

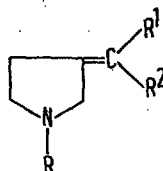
SPECIFICATION

3-Methyleneazetidine derivatives

5 The present invention relates to 3-methyleneazetidine derivatives.

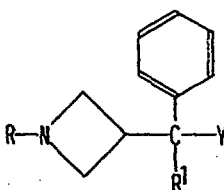
Of general background interest in connection with the present invention are prior art compounds such as α -(1-R-3-pyrrolidinyl)- α,α -diphenylacetamides (and -acetonitriles) and α -(1-R-3-pyrrolidinyl)- α -phenyl- α -(2-pyridyl)acetamides (and-acetonitriles) which are disclosed in U.S. Patents 3,192,206;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

10 Also of interest are the anti-depressant 3-disubstituted methylene pyrrolidines disclosed in U.S. 3,732,247:



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 loweralkyl 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.

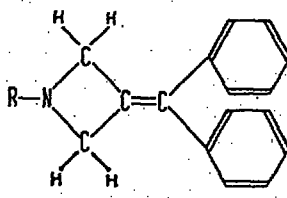
United States Patent 4,133,881 discloses a class of α -(1-R-3-azetidyl)- α -phenyl- α -substituted acetamides and -acetonitriles corresponding to the following formula:



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

It is a main object of the present invention to provide a novel class of 3-methyleneazetidine compounds which are characterized by one or more pharmacological properties useful for counteracting specific physiological abnormalities in humans and other mammals.

The present invention provides a novel class of pharmacologically active 3-methyleneazetidine derivatives. Illustrative of the compounds of the invention are 3-methyleneazetidine compounds corresponding to the formula:



wherein R represents a lower-alkyl, cycloalkyl or phenyl-lower alkyl group.

The present invention also contemplates the pharmaceutically acceptable acid addition salts of the novel class of 3-methyleneazetidine derivatives. Such salts have improved water solubility over the free bases. Typical acid addition salts are those derived from mineral acids such as hydrochloric, hydrobromic, sulphuric and phosphoric acids, and organic acids such as acetic, citric, lactic, maleic, oxalic, fumaric and tartaric acids. The acid addition salts are conveniently prepared by reaction of the basic compounds with the selected acid, either or both of which may be in the form of ether, alcohol, or acetone solutions.

The above described novel class of 3-methyleneazetidine compounds, and particularly the acid addition salts thereof, are characterized by useful pharmacological activity, which is indicative of their application in counteracting certain physiological abnormalities in humans. The 3-methyleneazetidine compounds in accordance with the invention possess a significant level of antidepressant activity, such as is observed in reserpine reversal and anti-tetrabenazine tests.

In the above represented structural formula, the lower-alkyl moiety contains from 1 to 8 carbon atoms, and

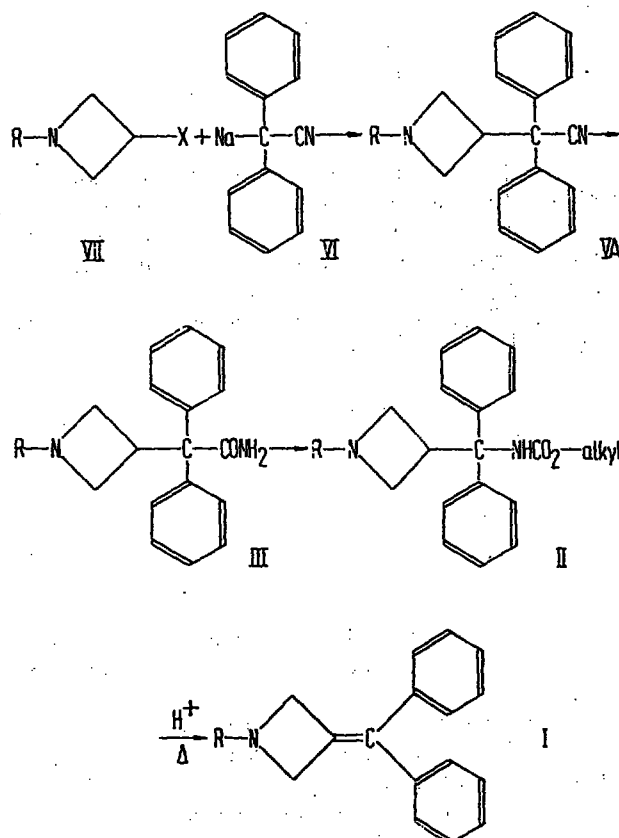
may be for example a methyl, ethyl, propyl, isopropyl, butyl, pentyl, hexyl, or octyl group.

