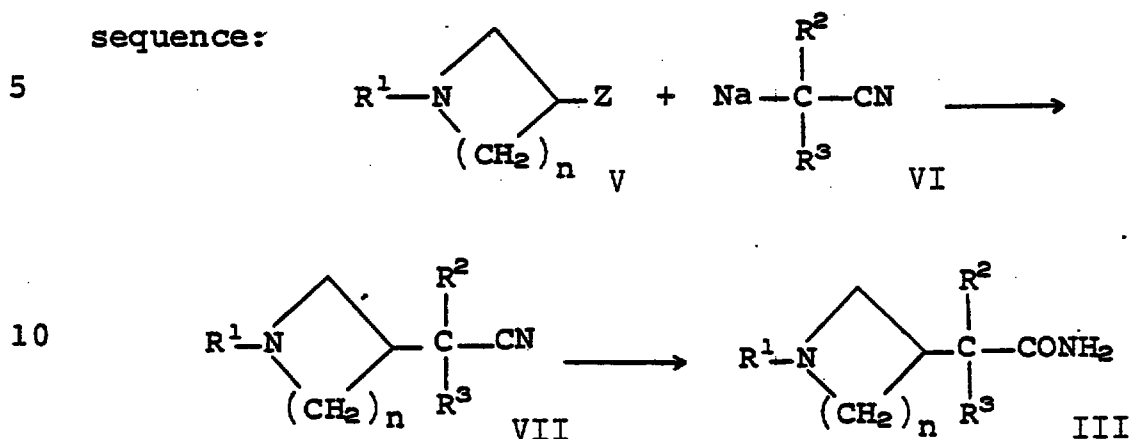
15 By "lower-alkyl" is meant alkyl groups having 1 to
8 carbon atoms. By "cycloalkyl" is meant cycloalkyl
groups having 1 to 9 carbon atoms.

Illustrative of R¹ groups as represented in Formula
III above which are lower alkyl groups are methyl, ethyl,
20 isopropyl, butyl, isobutyl, hexyl, octyl, and which are
cycloalkyl are cyclopropyl, cyclopentyl, cycloheptyl,
and which are phenyl-lower-alkyl are phenylethyl, α-
methylbenzyl, phenylpropyl, and other equivalent lower
alkyl, phenyl-lower-alkyl and cycloalkyl radicals.

25 Illustrative of R² and R³ groups are phenyl, 4-
methyl-phenyl, 2-ethylphenyl, and 4-isopropylphenyl.

The cycloamino-acetamide compounds employed as the
starting materials in the process of the present inven-
tion can be conveniently prepared by a synthesis pro-
cedure which is illustrated by the following reaction
30

sequence:



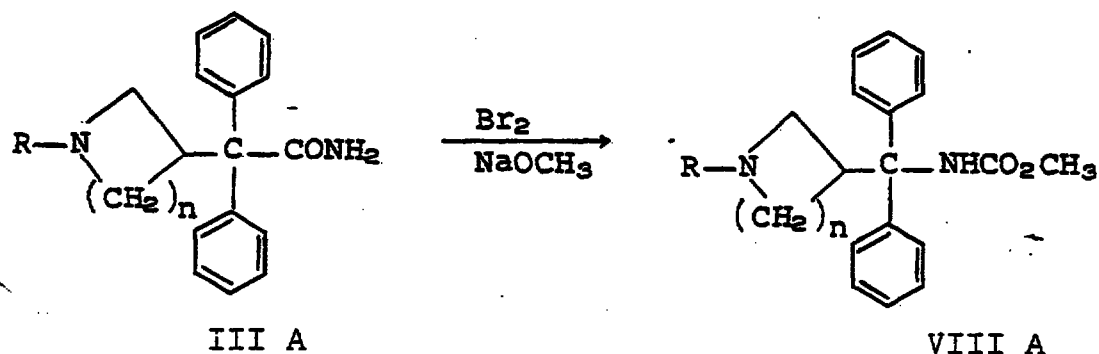
where R^1 , R^2 , R^3 and n are as previously defined and Z represents a $-\text{OSO}_2\text{CH}_3$ (mesyloxy) group or a halide atom.

15 The preparation of 1-substituted-3-azetidins and other 1,3-disubstituted azetidine derivatives are described in Tetrahedron Letters, No. 39, 4691 (1966); Tetrahedron Letters, No. 23, 2155 (1967); J. Org. Chem. 32, 2972 (1967); Chem. Pharm. Bull 22, 1490 (1974); and
 20 German OLS 1,932,219.

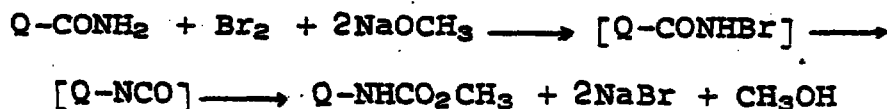
In the above illustrated reaction sequence flow diagram, a disubstituted acetonitrile (e.g. α,α -diphenyl acetonitrile) is first metalated in a dry aprotic solvent employing sodium hydride or sodamide to provide
 25 sodio α,α -diphenylacetonitrile (VI) which is reacted with a selected 1-R-3-mesyloxyazetidine (V) or a 1-R-3-haloazetidine (V) to yield an α -(1-R-3-zaetidiny)- α,α -diphenylacetonitrile (VII). The said acetonitrile derivative is then acid-hydrolyzed to α -(1-R-3-azetidinyl)-
 30 - α,α -diphenyl-acetamide (III), which is a key starting

material for the novel method of preparing methylene-
cycloamine compounds in accordance with the present
invention.

