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NO DRAWINGS

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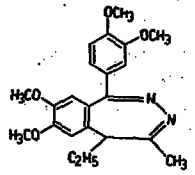
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(19)

(54) DIAZABICYCLOUNDECAPENTENE DERIVATIVE

(71) We, E GY T GYOGYSZERVEGYESZETI GYAR, a Hungarian Body Corporate of Kereszturi u. 32, Budapest X, Hungary, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed to be particularly described in and by the following statement:—

The invention relates to a new 2,3-diazabicyclo - [5.4.0] - undecapentene derivative having a tranquillizing effect and pharmaceutical products containing the same, as well as to processes for the preparation thereof. More particularly, it relates to 1-veratryl-4-methyl-5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo-[5.4.0]-undeca-1,3,6,8,10-pentene, of formula I

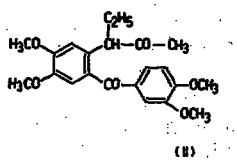


(I)

as well as to the acid addition salts thereof.

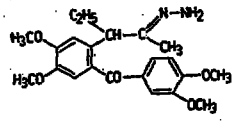
The compound of the invention can be prepared according to various methods, as described in the following:

A. According to one method, 3-(2-veratroyl-4,5 - dimethoxyphenyl) - pentan - 2 - one of the formula II



(II)

is reacted with hydrazine or hydrazine hydrate and the obtained 3-(2-veratroyl-4,5-dimethoxyphenyl)-pentan-2-one monohydrazone of the formula III

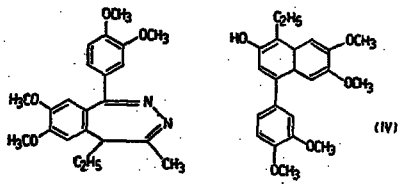


(III)

is reacted with an acid, preferably with a mineral acid, and if desired, the obtained salt of the compound of formula I is converted to the free base by treating it with an acid binding agent. These two reactions are preferably carried out in a single step.

B. According to another method, a 1-veratryl - 3 - methyl - 4 - ethyl - 6,7 - dimethoxy-isobenzopyrilium salt is reacted with hydrazine or hydrazine hydrate; if the hydrazine or hydrazine hydrate is used in only a slight excess, the 2,3 - diazabicyclo - [5.4.0] - undecapentene derivative of formula I is liberated with an acid binding agent.

C. According to a third process of the invention, 3 - (2 - veratroyl - 4,5 - dimethoxyphenyl)-pentan-2-one is treated with hydrazine or hydrazine hydrate in a mixture of one or more C_{1-4} alcohols and benzene. The mixture is allowed to stand at 0 to 5°C for at least one hour; thereafter the separated 1-ethyl-4-veratryl - 6,7 - dimethoxy - 2 - naphthol adduct of the formula IV



(IV)

is decomposed with an acid. The decomposition can be carried out after isolation of the intermediate, or directly in the reaction mixture. The free base is liberated by treating the mixture with an alkali.

If desired, the 2,3 - diazabicyclo - [5.4.0] - undecapent-ene derivative of formula I can be converted into its acid addition salts by reacting the free base with an acid.

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In the first step of the reaction described in Method A, 3 - (2 - veratroyl - 4,5 - dimethoxyphenyl) - pentan - 2 - one monohydrazone of formula III is formed. The above intermediate is converted to the desired compound of the formula I by reacting with an acid. The two reactions are preferably carried out in a single step.

If 3 - (2 - veratroyl - 4,5 - dimethoxyphenyl) - pentan - 2 - one monohydrazone of the formula III, obtained in the reaction of the compound having the formula II and hydrazine or hydrazine hydrate, is separated, and the mother liquor is left to stand at least for 36 hours at 0 to 5°C, an adduct of the formula IV is obtained. This compound is decomposed with an acid and thereafter the mixture is rendered alkaline. In this way, the compound of the formula I is obtained.

In the above reactions, ammonium hydroxide, alkali metal hydroxides, carbonates and bicarbonates can conveniently be used as acid binding agents.