The cycloalkyl moiety as designated in the structural formula is preferably a cyclic radical containing from 3 to 9 ring carbon atoms, and may be for example a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl group.

5 Representative of phenyl-lower-alkyl groups are methylbenzyl, phenylethyl, phenylpropyl, and phenylbutyl groups.

Illustrative of specific 3-methyleneazetidines in accordance with the present invention are 1-methyl-3-diphenylmethylenazetidines, 1-ethyl-3-diphenylmethylenazetidines, 1-isopropyl-3-diphenylmethylenazetidines, 1-cyclohexyl-3-diphenylmethylenazetidines, 1-(α -methylbenzyl)-3-diphenylmethylenazetidines, and pharmaceutically acceptable acid addition salts thereof.

10 The 3-methyleneazetidines of the present invention are conveniently prepared by a synthesis procedure which is illustrated by the following reaction sequence:



wherein R represents an alkyl, cycloalkyl or phenyl-lower-alkyl group, and X is preferably a halo or sulphonato substituent.

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 German OLS 1,932,219.

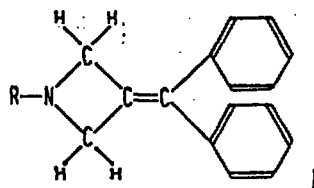
In the above illustrated reaction sequence flow diagram, the α, α -diphenylacetonitrile is first metalated in a dry aprotic solvent employing sodium hydride or sodamide to provide sodio α, α -diphenylacetonitrile (VI) which is reacted with a selected 1-R-3-mesyloxyazetidine or a 1-R-3-haloazetidine (VII) to yield an α -(1-R-3-azetidyl)- α, α -diphenylacetonitrile (VA). The said acetonitrile derivative is then acid-hydrolyzed to α -(1-R-3-azetidyl)- α, α -diphenylacetamide (III), which is a key starting material for a novel method for preparing the 3-methyleneazetidines of the present invention.

In the said novel method, the α -(1-R-3-azetidyl)- α, α -diphenylacetamide (III) is converted to a carbamate as in a stage of the Hofmann reaction (Organic Reactions Vol. III, p. 282 (John Wiley and Sons, New York, 1946)) by action of bromine and sodium methoxide or other alkali metal alkoxide in a suitable anhydrous solvent, preferably an alcohol, corresponding to the alcohol from which the alkali metal alkoxide is formed. The carbamate derivative (II) is converted to a 3-methyleneazetidine (compound (I) of the present invention) by the novel step of refluxing the carbamate in contact with a strong acid to eliminate the equivalent of an alkyl carbamate molecule.

This novel method of preparation forms the subject matter of our copending application No. 80/22967.

In one of its embodiments, this invention provides a pharmaceutical composition adapted for alleviating the symptoms of depression in humans and other mammals. The pharmaceutical composition comprises a pharmaceutical carrier and an antidepressant quantity of a 3-methyleneazetidine compound corresponding

to the formula:



wherein R represents a lower-alkyl, cycloalkyl or phenyl-lower-alkyl group.

The pharmaceutical compositions of the present invention are prepared in a form suitable for administering to a living animal.

Antidepressant agents block many of the behavioral and physiological effects of tetrabenazine and reserpine, such as motor depression, hypothermia, and ptosis. Tetrabenazine is chemically related to reserpine which produces depression in humans (Davies, E.D., *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 anti-depressant drugs.

For the purpose of testing the antidepressant activity of the 3-methyleneazetidinium compounds of the present invention, 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 sulphate 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 ED_{50} value is obtained using a minimum of three geometrically spaced doses with five mice per dose. Protective ED_{50} 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 ED_{50} values for reference antidepressant agents are shown in Table 1.

TABLE 1

Blockade of tetrabenazine-induced ptosis in mice

Compounds	ED_{50} (95% Confidence Limits) Slope - mg/kg IP
imipramine (A.H. Robins)	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

In accordance with the above described test and evaluation procedures, 1-isopropyl-3-diphenyleneazetidinium oxalate has an ED_{50} mg/kg (IP) of 2.18 (confidence limits, 1.18-4.03), and 1-methyl-3-diphenylmethylenazetidinium has an ED_{50} mg/kg (IP) of 1.48 (confidence limits 0.84-2.5).