The first step of the process of the present inven-
tion involves reacting the substituted acetamide start-
ing material (e.g., the α -(1-R-3-azetidiny)- α,α -diphen-
ylacetamide (III) described above) with bromine and an
alkoxide ion in the presence of an alkonal to form a
carbamate intermediate. The following reaction sequence
illustrates the first step of the process employing
bromine and sodium methoxide in methanolic solution:



The said reaction sequence essentially corresponds to a
modified Hofmann Rearrangement synthesis procedure for
converting an amide to a carbamate derivative via a
bromamide intermediate:



5 The alkali metal alkoxide employed is preferably a sodium or potassium alcoholate of an alkanol containing between one and eight carbon atoms, e.g., methanol, ethanol, butanol, hexanol, or octanol.

10 For purposes of efficiency, it is preferred to employ the alkali metal alkoxide and bromine in at least stoichiometric quantities with respect to the quantity of substituted acetamide starting material. For example for each mole of substituted acetamide there can be employed between about 1 and 1.5 moles of bromine, and between about 2 and 2.5 moles of alkali metal alkoxide.

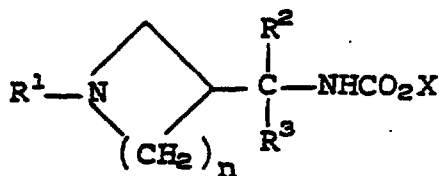
15 The reaction medium for the substituted acetamide conversion to the carbamate derivative can be any anhydrous solvent which has acceptable solubility characteristics and which is stable under Hofmann Reaction conditions. Illustrative of suitable solvents are alcohols, 20 ketones, ethers, hydrocarbons, and halocarbons. It is particularly advantageous to employ methanol as a reaction medium in combination with bromine and alkali metal methoxide.

25 The substituted acetamide conversion step of the invention process may be conducted at a temperature in the range of -10°C to 75°C and preferably at a temperature in the range of 0°C to 50°C .

30 A more complete description of the variations and modifications of Hofmann Reaction conditions is presented in Organic Reactions, 3, 267 (John Wiley & Sons,

New York, 1970); and Chem. Ber., 87, 1294 (1954)

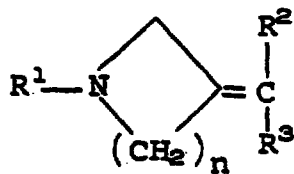
5 The carbamate intermediate produced in the first step of the process of the present invention corresponds to the formula:



VIII

wherein R^1 , R^2 , R^3 and n are as previously defined, and X represents an alkyl group containing between one and eight carbon atoms.

15 In the second step of the process of the present invention the carbamate intermediate is heated in an acidic medium preferably at a temperature in the range of 75°C to 200°C , to yield a methylene-cycloamine product corresponding to the formula:



IV

where R^1 , R^2 , R^3 and n are as previously defined.

30 The acidic medium normally will be an aqueous acid

5 solution, or an acidic aqueous mixture of an water-
miscible solvent such as tetrahydrofuran. If desired,
the second step can be conducted in a reaction medium of
an organic phase and an aqueous phase with suitable
stirring means for efficient contacting of the phases.

The acidity of the reaction medium is preferably
10 adjusted with an inorganic acid so as to maintain at
least a normality of 1 during the heating phase. The
acidity preferably is provided by the use of a mineral
acid such as sulphuric acid, preferably at about 6 to
18 normality. Illustrative of other suitable acids are
15 hydrochloric acid and phosphoric acid.

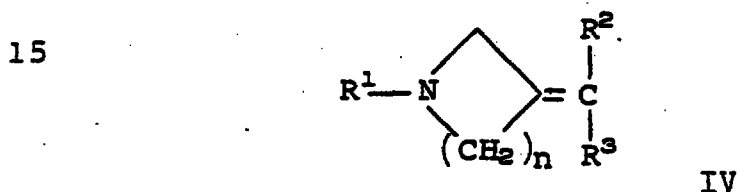
The heating phase of the second step of the inven-
tion process is conducted for a period of time suffici-
ent to complete the conversion of carbamate intermed-
iate to methylene-cycloamine product. A typical
20 reaction time will vary in the range of 1 hour to 20
hours, depending on the acid strength and the tempera-
ture of the reaction medium. The reaction temperature
during the heating phase can be varied in the range of
50°C to 250°C, and is preferably maintained in the
25 range of 75°C to 200°C.

At the completion of the heating phase, the
methylenecycloamine product can be recovered by
conventional extraction and distillation means. In a
typical product recovery procedure, the reaction
30 product medium is neutralized with a basic reagent,

22

and the methylene-cycloamine product is extracted with
5 a water-immiscible solvent such as benzene or ethyl
acetate, and the final product is isolated by fractional
distillation.

As previously described hereinabove, the process of
the present invention is applicable to the production of
10 pharmacologically active methylene-cycloamine compounds,
such as those exhibiting imipramine-like antidepressant
activity, which correspond to the formula:



20 where R¹, R², R³ and n are as previously defined.