The product obtained in Method B can be purified according to known methods, e.g. by forming a methanol-adduct. According to a special method of purification, the compound of the formula I is reacted with 1-ethyl-4-veratryl - 6,7 - dimethoxy - 2 - naphthol, and the obtained adduct is decomposed.

The reactions described in Method A and B are preferably carried out in a solvent, such as an aliphatic alcohol having 1 to 4 carbon atoms or a mixture thereof. The salts are preferably converted to the free base in aqueous medium.

The free base of the formula I normally separates with one mole of water of crystallization. This monohydrate melts at 95—115°C. When the monohydrate is heated, preferably in vacuo, or is recrystallized from an alcohol, the water of crystallization is split off, and a compound melting at 156—157°C is obtained.

The compound of the invention, as well as its physiologically compatible acid addition salts, can be transformed into pharmaceutically usable products, either alone or combined with other pharmaceutically active compounds, by association with a pharmaceutical carrier or excipient, such as the binding, filling, surface-active, and flavouring agents conventionally used in the pharmaceutical industry.

The preparation of the starting compounds is described in the following papers:

3 - (2 - Veratroyl - 4,5 - dimethoxyphenyl) - pentan-2-one: Ber. *75*, 891 (1942); J.Am. Chem.Soc. *72*, 1118 (1950).

Isobenzopyrilium salts: Ber. *77* pp. 6, 12 (1944); J.Org.Chem. *19*, 472 (1954).

The compound of the invention inhibits significantly the aggresive behaviour of mice. It decreases the spontaneous motor activity of rats and mice, and antagonizes the hyperactivity induced by amphetamine or other central stimulants. It exerts a taming effect on hamsters. In behaviour tests oral administration of the compound in doses of 12.5 to 200 mg/kg into cats after transitory agitation induces inhibition and poor response to outer stimuli. This action lasts from 4 to 48 hours, depending on the dosage.

The compound does not possess any anticonvulsive activity (tested in maximal electric shock, and convulsions provoked by metrazol, nicatin and strychnine), and at the same time, it decreases the metrazol-convulsion threshold.

The compound does not possess appreciable muscle relaxant activity. It potentiates the effect of barbiturates and alcohol in mice and rats only when given at least in motility-inhibitory dosage. These valuable properties are very advantageous in the treatment of outpatients.

In mice and rats, it evokes catalepsy in the 5—6 folds of the depressive and aggressivity inhibitory doses; in this dosage range it develops ptosis.

In rats, the compound decreases the toxicity of noradrenaline.

It slightly antagonizes the ptosis evoked by reserpine.

Among the cardiovascular effects of the compound, its adrenolytic, blood-pressure reflex-inhibitory and coronarydilatory action can be mentioned.

The favourable resorption of the compound is demonstrated by the fact that the effects can be observed 15 to 30 minutes after oral administration. The therapeutic index of the compound established in motility inhibition effect is 60.5 when given orally.

The acute toxicity values of the compound are:

LD_{50} p.o. in mice 2300 mg/kg (2785—1899)
LD_{50} p.o. in rats 2050 mg/kg (2316—1805).

On the basis of the above data, the new compound of the invention cannot be classified into any of the known classes of psychopharmaceutical. This new compound can be used in the clinical practice as a potent agent for releasing anxiety and tension, and in the normalisation of aggressive behaviour reactions. Its weak, but detectable antireserpine effect can explain its moderate antidepressive and emotion stimulant activities.

The 3 - (2 - veratroyl - 4,5 - dimethoxyphenyl)-pentan-2-one monohydrazone intermediate of the formula III has a tranquillizing effect of the same order as the minor tranquillizers. Its ED_{50} value is 160 mg/kg, while the LD_{50} value is 1600 mg/kg.

The invention is further elucidated by the aid of the Examples. These are given for the purpose of illustration only, and in no way limit the invention.