Amphetamines and barbiturates are frequently useful in depression therapy, as well as tranquilizers. In particular, the use of tranquilizing drugs as with sedatives and the amphetamine group have shown valuable results especially with disturbed and agitated cases of depression. This invention is, therefore, intended to encompass the combined use the foregoing with the anti-depressant compounds of the present invention, as well as with other drugs used adjunctively in the control and treatment of depression. Thus, the compounds of this invention may be administered alone or in combination with other pharmacologically effective agents such as psychomotor stimulants, sedatives, tranquilizers and sedative-level dosages of tranquilizers, as well as buffers and usual pharmaceutical carriers or diluents.

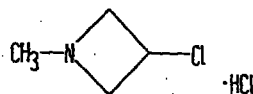
The present invention may be put into practice in various ways and a number of specific embodiments will be described to illustrate the invention with reference to the accompanying examples.

The following examples are illustrative of the preparation of the 3-methyleneazetidinium compounds of the present invention, and of the synthesis of starting materials suitable for 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.

Example 1

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

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VII A

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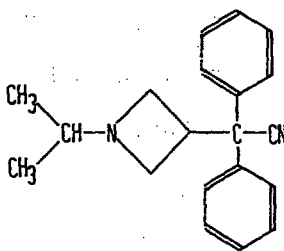
10 A mixture of dilute sodium hydroxide solution and 700ml of toluene was used to partition 46 g (0.18 mole) of 3-diphenylmethoxy-1-methylazetidine oxalate. The toluene solution was dried over anhydrous sodium sulphate and further dried by azeotropic distillation of toluene to 300ml final volume. The dried toluene solution was treated with 10% palladium-on-charcoal and hydrogenated at 45 psi at 80°C for 5 hours. The 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 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 8.5g of product (45%).

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

Example 2

25 This example illustrates the preparation of α - α diphenyl- α -(1-isopropyl-3-azetidiny) acetonitrile which is the starting material for Example 9.

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I B

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Procedure A. To 250 ml of triethylamine was added 114 g (0.4 mole) of 1-isopropyl-3-azetidiny mesylate oxalate. About 250 ml of dry toluene was added followed by 77 g of anhydrous magnesium sulphate, and the mixture blended for about one minute and then filtered. The filtrate was added over a period of one hour to a refluxing 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 for 3 hours. The mixture was refluxed for 2 hours, cooled and extracted with dilute hydrochloric acid. The 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 concentrated. The residue was crystallized from isooctane, yielding 68 g (58%) of product, m.p. 92-95°C. Recrystallization from isooctane raised the melting point to 93-95°C.

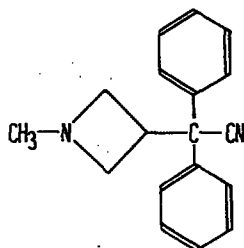
Analysis: Calculated for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.65

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) of diphenylacetonitrile was refluxed in one litre of dry toluene for 3 hours. In a separate flask 100 g (0.87 mole) of methanesulphonyl 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 benzene. The combined filtrates were added dropwise over a period of about 30 minutes to the prepared refluxing suspension of the sodium salt of diphenylacetonitrile. After refluxing for 1.5 hours, the cooled solution was washed with water and extracted with dilute hydrochloric acid followed by extraction with water. The aqueous extracts were combined, made basic with sodium hydroxide and extracted with chloroform. The chloroform solution was dried (sodium sulphate) and concentrated. The residue was crystallized from isooctane, yielding 142 g (56%) of product.

Example 3

This example illustrates the preparation of α,α -diphenyl- α -(1-methyl-3-azetidiny)l acetonitrile which is the starting material for example 8.