Antidepressant agents block many of the behavioral
and physiological effects of tetrabenazine and reser-
pine, such as motor depression, hypothermia, and ptosis.
Tetrabenazine is chemically related to reserpine which
25 produces depression in humans (Davies, E.G. Depression,
Cambridge University Press, New York, 1964). Because
the onset of action of tetrabenazine is faster than
that of reserpine, the former compound is more widely
used as a tool for screening potential antidepressant
30 drugs.

For the purpose of testing the antidepressant activity of methylene-cycloamine compounds, five adult female mice (ICR-DUB strain) are given 20 mg/kg IP of test compound 30 minutes prior to the administration of a ptotic dose (32 mg/kg IP) of tetrabenazine (as the methane sulphonate salt). Thirty minutes later the presence or absence of complete eyelid closure (ptosis) is assessed in each animal.

For compounds which produced blockage of ptosis in all animals, an ED₅₀ value is obtained using a minimum of three geometrically spaced dosages with five mice per dose. Protective ED₅₀ values are determined by probit analysis with 95% confidence limits and slope functions calculated by the method of Litchfield and Wilcoxon (Litchfield, J.T., Jr. and Wilcoxon, F.A. simplified method of evaluating dose-effect experiments J. Pharm. Exp. Ther 96, 99-113, 1949).

Typical ED₅₀ values for reference antidepressant agents are shown in Table 1.

Table 1

Blockade of Tetrabenazine-Induced Ptosis in Mice

<u>Compound</u>	<u>ED₅₀ (95% confidence limits) slope - mg/kg IP</u>		
imipramine	0.3	(0.1 - 0.6)	2.6
	0.4	(0.2 - 0.9)	2.5
	0.5	(0.2 - 1.2)	2.3
viloxazine	1.5	(0.7 - 3.2)	2.5

24

In accordance with the above described test and
5 evaluation procedures, 1-isopropyl-3-diphenyleneaze-
tidineoxalate has an ED₅₀ mg/kg (IP) of 2.18 (confidence
limits, 1.18-4.03), and 1-methyl-3-diphenylmethylenaze-
tidine has an ED₅₀ mg/kg of 1.48 (confidence limits,
0.84-2.5). The antidepressant properties of 3-di-sub-
10 stituted methylenepyrrolidine compounds are disclosed in
U.S. 3,732,247.

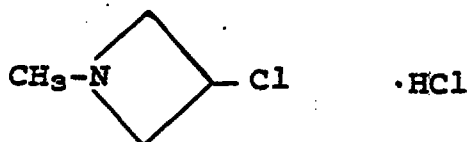
The present invention may be put into practice in
various ways and a number of specific embodiments will
be described to illustrate it with reference to the
15 accompanying examples.

The following examples are illustrative of the
application of the process of the present invention
process for production of methylene-cycloamine compounds
and the synthesis of starting materials suitable for
20 their preparation. The reactants and other specific
ingredients are presented merely as being typical, and
various modifications can be devised in view of the
foregoing disclosure within the scope of the invention.

25 Example 1

This example illustrates the preparation of 3-
chloro-1-methylazetidine hydrochloride, which is a
starting material for the process of the present
invention.

30



V A

10

A mixture of dilute sodium hydroxide solution and 700 ml of toluene was used to partition 46 g (0.134 mole) of 3-diphenylmethoxy-1-methylazetidine oxalate.

15 The toluene solution was dried over anhydrous sodium sulphate and further dried by azeotropic distillation of toluene to 300 ml final volume. The dried toluene solution was treated with 10% palladium-on-charcoal and hydrogenated at 45 psi at 80°C for 5 hours. The

20 mixture was filtered and 41 g (0.264 mole) of carbon tetrachloride was added to the filtrate. After cooling the resulting solution in an ice methanol bath, 53.5 g (0.145 mole) of trioctylphosphine was added in one portion with stirring. The temperature rose rapidly to

25 a maximum of 50°C. The solution was stirred for 30 minutes and distilled to a pot temperature of 150°C. The distillate was acidified with ethereal hydrogen chloride. The resulting crystals were separated by filtration and dried in vacuo, yielding 8.5 g of product

30 (45%).

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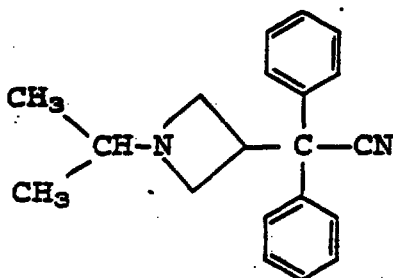
5 A solution of the base, 3-chloro-1-methylazetidine
was prepared by partitioning 3-chloro-1-methylazetidine
hydrochloride between toluene and dilute sodium hydrox-
ide drying the toluene solution with anhydrous sodium
sulphate and passing the solution through a 3/4" x 21"
column of No. 4A molecular sieve.

10

Example 2

This example illustrates the preparation of α,α -
diphenyl- α -(isopropyl-3-azetidiny)acetonitrile, which
is the starting material for Example 6.