Example 1

4.00 g. (0.01 moles) of 3-(2-veratroyl-4,5-dimethoxy - phenyl) - pentan - 2 - one monohydrazone are added to 20 ml. of methanol or ethanol saturated with gaseous hydrochloric acid. Thereafter the mixture is evaporated to dryness. In the course of this procedure the condensation reaction takes place, and a hydrochloride is formed. 20 ml. of 5% aqueous sodium hydroxide solution are added to the residue. White 1 - veratryl - 4 - methyl - 5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene, containing one mole of water of crystallisation separates, and the solution become colourless. The product is filtered off, washed with 2×2 ml. of water, dried, and the dry product is recrystallized from a ten-fold amount of isopropanol, in the presence of charcoal.

Yield: 2.7 g. (71%), m.p. 156—157°C.

Analysis:

Calculated for $C_{22}H_{26}N_2O_4$ (382.45):
C 69.07%; H 6.63%; N 7.39%
Found: C 69.09%; H 6.85%; N 7.33%

NMR spectrum (in deuterochloroform): 6.77—7.58 ppm (5 - aromatic protons),

3.73—3.97 ppm (4—OCH_3),

2.76 ppm (CH_3—CH_2—CH),

2.08 ppm (CH_3—CH_2—CH),

1.9 ppm (=C—CH_3),

1.1 ppm (CH_3—CH_2—CH).

IR spectrum (in potassium bromide discs): carbonyl and NH bands do not appear.

λ_{max}: in ethanol: 312, 273 and 238 nm
in chloroform: 312 and 273 nm
in benzene: 311 nm

Mass spectrum: molecular weight: 382.189865 (calculated: 382.189245), ion fragments: m/e=341, 326, 312, 310, 204.

Thermogravimetric analysis: weight loss at 220 to 310°C, corresponding to the cleavage of acetonitrile.

Physical constants of the salts of 1-veratryl-4 - methyl - 5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene:

Hydrochloride ($C_{22}H_{26}N_2O_4$. HCl): m.p. 220—221°C (decomp)

Hydrobromide ($C_{22}H_{26}N_2O_4$. HBr): m.p. 218—219°C (decomp)

Perchlorate ($C_{22}H_{26}N_2O_4$. $HClO_4$): m.p. 200—202°C (decomp)

Picrate ($C_{22}H_{26}N_2O_4$. $C_6H_3N_3O_7$): m.p. 207°C (decomp).

The starting substance, 3-(2-veratroyl-4,5-dimethoxy - phenyl) - pentan - 2 - one monohydrazone has been prepared as follows:

A mixture of 38.64 g. (0.1 moles) of 3-(2-veratroyl - 4,5 - dimethoxyphenyl) - pentan - 2-one, 15 g. (0.3 moles) of pure hydrazine hydrate and 200 ml. of abs. ethanol is refluxed for 3 hours, and the mixture is then kept in a refrigerator overnight. The separated white, granular substance is filtered off, washed with 2×20 ml. of abs. ethanol and dried at ambient temperature. Yield 24.8 g. (62%); m.p. 134—136°C. Nitrogen-content: 6.90%.

The thus-obtained crude substance is crystallized from an 8-fold quantity of ethanol. The purified product weighs 22.5 g. and melts at 136°C.

Analysis:

Calculated for $C_{22}H_{28}N_2O_5$ (400.46):
C 65.98%; H 7.05%; N 7.00%
Found: C 66.16%; H 7.53%; N 7.05%

If only 0.1 moles of hydrazine hydrate are added in the above process, the crude substance separates with a yield of 49% and melts at 133—136°C. This crude product is recrystallized from methanol five times. A chromatographically pure substance is obtained, m.p. 136°C.

IR spectrum (in potassium bromide discs): υ CO (aromatic): 1630 $cm.^{-1}$; υ_{as} NH_2—υ_s NH_2 band-pairs: 3580 and 3410 cm^{-1}.

NMR spectrum: 2 removable NH-protons at δ=5.02 pp.

Example 2

A mixture of 3.86 g. (0.01 moles of 3-(2-veratroyl - 4,5 - dimethoxyphenyl) - pentan - 2-one, 0.011 moles of hydrazine (or equimolar quantity of hydrazine hydrate, purity grade 60 to 100 per cent), 60 ml. of ethanol and 0.005 moles of sulfuric acid is refluxed for 10 hours, and the mixture is then evaporated. The residue is worked up as described in Example 1. 2.55 g. of 1-veratryl-4-methyl-5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene are obtained, m.p. 156°C.