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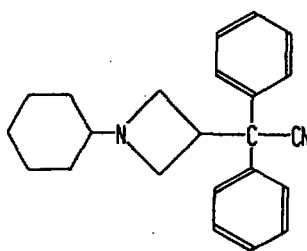
- 15 **Procedure A.** To 4g (0.11 mole) sodium amide in 300 ml toluene was added 21 g (0.11 mole) of
diphenylacetonitrile and the stirred mixture was refluxed in a nitrogen atmosphere for 4 hours. The heat was
removed and a solution of 3-chloro-1-methylazetidine (see Example 1) was added at a rate to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

- 25 **Procedure B** To 800 ml of ethanol was added 59g (0.13 mole) of α,α -diphenyl- α -[1(1-phenylethyl)-3-
azetidiny]acetonitrile methobromide (see Example 7), 7.12g (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
30 filtrate concentrated in vacuo. The residue was crystallized from isooctane. The yield of product was 21.7 g
(64%), melting at 112-115°C.

Example 4

This example illustrates the preparation of α,α -diphenyl- α -(1-cyclohexyl-3-azetidiny)l acetonitrile, which is
35 the starting material for Example 12.



V0

- 40 Methylene chloride containing 191 g (1.0 mole) of 1-cyclohexyl-3-azetidinol hydrochloride was extracted
with dilute aqueous sodium hydroxide solution and the 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
50 g (1.05 mole) of triethylamine and thereafter cooled with an ice bath. To the cold stirred solution was added
dropwise 115 g of methanesulphonyl chloride and stirring was continued at room temperature for three
hours and the mixture thereafter filtered. To one litre of dry toluene containing 50.0 g (1.0 mole) of sodium
hydride was added at 45-50°C, 193 g (1 mole) of diphenylacetonitrile and the mixture refluxed with stirring
for two hours. To this stirred refluxing solution the foregoing filtrate was added at a fast drop wise rate. After
55 addition was complete, reflux was continued for two hours and thereafter the solution was stirred overnight.
An equivalent volume of isooctane was added and the solution extracted four times with dilute hydrochloric
acid solution. The acid layers obtained in each extraction were combined, 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 thereafter the solid
60 recrystallized from isopropyl ether to yield 58.0 g (18%) of product melting at 111-114°C.

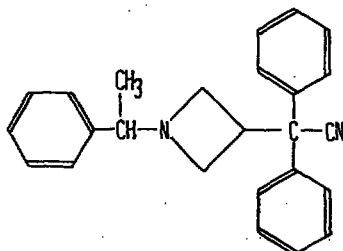
Analysis: Calculated for $C_{29}H_{26}N_2$: C, 83.59 H, 7.93 N, 8.48
Found : C, 83.24 H, 7.94 N, 8.27

Example 5

Following the same procedure as in Example 4 but employing 1-ethyl-3-azetidinol hydrochloride instead of 1-cyclohexyl-3-azetidinol hydrochloride yields α,α -diphenyl- α -(1-ethyl-3-azetidiny)-acetonitrile.

Example 6

This example illustrates the preparation of α,α -diphenyl- α -[1-(1-phenylethyl)-3-azetidiny]acetonitrile which is the starting material for example 11.



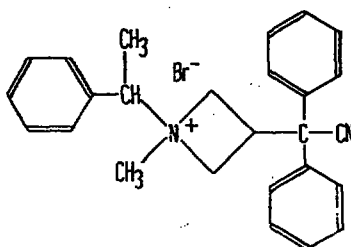
VI E

To a solution of 67.9 g (0.67 mole) of triethylamine and 114 g (0.64 mole) of 1-(1-phenylethyl)-3-azetidinol in 800 ml of dry benzene was added dropwise 73.6 g (0.65 mole) of methanesulphonyl chloride while cooling in an ice bath. After stirring for two hours at room temperature the mixture was filtered. The filtrate was added dropwise over a 4-minute period to a refluxing suspension of the sodium salt of diphenylacetonitrile prepared by refluxing 123.5 g (0.64 mole) of the nitrile and 28.2 g (0.7 mole) of 57% sodium hydride in one litre of dry toluene for 2.5 hours. The toluene solution was extracted with dilute hydrochloric acid. The toluene-organic layer was treated with water and a volume of isooctane equal to the toluene layer. The oily layer and aqueous layer were separated together. The toluene layer was washed several times with water. All aqueous layers (and the oil) were combined and made basic with dilute sodium hydroxide and extracted with chloroform. The chloroform layer was dried over sodium sulphate and concentrated by distillation. The residue was crystallized from isooctane isopropyl ether, yielding 94 g (42%) of product melting at 122-130°C.