15



20

VII A

Procedure A. To 250 ml of triethylamine was added
114 g (0.4 mole) of 1-isopropyl-3-azetidinyl mesylate
oxalate. About 250 ml of dry toluene was added followed
by 77 g of anhydrous magnesium sulphate, and the mixture
25 blended for about one minute and then filtered. The
filtrate was added over a period of one hour to a re-
fluxing mixture prepared by refluxing 18.5 g (0.44 mole)
of 57% sodium hydride (in mineral oil) and 77.2 g (0.4
mole) of diphenylacetonitrile in 1500 ml of dry toluene
30 for 3 hours. The mixture was refluxed for 2 hours,

cooled and extracted with dilute hydrochloric acid. The
5 organic layer was extracted five times with water and all
the aqueous layers combined. The aqueous solution was
made basic with sodium hydroxide and extracted with
chloroform which was dried (sodium sulphate) and concen-
trated. The residue was crystallized from isooctane,
10 yielding 68 g (58%) of product, m.g. 92-95°C. Recrysta-
llization from isooctane raised the melting point to
93-95°C.

Analysis: Calculated for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64;
N, 9.65

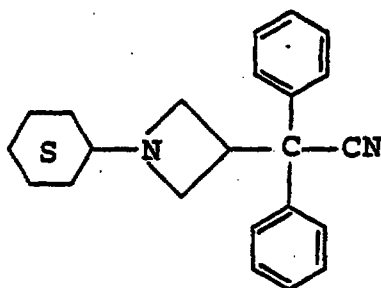
15 Found : C, 82.72; H, 7.73; N, 9.55

Procedure B. A mixture of 40.42 g (0.96 mole) of
57% sodium hydride and 168 g (0.87 mole) diphenylaceton-
itrile was refluxed in one litre of dry toluene for 3
hours. In a separate flask 100 g (0.87 mole) of methan-
20 esulphonyl chloride was added dropwise at 20°C to a
stirred solution of 100 g (0.87 mole) of 1-isopropyl-3-
azetidinol and 101 g (1 mole) of triethylamine in 700
ml dry benzene. The mixture was stirred at 25°C for 2
hours and filtered. The filter cake was washed with
25 benzene. The combined filtrates were added dropwise
over a period of about 30 minutes to the prepared re-
fluxing suspension of the sodium salt of diphenylace-
tonitrile. After refluxing for 1.5 hours, the cooled
solution was washed with water and extracted with
30 dilute hydrochloric acid followed by extraction with

water. The aqueous extracts were combined, made basic
 5 with sodium hydroxide and extracted with chloroform.
 The chloroform solution was dried (sodium sulphate) and
 concentrated. The residue was crystallized from isooc-
 tane, yielding 142 g (56%) of product.

Example 3

This example illustrates the preparation of α, α -
 diphenyl- α -(1-cyclohexyl-3-azetidiny) acetonitrile.



VII B

Methylene chloride containing 191 (1.0 mole) of
 1-cyclohexyl-3-azetidinol hydrochloride was extracted
 with dilute aqueous sodium hydroxide solution and the
 25 organic layer separated, dried over sodium sulphate,
 filtered and concentrated in vacuo. The residue was
 dissolved in dry benzene and mixed by stirring with
 116 g (1.05 mole) of triethylamine and thereafter
 cooled with an ice bath. To the cold stirred solution
 30 was added dropwise 115 g of methanesulphonyl chloride

and stirring was continued at room temperature for three
5 hours and the mixture thereafter filtered. To one litre
of dry toluene containing 50.0 g (1.0 mole) of sodium
hydride at 45-50°C was added 193 g (1 mole) of diphenyl-
acetonitrile and the mixture refluxed with stirring for
10 two hours. To this solution the foregoing filtrate was
added at a fast dropwise rate. After addition was
complete, reflux was continued for two hours and there-
after the solution was stirred overnight. An equival-
ent volume of isooctane was added and the solution extr-
acted four times with dilute hydrochloric acid solution.
15 The acid layers obtained in each extraction were combin-
ed, made basic with a mixture of 50% sodium hydroxide
and ice and extracted with chloroform. The chloroform
layer was dried, filtered and concentrated in vacuo. The
residue was crystallized by adding isopropyl ether and
20 thereafter the solid recrystallized from isopropyl ether
to yield 58.0 g (18%) of product melting at 111-114°C.
Analysis: Calculated for $C_{23}H_{26}N_2$: C, 83.59; H, 7.93;
N, 8.48

Found : C, 83.24; H, 7.94; N, 8.27

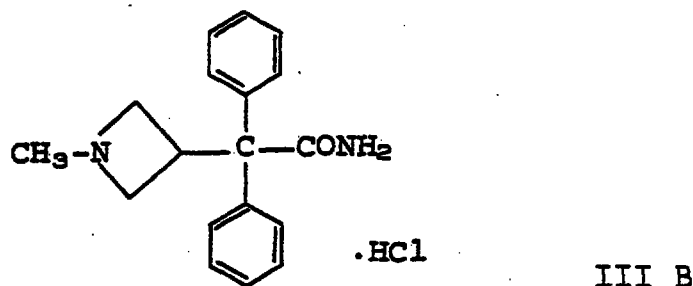
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Example 4

Following the same procedure as in Example 3 but
employing 1-ethyl-3-azetidinol hydrochloride instead of
1-cyclohexyl-3-azetidinol hydrochloride yields α, α -diph-
30 enyl- α -(1-ethyl-3-azetidiny1) acetonitrile.