Example 3

4.41 g. (0.01 moles) of 1-veratryl-3-methyl-4 - ethyl - 6,7 - dimethoxy - isobenzopyrilium - chloride hydrochloride ($C_{22}H_{26}Cl_2O_5$) are dissolved in 35 ml. of methanol at 40°C. The solution is cooled to 20—25°C, and 0.75 g. (0.015 moles) of pure hydrazine hydrate in 5 ml. of methanol are added. The orange solution turns light yellow. The mixture is evaporated to dryness, the residue is treated with 3 ml. of water, the obtained suspension is cooled to 0°C and the product filtered off. The yellowish, crude 1-veratryl-4-methyl-5-ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene hydrochloride melts at 205°C (decomposition). The

crude product is triturated with ethyl acetate. The purified product melts at 217.5°C (decomposition).

Analysis:
Calculated for $C_{22}H_{26}N_2O_4 . HCl$ (418.92): N 6.69%; Cl 8.46%
Found: N 6.52%; Cl 8.21%

2 g. of the hydrochloride obtained in the above reaction are dissolved in 15 ml. of water, and the pH of the solution is adjusted to 11—12 with concentrated ammonium hydroxide or sodium hydroxide solution. The separated voluminous precipitate is filtered off, washed several times with small portions of water, and dried to constant weight at 30°C. 1.6 g. of 1 - veratryl - 4 - methyl - 5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene are obtained. m.p.: the sample looses water of crystallization at 100 to 116°C and then solidfies, finally melting at 154—156°C.

Analysis:
Calculated for $C_{22}H_{26}N_2O_4 . H_2O$ (400.46): C 65.98% H 7.05% N 7.00%
Found: C 65.59% H 7.29% N 6.95%

The monohydrate also looses its water of crystallisation when recrystallized from organic solvents. Thus 0.5g. of the above product are dissolved in 5 ml. of hot isopropanol, the solution is evaporated to 2.5 ml., and this concentrated solution is kept in a refrigerator. 0.45 g. of light cream-coloured, transparent crystal grains are obtained, m.p. 156—157°C.

Similar results are obtained if 1-veratryl-3 - methyl - 4 - ethyl - 6,7 - dimethoxy - isobenzopyrilium hydrosulfate ($C_{22}H_{26}O_9S$) is used as starting substance in the above process.

Example 4

0.01 moles of an isobenzopyrilium salt used in Example 3 are dissolved in 50 ml. of lukewarm methanol, and 1.25 g. (0.025 moles) of pure hydrazine hydrate are added to the dark yellow solution. The solution lightens in colour. The mixture is evaporated nearly to dryness, then 20 ml. of water are added to the residue. The separated product is filtered off and washed with 2×2 ml. of water, and the product is dried. The obtained 3.3 g. of 1-veratryl - 4 - methyl - 5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10-pentene are recrystallized from a 10-fold quantity of isopropanol in the presence of charcoal. Yield: 2.8 g. (73.5%) of purified product, m.p. 156—157°C.