Analysis: Calculated for $C_{25}H_{24}N_2$: C, 85.19; H, 6.86; N, 7.95
 Found : C, 84.98; H, 6.84; N, 7.84

Example 7

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



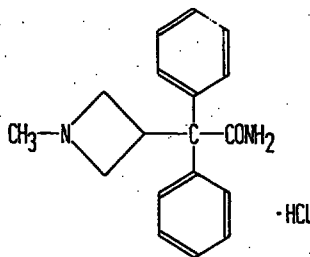
VI F

To 70 g (0.2 mole) of α,α -diphenyl- α -[1-(1-phenylethyl)-3-azetidiny]acetonitrile (see Example 6) in 200 ml of isobutyl methyl ketone was added 17.5 g of methyl bromide in 800 ml of the same solvent. The mixture was allowed to stand 4 days and filtered to give 65 g (72%) of product at 205-208°C.

Analysis: Calculated for $C_{26}H_{27}BrN_2$: C, 69.79; H, 6.08; N, 6.26
 Found : C, 69.63; H, 6.10; N, 6.25

Example 8

This example illustrates the preparation of α,α -diphenyl- α -(1-methyl-3-azetidiny)acetamide hydrochloride, which is a starting material for the preparation of a compound in accordance with the present invention as shown in Example 13.

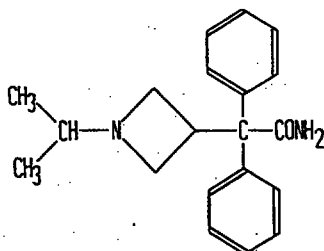


To 60 ml of concentrated sulphate acid preheated to 60°C was added 21.7 g (0.082 mole) of α, α -diphenyl- α -(1-methyl-3-azetidiny)acetonitrile (see example 3) at a rate so as to maintain a temperature of 60-70°C. The solution obtained was heated to 70°C for 18 hours, poured on ice, made basic with 50% sodium hydroxide and extracted with chloroform. The chloroform extract was dried over sodium sulphate and concentrated and the 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 recrystallized from isopropyl alcohol, yielding 9 g of product melting at 182-185°C.

Analysis: Calculated for $\text{C}_{18}\text{H}_{21}\text{ClN}_2\text{O}$: C, 68.24; H, 6.68; N, 8.84
Found : C, 67.88; H, 6.72; N, 8.78

Example 9

This example illustrates the preparation of α, α -diphenyl- α -(1-isopropyl-3-azetidiny) acetamide, which is the starting material for the preparation of the compounds in according with the present invention which is shown in Example 16.



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-azetidiny)acetonitrile (see Example 2) at a rate to maintain a temperature of 65-75°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°C.

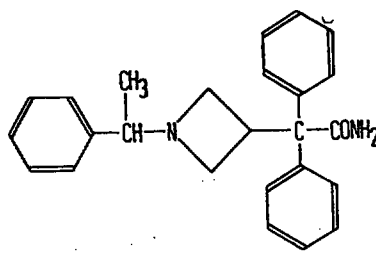
Analysis: Calculated for $\text{C}_{20}\text{H}_{24}\text{N}_2\text{O}$: C, 77.89; H, 7.84; N, 9.08
Found : C, 77.89; H, 7.88; N, 8.99

Example 10

Following the same procedure as in Example 9 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 11

This example illustrates the preparation of α, α -diphenyl- α -[1-(1-phenylethyl)-3-azetidiny]acetamide which is a starting material for the preparations of compounds in accordance with the present invention.



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 (see Example 6) at a rate to maintain a temperature of 65-70°C. The solution was heated at 72-75°C for 18 hours. The acidic solution was poured into 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 material 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

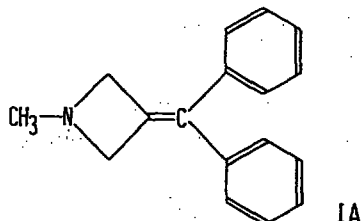
Found : C, 80.83; 7.07; N, 7.40

Example 12

Following the same procedure as in Example 11 but employing α,α -diphenyl- α -(1-cyclohexyl-3-azetidiny]acetonitrile (see Example 4) instead of the 1-phenylethyl derivative yields α,α -diphenyl- α -(1-cyclohexyl-3-azetidiny]acetamide, which is a starting material for example 15.

Example 13

This example illustrates the preparation of 1-methyl-3-diphenylmethylenesazetidide, a compound in accordance with the present invention.