Example 5

5 This example illustrates the preparation of α,α -diphenyl- α -(1-methyl-3-azetidiny) acetamide hydrochloride, which is the starting material for Example 12.



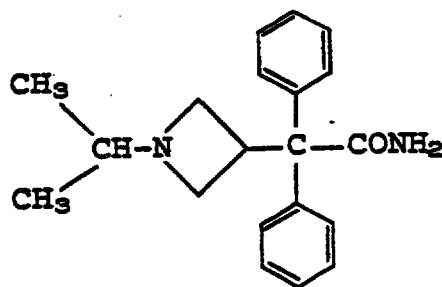
To 60 ml of concentrated sulphuric acid preheated to 60°C was added 21.7 g (0.082 mole) of α,α -diphenyl- α -
20 -(1-methyl-3-azetidiny) acetonitrile (see Example 2I) at a rate so as to maintain a temperature of 60-70°C. The solution obtained was heated to 70°C for 18 hours and extracted with chloroform. The chloroform extract was dried over sodium sulphate and concentrated and the
25 residue crystallized from ethyl acetate-isopropyl alcohol to give 13.8 g of the free base (60%) melting at 171-174°C. The base was treated with hydrogen chloride in isobutyl methyl ketone and the salt re-crystallized from isopropyl alcohol, yielding 9 g of
30 product melting at 182-185°C.

Analysis: Calculated for $C_{18}H_{21}ClN_2O$: C, 68.24; H, 6.68;
N, 8.84

Found : C, 67.88; H, 6.72; N, 8.78

Example 6

This example illustrates the preparation of α, α -diphenyl- α -(1-isopropyl-3-azetidiny1) acetamide, which is the starting material for Example 15.



III C

To 80 ml of concentrated sulphuric acid preheated to 70°C was added 25 g (0.86 mole) of α, α -diphenyl- α -(1-isopropyl-3-azetidiny1) acetonitrile (see Example 2) at a rate to maintain a temperature of $65-75^{\circ}\text{C}$. The solution was heated at 70°C for 18 hours and poured on ice. The mixture was made basic with 50% sodium hydroxide (while cooling with ice) and extracted with chloroform. The chloroform was dried (sodium sulphate) and concentrated. The residue was crystallized from ethyl acetate-ethanol to yield 15.7 g (59%) of product melting at $181-184^{\circ}\text{C}$.

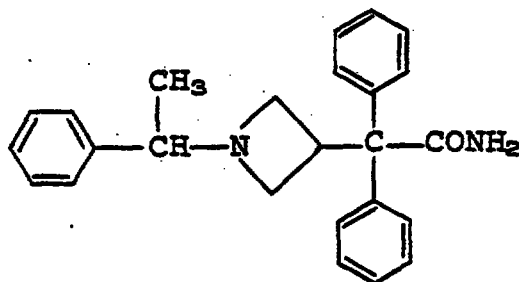
Analysis: Calculated for $C_{20}H_{24}N_2O_1$: C, 77.89; H, 7.84
N, 9.08
Found : C, 77.89; H, 7.88; N, 8.98

Example 7

Following the same procedure as Example 6 but employing α, α -diphenyl- α -(1-ethyl-3-azetidiny) acetonitrile instead of the 1-isopropyl derivative yields α, α -diphenyl- α -(1-ethyl-3-azetidiny) acetamide.

Example 8

This example illustrates the preparation of α, α -diphenyl- α -[1-(1-phenylethyl)-3-azetidiny] acetamide, which is the starting material for Example 17.



III D

To 100 ml of concentrated sulphuric acid preheated to 70°C was added with stirring, 50 g (0.142 moles) of α, α -diphenyl- α -[1-(1-phenylethyl)-3-azetidiny] acetonitrile at a rate to maintain a temperature of 65-70°C. The solution was heated at 72-75°C for 18 hours. The acid solution was poured onto ice and thereafter made basic with 50% aqueous sodium hydroxide solution and extracted with chloroform. The chloroform extract was

dried over anhydrous sodium sulphate and concentrated by distillation. The residue was crystallized from isopropyl ether to give 28.5 g (54%) of materials melting at 152-153.5°C. A sample was recrystallized from isopropyl ether-isopropyl alcohol, yielding a product melting at 153-154°C.

Analysis: Calculated for $C_{25}H_{26}N_2O$: C, 81.05; H, 7.07; N, 7.56

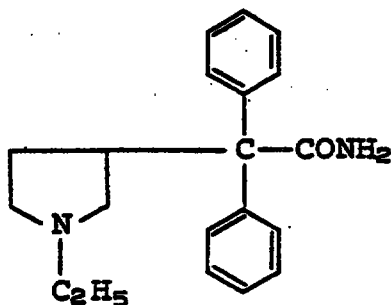
Found : C, 80.83; H, 7.07; N, 7.40

Example 9

Following the same procedure as in Example 8 but employing α, α -diphenyl- α -(1-cyclohexyl-3-azetidiny) acetonitrile (see Example 3) instead of the 1-phenylethyl derivative yields α, α -diphenyl- α -(1-cyclohexyl -3-azetidiny) acetamide.

Example 10

This example illustrates the preparation of α, α -diphenyl- α -(1-ethyl-3-pyrrolidiny) acetamide, which is the starting material for Example 18.