Example 5

138 g. (0.357 moles) of finely powdered 3 - (2 - veratroyl - 4,5 - dimethoxyphenyl) - pentan-2-one and 615 ml. of isopropanol are introduced into a 1 l. round bottomed flask. 20 ml. (0.366 moles) of concentrated sulfuric acid are then added dropwise to the suspension within 15 minutes, with stirring and cooling. The mixture turns yellow, and its temperature rises to 30—35°C. Thereafter the mixture is heated to boiling in a water bath within 30 minutes. The major part of the formed yellow 1 - veratryl - 3 - methyl - 4 - ethyl - 6,7 - dimethoxy - isobenzopyrilium hydrosulfate is dissolved. The mixture is cooled to 60°C. and 39.2 g. (0.74 moles) of hydrazine hydrate (purity grade: 94%) in 32 ml. of isopropanol are added dropwise to the mixture within 30 to 60 minutes. Although the reaction is slightly exothermic, the temperature of the mixture falls to 35—40°C at the end of the addition, and the vivid yellow colour of the mixture disappears. Thereafter 16.8 g. (0.2 moles) of sodium bicarbonate are added in portions (1 to 2 g. each) to the mixture within 30 minutes, followed by 4.5 g. of charcoal, and the mixture is heated again to boiling within 30 minutes. The mixture is filtered hot, the filter cake is washed with 10 ml. of hot isopropanol, and the solution is evaporated to dryness. The residue is recrystallized from 445 ml. of methanol in the presence of 5 g. of charcoal. The charcoal is filtered off, washed with hot methanol, the filtrate and the wash are combined, and the light yellow, transparent solution is cooled. The methanol adduct of 1-veratryl-4-methyl - 5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene separates in the form of white crystals. The mixture is cooled for 4 to 5 hours with ice water, and the precipitate is then filtered off and washed with 50 ml. of ice cold methanol. 103.0 g. (70%) of the above product are obtained. M.p.: the product looses methanol at 95 to 98°C, and then solidifies, melting at 156°C.

Analysis:
Calculated for $C_{22}H_{26}N_2O_4 . CH_3OH$ (414.51): C 66.65%; H 7.30%; N 6.76%
Found: C 66.50%; H 7.20%; N 6.82%

The removal of the methanol from the crystalline substance can be carried out by drying the product at a temperature of 60 to 70°C. According to a more preferred method, the methanol adduct is suspended in distilled water at 70 to 80°C, and the solid is filtered off. The thus obtained 1-veratryl-4-methyl-5-ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene contains no traces of sulfate. Yield: 93.5 g. (68%), m.p. 156—157°C.

Example 6

a) The ethanolic mother liquor, obtained in the preparation of the starting monohydrazone derivative as described in Example 1, is kept in a refrigerator for three days. 8 to 12 g. of a light cream-coloured crystal powder separ-

ates, m.p. 166—168°C. The obtained substance is recrystallized from abs. ethanol with a recovery of 80 to 85%; the purified, light yellowish crystal powder melts at 168°C. On the basis of the structure analysis, the product is the 1 - ethyl - 4 - veratryl - 6,7 - dimethoxy - 2 - naphthol adduct of 1-veratryl-4-methyl - 5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene.

IR spectrum: maximum at 2650 cm^{-1} (ionic structure); the double band of NH_2 does not appear.

Analysis:

Calculated for $C_{22}H_{26}H_2O_4 . C_{22}H_{24}O_5$ (750.90):

C 70.38% H 6.74% N 3.73%

Found: C 70.27% H 6.84% N 3.76%

b) The above adduct (m.p. 168°C) can easily be prepared from the components as follows:

3.82 g. (0.01 moles) of 1-veratryl-4-methyl-5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene and 3.68 g. (0.01 moles) of 1-ethyl-4-veratryl - 6,7 - dimethoxy - 2 - naphthol are dissolved in 40 ml. of hot abs. ethanol, and the solution is cooled. 6.55 g. of pure adduct separate (m.p. 168°C; nitrogen content: 3.65%). The melting point of the product does not rise even after recrystallization from methanol or isopropanol. The mixture of the products obtained according to paragraphs a) and b) does not show melting point depression.

1 - Veratryl - 4 - methyl - 5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene is prepared from the adduct obtained in paragraphs a) or b) as follows:

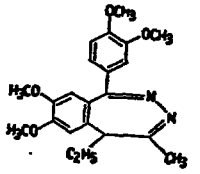
30 ml. of water and 5 ml. of concentrated hydrochloric acid are added to 7.50 g. (0.01 moles) of the above adduct. The solution turns dark yellow, and about half of the solid dissolves. The suspension is heated to boiling, and the insoluble 1 - ethyl - 4 - veratryl - 6,7 - dimethoxy - 2 - naphthol is filtered off. The hot acidic filtrate is cooled, rendered alkaline with concentrated ammonium hydroxide solution and is thereafter worked up as described in Example 1. 2.7 g. of almost pure 1 - veratryl - 4 - methyl - 5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0.] - undeca - 1,3,6,8,10 - pentene are obtained, m.p. 150 to 154°C. This product is preferably purified as described in Example 5.