To 150 ml of methanol was added 4.6 g (0.20 mole) of sodium pellets, and upon dissolution, 14.0 g (0.05 mole) of α,α -diphenyl- α -(1-methyl-3-azetidiny]acetamide (see example 8) was added. To this stirring suspension was added dropwise 16.0 g (0.10 mole) of liquid bromine, room temperature being maintained by means of cooling with an ice-bath. Stirring was continued for two hours. The solution was concentrated *in vacuo*, and the residue was treated with 100ml of 6N sulphuric acid and refluxed for 18 hours. The acidic 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 ethereal fraction 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

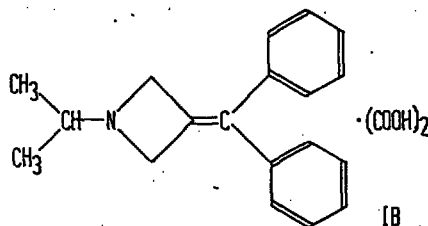
Found : C, 86.74; H, 7.34; N, 5.81

Example 14 and 15

Following the same procedure as in Example 13 but employing the 1-ethyl derivative (see Example 10) or the 1-cyclohexyl derivative (see Example 12) in place of the 1-methyl derivative, yields 1-ethyl-3-diphenylmethylenesazetidide (Example 14) and 1-cyclohexyl-3-diphenylmethylenesazetidide (Example 15) respectively.

Example 16

This example illustrates the preparation of 1-isopropyl-3-diphenylmethylenesazetidide oxalate, a compound in accordance with the present invention.



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 (see Example 9). 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 oxalic acid in ethanol. The resulting crystals were 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,71.36; H,6.56; N,3.96
Found : C,70.95; H,6.53; N,3.90

10 *Examples 17 and 18*

Following the same procedure as in Example 16 but employing the 1-phenylethyl derivative or the 1-(α -methylbenzyl) derivative instead of the 1-isopropyl derivative yields 1-phenylethyl-3-diphenylmethylenaezetidine oxalate (Example 17) and 1-(α -methylbenzyl)-3-diphenylmethylenaezetidine oxalate (Example 18), respectively.

15 *Example 19*

Following the procedure of Example 16 up to the addition of oxalic acid but employing α,α -diphenyl- α -(1-phenylethyl-3-azetidiny)acetamide (see Example 11) as the starting material yields 1-(α -methylbenzyl)-3-diphenylmethylenaezetidine.

20 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.

The parenteral administration the carrier or excipient can be a sterile parenterally acceptable liquid (e.g. water) or a parenterally acceptable oil (e.g. archis oil) contained in ampoules.

25 In compositions for rectal administration the carrier can comprise a suppository base such as cocoa 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 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 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.

35 Examples of compositions within the preferred ranges given are as follows:

Example 20

40	Capsules		40
	Ingredients	Per Capsule	
	1. Active ingredient	10.00 mg	
45	2. Lactose	146.000 mg	45
	3. Magnesium stearate	4.000 mg	

The procedure for making the capsule is to blend ingredients, 1 2 and 3, mill this blend and blend it again and then fill this milled blend into #1 hard gelatin capsules.

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Example 21

	Tablets		
5	Ingredients	Per Tablet, mg	5
	1. Active ingredient	10.0 mg	
	2. Corn starch	20.0 mg	
10	3. Kelacid	20.0 mg	10
	4. Keltose	20.0 mg	
15	5. Magnesium stearate	1.3 mg	15

Procedure

The procedure for making the tablets is to blend ingredients 1,2,3 and 4 and add sufficient water portionwise to the blend with careful stirring after each addition. Such additions of water and stirring continue until the mass is of a consistency to permit its conversion to wet granules. 20

The wet mass is converted to granules by passing it through the oscillating granulator, using 8-mesh screen.

The wet granules are then dried in an oven at 140°F.

The dried granules are then passed through an oscillating granulator, using a 10-mesh screen.

25 The dry granules are then lubricated with 0.5% magnesium stearate. 25

The lubricated granules are compressed on a suitable tablet press.