III E

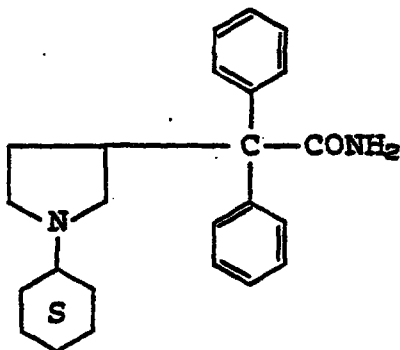
To 240 ml of concentrated sulphuric acid was added
5 60 g (0.21 mole) of α,α -diphenyl- α -(1-ethyl-3-pyrrolidin-
inyl)-acetonitrile. The mixture was shaken until solu-
tion took place and allowed to stand at 70°C for 24
hours. The solution was poured on ice, made basic with
ammonium hydroxide and extracted with about 1000 ml of
10 ethyl acetate. The ethyl acetate solution was dried
with anhydrous sodium sulphate and concentrated to about
200 ml. The white crystals that were obtained on cool-
ing were recrystallized from an ethyl acetate-ligroin
mixture, yielding 34 g (52.5%); m.p. 141-142°C.
15 Analysis: Calculated for $C_{20}H_{24}N_2O$: C, 77.88; H, 7.84;

N, 9.09

Found : C, 79.70; H, 8.18; N, 8.83

Example 11

20 This example illustrates the preparation of α -(1-
cyclohexyl-3-pyrrolidinyl)- α,α -diphenylacetamide start-
ing material.

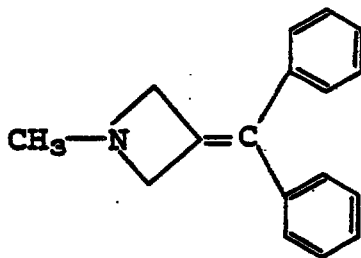


III F

To 80 ml of concentrated sulphuric acid was added
5 20 g (0.057 mole) of α -(cyclohexyl-3-pyrrolidiny1)- α,α -
diphenylacetoneitrile. The mixture was shaken until
solution occurred while being cooled in an ice bath
until heat was no longer evolved. The solution was heat-
ed at 70°C for 48 hours, poured on ice and made basic
10 with ammonium hydroxide. The resulting white solid
precipitate was taken up in ethyl acetate and the solu-
tion dried over sodium sulphate. The solution was con-
centrated and the residual oil taken up in hot ligroin,
filtered and allowed to stand overnight at room tempera-
15 ture. The resulting crystals were recrystallized from
ligroin, yielding 9.0 g (42.5%); m.p. 119-121°C.
Analysis: Calculated for $C_{24}H_{30}N_2O$: C, 79.51; H, 8.34;
N, 7.73
Found : C, 79.69; H, 8.51; N, 7.58

Example 12

This example illustrates the preparation of 1-meth-
yl-3-diphenylmethylenearzetidine.



IV A

To 150 ml of methanol was added 4.6 (0.20 mole) of sodium pellets, and upon dissolution, 14.0g (0.05 mole) of α,α -diphenyl- α -(1-methyl-3-azetidiny)acetamide (see Example 5) was added. To this stirring suspension was added, dropwise, 16.0 g (0.10 mole) of liquid bromine, maintaining room temperature with ice-bath cooling. Stirring was continued for two hours. The solution was concentrated in vacuo, and the residue was treated with 100 ml of 6N sulphuric acid, and refluxed for 18 hours. The acid mixture was made basic with sodium hydroxide and extracted with chloroform. The chloroform layer was dried, filtered, and concentrated in vacuo.

The residue was dissolved in isopropanol and treated with maleic acid, and the salt was recrystallized in isopropanol. The salt was partitioned between isopropyl ether and dilute sodium hydroxide. The ether was dried, filtered, and concentrated in vacuo. The residue was crystallized from isooctane, yielding 7.0g; m.p. 93-95°C.

Analysis: Calculated for $C_{17}H_{17}N$: C, 86.76; H, 7.28;
N, 5.95

Found : C, 86.74; H, 7.34; N, 5.81

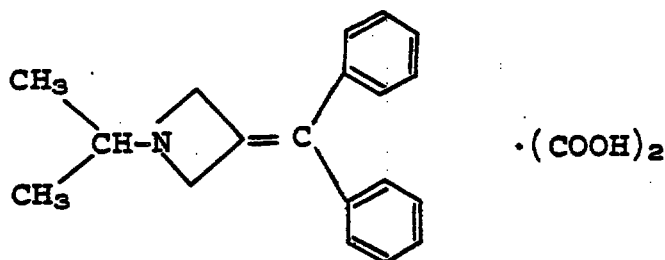
Examples 13 and 14

Following the same procedure as in Example 12 but employing the 1-ethyl derivatives or the 1-cyclohexyl derivative in place of the 1-methyl derivative, yields

1-ethyl-3-diphenylmethylenesazetidide (Example 13) and
5 1-cyclohexyl-3-diphenylmethylenesazetidide (Example 14)
respectively.

Example 15

This example illustrates the preparation of 1-isopropyl-3-diphenylmethylenesazetidide oxalate.
10



IV B

To 125 ml of methanol was added 18.1 g (0.336 mole) of sodium methoxide and 26 g (0.084 mole) of α,α -diphenyl- α -(1-isopropyl-3-azetidiny)acetamide. To the stirred mixture was added dropwise 26.8 g (0.168 mole) of bromine over a period of 30 minutes, and the resulting solution was brought to reflux for 2 hours and concentrated. The residue was dissolved in 6N sulphuric acid and brought to reflux for 24 hours and extracted with isopropyl ether. The acid layer was made basic with sodium hydroxide and extracted with chloroform. The chloroform was dried over sodium sulphate and concentrated. The residue was treated with 0.08 mole of
20
25
30 oxalic acid in ethanol. The resulting crystals were

28

recrystallized three times from ethanol, yield 3 g (10%);
m.p. 204-205°C.

Analysis: Calculated for $C_{21}H_{23}N_1O_4$: C, 71.35; H, 6.56;
N, 3.96

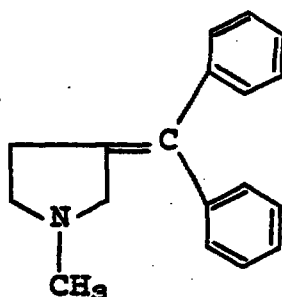
Found : C, 70.95; H, 6.53; N, 3.90

Examples 16 and 17

Following the same procedure as in Example 15 up to the addition of oxalic acid but employing the 1-phenylethyl derivative or the 1-(1-phenylethyl) derivative (see Example 8) instead of the 1-isopropyl derivative yields 1-phenylethyl-3-diphenyl-methylene-azetidine (Example 16) and 1-(1-phenylethyl)-3-diphenyl-methylene-azetidine (Example 17).

Example 18

This example illustrates the preparation of 1-methyl 3-diphenylmethylenepyrrolidine.



IV C

To a solution of 59.5 g (1.1mole) of sodium methoxide in 850 ml of methanol was added 81 g (0.276 mole) of α,α -diphenyl- α -(1-methyl-3-pyrrolidiny)acetamide (see Example 10). To this stirred solution was added dropwise 90 g (0.56 mole) of bromine in 150 ml of methanol and the solution brought to reflux for 1.5 hours. The solution was concentrated in vacuo and the residue partitioned between chloroform and water. The chloroform was concentrated and the residue dissolved in 600ml of 6N sulphuric acid which was heated to 100°C for 2.5 hours. The solution was made basic with sodium hydroxide and extracted with ethyl acetate. The extract was concentrated and distilled. Yield 42 g; b.p. 150-160°C at 0.2 mm of mercury. A portion was crystallized several times from isooctane; m.p. 73-74°C.

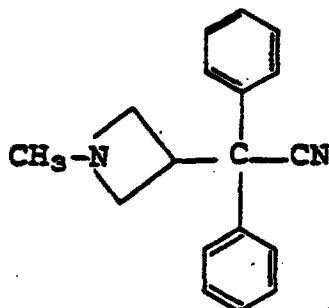
Analysis: Calculated for $C_{18}H_{19}N$: C, 86.70; H, 7.68;
N, 5.62
Found : C, 86.77; H, 7.62; N, 5.60

Examples 19 and 20

Following the same procedure was in Example 18 but employing α,α -diphenyl- α -(1-ethyl-3-piperidiny)acetamide or α,α -diphenyl- α -(1-ethyl-4-azepiny)acetamide as the starting material yields 1-ethyl-3-diphenylmethylenepyrrolidine (Example 19) or 1-ethyl-4-diphenylmethylenazepine (Example 20) respectively.

Example 21

This example illustrates the preparation of α,α -diphenyl- α -(1-methyl-3-azetidiny1) acetonitrile, which is a starting material for Example 5.



VII C

Procedure A. To 4 g (0.11 mole) sodium amide in 300 ml toluene was added 21 g (0.11 mole) of diphenylacetonitrile and the stirred mixture was refluxed in a nitrogen atmosphere for 4 hours. The heat was removed and a solution of 3-chloro-1-methylazetidine (see Example 1) was added at a rate to maintain reflux. The solution was refluxed 4 hours, allowed to stand overnight, washed with water and extracted with dilute hydrochloric acid. The aqueous layer was made basic with dilute sodium hydroxide and extracted twice with isopropyl ether. The solution was dried (sodium sulphate) and concentrated. The residue was recrystallized from ligroin to yield 6.7 (27%) of product, m.p. 113-115°C.

Analysis: Calculated for $C_{18}H_{18}N_2$: C, 82.41; H, 6.92;
N, 10.68

Found : C, 82.31; H, 6.98; N, 10.51

Procedure B. To 800 ml of ethanol was added 59 g (0.13 mole) of α, α -diphenyl- α -[1(1-phenylethyl)-3-azetidiny] acetonitrile methobromide, 7.12 g (0.013 mole) of potassium hydroxide, and 0.25 g 10% palladium-on-charcoal. The mixture was shaken in a Parr hydrogenation apparatus at room temperature under an initial pressure of 45 psi of hydrogen for 24 hours. The mixture was filtered and the filtrate concentrated in vacuo. The residue was crystallized from isooctane. The yield of product was 21.7 g (64%), melting at 112-115°C.