Example 22

30	Intravenous Injection		30
	Ingredients	Per ml	
	1. Active ingredient	1.0 mg	
35	2. pH 4.0 Buffer solution qs to	1.0 ml	35

Procedure

The procedure for making an intravenously injectable dose is to dissolve the active ingredient in the buffer solution and then aseptically filter the solution. The sterile solution is now aseptically filled into sterile ampoules, which are sealed under aseptic conditions. 40

Example 23

	Intramuscular Injection		
45	Ingredients	Per ml	45
	1. Active ingredient	5.0 mg	
50	2. Isotonic buffer qs to solution 4.0	1.0 ml	50

The procedure for making the intramuscularly injectable dose is to dissolve the active ingredient in the buffer solution, and then aseptically filter the solution. The sterile solution is now aseptically filled into sterile ampoules which are sealed under aseptic conditions. 55

Example 24

Suppositories

5	Ingredients	Per Supp.	5
	1. Active ingredient	10.0 mg	
	2. Polyethylene Glycol 1000	1350.0 mg	
10	3. Polyethylene Glycol 4000	450.0 mg	10

The procedure for making suppositories is to melt ingredients 2 and 3 together and stir until uniform. Ingredient 1 is now dissolved in the molten mass and the mixture stirred until uniform.

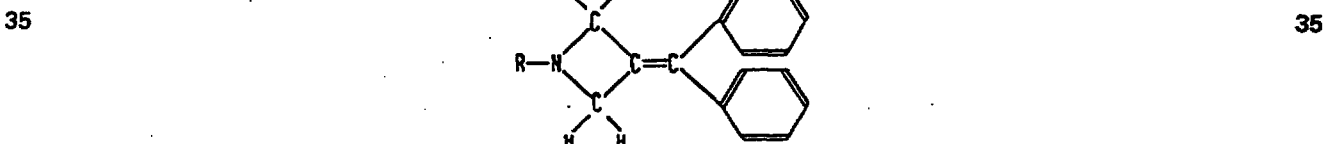
15 The molten mass is now poured into suppository molds and chilled. When the suppositories have solidified they are removed from the molds and wrapped. 15

Although very small quantities of the active materials of the present invention are effective when minor therapy is involved or in cases of administration to subjects having a relatively low body weight, unit dosages are usually from 5 milligrams or above and preferably 25, 50 or 100 milligrams or even higher, depending of course upon the emergency of the situation and the particular result desired. Five to 50 milligrams appears optimum per unit dose, or usual broader ranges appear to be 1 to 100 milligrams per unit dose. 20

Daily dosages should preferably range from 10mg to 100 mg. The active ingredients of the invention may be combined with other pharmacologically active agents as stated above. It is only necessary that the active ingredients constitute an effective amount, i.e. such that a suitable effective dosage will be obtained consistent with the dosage form employed. Obviously, several unit dosage forms may be administered at about the same time. The exact individual dosages as well as daily dosages will, of course, be determined according to standard medical principles under the direction of a physician or veterinarian. 25

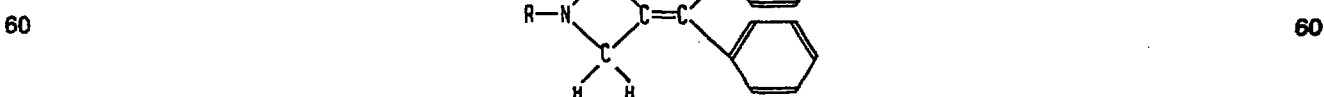
30 CLAIMS 30

1. 3-Methyleneazetidine compounds corresponding to the formula:



wherein R represents a lower-alkyl, cycloalkyl or phenyl-lower-alkyl group and the pharmaceutically acceptable acid addition salts thereof.

2. 1-Methyl-3-diphenyl-methyleneazetidine or a pharmaceutically acceptable acid addition salt thereof.
3. 1-Ethyl-3-diphenyl-methyleneazetidine or a pharmaceutically acceptable acid addition salt thereof.
- 45 4. 1-Isopropyl-3-diphenylmethylenazetidine or a pharmaceutically acceptable acid addition salt thereof. 45
5. 1-Isopropyl-3-diphenylmethylenazetidine oxalate.
6. 1-Cyclohexyl-3-diphenylmethylenazetidine or a pharmaceutically acceptable acid addition salt thereof.
7. 1-Phenylethyl-3-diphenylmethylenazetidine or a pharmaceutically acceptable acid addition salt thereof.
- 50 8. 1-(α -Methylbenzyl)-3-diphenylmethylenazetidine or a pharmaceutically acceptable acid addition salt thereof. 50
9. A pharmaceutical composition for the treatment of depression in humans comprising a pharmaceutical carrier and an antidepressant quantity of a 3-methyleneazetidine compound corresponding to the formula: 55



wherein R represents a lower-alkyl, cycloalkyl or phenyl-lower-alkyl group and the pharmaceutically acceptable acid addition salts thereof. 65