A compound corresponding to the above formula IV can be incorporated as an active therapeutic agent in pharmaceutical compositions. The pharmaceutical compositions are prepared in a form suitable for administering to a living animal.

Pharmaceutical compositions for oral administration are preferably solids and can take the form of capsules, tablets or coated tablets containing carriers conveniently used in the pharmaceutical art. Suitable tableting excipients include lactose, potato and maize starches, talc, gelatin, and stearic and silicic acids, magnesium stearate, and polyvinyl pyrrolidone.

For parenteral administration the carrier or
5 excipient can be a sterile parenterally acceptable
liquid (e.g., water), or a parenterally acceptable oil
(e.g., arachis oil), contained in ampoules.

In compositions for rectal administration the
carrier can comprise a suppository base such as cocoa
10 butter or a glyceride.

Advantageously, the compositions are formulated as
dosage units, each unit being adapted to supply a fixed
dose of active ingredients. Tablets, coated tablets,
capsules, ampoules and suppositories are examples of
15 preferred dosage unit forms according to the invention.
Each dosage unit adapted for oral administration may
conveniently contain 10 to 40 mg of the active
ingredient; each dosage unit adapted for intracardial
or intravenous administration may conveniently contain
20 1 to 2 mg per cc of the active ingredient; whereas each
dosage unit adapted for intramuscular administration may
conveniently contain 5 to 10 mg per cc of the active
ingredient. Daily dosages should preferably range from
10 mg to 100 mg. The exact individual dosages as well
25 as daily dosages are determined according to standard
medical principles under the direction of a physician
or veterinarian.

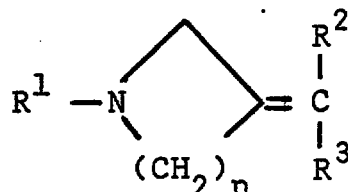
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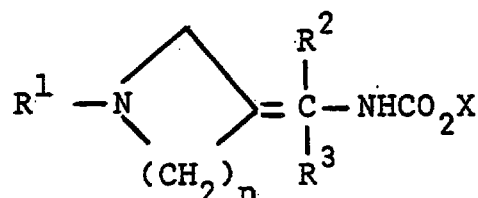
31.

CLAIMS

1. A process for preparing methylene-cycloamine derivatives corresponding to the formula:



where R^1 represents a lower-alkyl, phenyl-lower-alkyl or cycloalkyl group, R^2 and R^3 represent a phenyl or lower-alkylphenyl group, and n is an integer from 1 to 4; the said process comprising heating in an acidic medium a carbamate compound corresponding to the formula:



where R^1 , R^2 , R^3 and n are as previously defined, and X represents an alkyl group containing between one and eight carbon atoms.

2. A process as claimed in claim 1 in which the carbamate compound is heated in an aqueous medium at a temperature in the range of 75°C to 200°C .



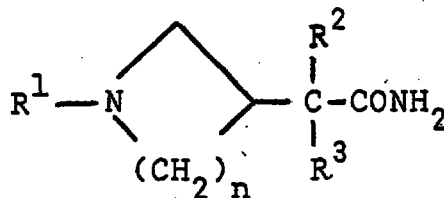
3. A process as claimed in claim 1 or claim 2 in which the acidic medium has an acid strength of at least 1 normal provided by a mineral acid.

4. A process as claimed in claim 1, 2 or 3 in which the methylene-cycloamine product is 1-isopropyl-3-diphenyl-methyleneazetidene.

5. A process as claimed in claim 1, 2 or 3 in which the methylene-cycloamine product is 1-methyl-3-diphenyl methyleneazetidene.

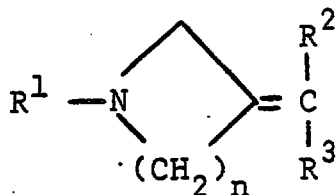
6. A process as claimed in claim 1, 2 or 3 in which the methylene-cycloamine product is 1-ethyl-3-diphenyl-methylenepyrrolidine.

7. A process for preparing methylene-cycloamine derivatives which comprises (1) reacting a substituted acetamide compound with bromine and an alkali metal alkoxide to produce a carbamate intermediate, wherein the said substituted acetamide starting material corresponds to the formula:





where R^1 represents a lower-alkyl, phenyl-lower-alkyl or cycloalkyl group, R^2 and R^3 , which may be the same or different, represent a phenyl or a lower-alkylphenyl group, and n is an integer between 1 and 4; and (2) heating the said carbamate intermediate in an acidic medium to yield a methylene-cycloamine product corresponding to the formula:



where R^1 , R^2 , R^3 and n are as previously defined.

8. A process as claimed in claim 7 in which the alkali metal alkoxide in step (1) is sodium or potassium methoxide.

9. A process as claimed in claim 7 or claim 8 in which the reaction temperature in step (1) is maintained in the range of 0°C to 50°C .

10. A process as claimed in claim 7, 8 or 9 in which the reaction temperature in step (2) is maintained in the range of 75°C to 200°C .

11. A process as claimed in any one of claims 7 to 10 in which the acid strength of the acidic medium in step (2) is at least 1 normal.



12. A process as claimed in any one of claims 7 to 11 in which n is the integer 1 or 2.

13. A process as claimed in claim 1 substantially as specifically described herein with reference to Example 12, 13, 14, 15, 16, 17, 18, 19 or 20.

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