Example 24

Suppositories

Ingredients	Per Supp.	
1. Active ingredient	10.0 mg	5
2. Polyethylene Glycol 1000	1350.0 mg	10
3. Polyethylene Glycol 4000	450.0 mg	10

The procedure for making suppositories is to melt ingredients 2 and 3 together and stir until uniform. Ingredient 1 is now dissolved in the molten mass and the mixture stirred until uniform.

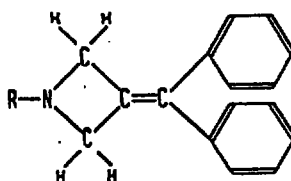
The molten mass is now poured into suppository molds and chilled. When the suppositories have solidified they are removed from the molds and wrapped.

Although very small quantities of the active materials of the present invention are effective when minor therapy is involved or in cases of administration to subjects having a relatively low body weight, unit dosages are usually from 5 milligrams or above and preferably 25, 50 or 100 milligrams or even higher, depending of course upon the emergency of the situation and the particular result desired. Five to 50 milligrams appears optimum per unit dose, or usual broader ranges appear to be 1 to 100 milligrams per unit dose.

Daily dosages should preferably range from 10mg to 100 mg. The active ingredients of the invention may be combined with other pharmacologically active agents as stated above. It is only necessary that the active ingredients constitute an effective amount, i.e. such that a suitable effective dosage will be obtained consistent with the dosage form employed. Obviously, several unit dosage forms may be administered at about the same time. The exact individual dosages as well as daily dosages will, of course, be determined according to standard medical principles under the direction of a physician or veterinarian.

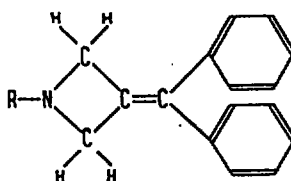
CLAIMS

1. 3-Methyleneazetidine compounds corresponding to the formula:



wherein R represents a lower-alkyl, cycloalkyl or phenyl-lower-alkyl group and the pharmaceutically acceptable acid addition salts thereof.

2. 1-Methyl-3-diphenyl-methyleneazetidine or a pharmaceutically acceptable acid addition salt thereof.
3. 1-Ethyl-3-diphenyl-methyleneazetidine or a pharmaceutically acceptable acid addition salt thereof.
4. 1-Isopropyl-3-diphenylmethyleneazetidine or a pharmaceutically acceptable acid addition salt thereof.
5. 1-Isopropyl-3-diphenylmethyleneazetidine oxalate.
6. 1-Cyclohexyl-3-diphenylmethyleneazetidine or a pharmaceutically acceptable acid addition salt thereof.
7. 1-Phenylethyl-3-diphenylmethyleneazetidine or a pharmaceutically acceptable acid addition salt thereof.
8. 1-(α -Methylbenzyl)-3-diphenylmethyleneazetidine or a pharmaceutically acceptable acid addition salt thereof.
9. A pharmaceutical composition for the treatment of depression in humans comprising a pharmaceutical carrier and an antidepressant quantity of a 3-methyleneazetidine compound corresponding to the formula:



wherein R represents a lower-alkyl, cycloalkyl or phenyl-lower-alkyl group and the pharmaceutically acceptable acid addition salts thereof.

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10. A pharmaceutical composition as claimed in claim 9 in which the 3-methylenediphenylazetidine compound is 1-isopropyl-3-diphenylmethylenazetidine.
11. A pharmaceutical composition as claimed in claim 9 in which the 3-methylenediphenylazetidine compound is 1-methyl-3-diphenylmethylenazetidine.
- 5 12. A pharmaceutical composition as claimed in claim 9 in which the 3-methylenediphenylazetidine compound is 1-isopropyl-3-diphenylmethylenazetidine oxalate. 5
13. A pharmaceutical composition as claimed in claim 9 substantially as specifically described herein with reference to Example 20, 21, 22, 23, or 24.

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