Example 7

A mixture of 3.86 g. (0.01 moles) of 3-(2-veratroyl - 4,5 - dimethoxyphenyl) - pentan - 2-one, 0.60 g. (0.0125 moles) of pure hydrazine hydrate, 30 ml. of abs. ethanol and 10 ml. of benzene is refluxed for 10 hours; thereafter 20 ml. of the solvent mixture are distilled off. The residue is kept in a refrigerator for one day, after which the separated light cream-coloured compound of the formula IV is filtered off and washed with 5 ml. of methanol. Yield: 2.7 g. (72%), m.p. 164—167°C. The product is recrystallized from an 18-fold quantity of isopropanol or a 30-fold quantity of methanol with a recovery of 80%. The purified product melts at 168°C, and does not show melting point depression in admixture with the compound prepared in Example 6. The above reaction is preferably carried out in aqueous alcoholic medium, or in the presence of traces of an alkali metal hydroxide.

WHAT WE CLAIM IS:—

1. 1 - Veratryl - 4 - methyl - 5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene having the formula I:

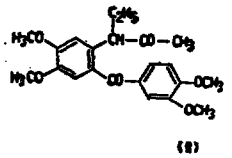


(I)

and acid addition salts thereof.

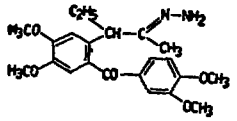
2. Pharmaceutical products containing the compound of formula I as claimed in claim 1 and/or one or more physiologically compatible acid addition salts thereof, in association with a pharmaceutical carrier or excipient.

3. A process for preparing the compound of formula I as claimed in claim 1 which comprises reacting 3 - (2 - veratroyl - 4,5 - dimethoxyphenyl)-pentan-2-one of the formula II



(II)

with hydrazine or hydrazine hydrate and reacting the obtained 3 - (2 - veratroyl - 4,5 - dimethoxyphenyl) - pentan - 2 - one monohydrazone of the formula III



(III)

with an acid.

4. A process as claimed in claim 3 wherein the compound of formula I by reaction with a mineral acid.

ates, m.p. 166—168°C. The obtained substance is recrystallized from abs. ethanol with a recovery of 80 to 85%; the purified, light yellowish crystal powder melts at 168°C. On the basis of the structure analysis, the product is the 1 - ethyl - 4 - veratryl - 6,7 - dimethoxy - 2 - naphthol adduct of 1-veratryl-4-methyl - 5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene.

IR spectrum: maximum at 2650 cm^{-1} (ionic structure); the double band of NH_2 does not appear.

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Calculated for $C_{22}H_{26}H_2O_4 . C_{22}H_{24}O_5$ (750.90):

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b) The above adduct (m.p. 168°C) can easily be prepared from the components as follows:

3.82 g. (0.01 moles) of 1-veratryl-4-methyl-5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene and 3.68 g. (0.01 moles) of 1-ethyl-4-veratryl - 6,7 - dimethoxy - 2 - naphthol are dissolved in 40 ml. of hot abs. ethanol, and the solution is cooled. 6.55 g. of pure adduct separate (m.p. 168°C; nitrogen content: 3.65%). The melting point of the product does not rise even after recrystallization from methanol or isopropanol. The mixture of the products obtained according to paragraphs a) and b) does not show melting point depression.

1 - Veratryl - 4 - methyl - 5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene is prepared from the adduct obtained in paragraphs a) or b) as follows:

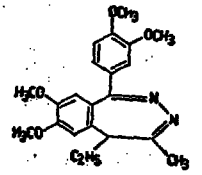
30 ml. of water and 5 ml. of concentrated hydrochloric acid are added to 7.50 g. (0.01 moles) of the above adduct. The solution turns dark yellow, and about half of the solid dissolves. The suspension is heated to boiling, and the insoluble 1 - ethyl - 4 - veratryl - 6,7 - dimethoxy - 2 - naphthol is filtered off. The hot acidic filtrate is cooled, rendered alkaline with concentrated ammonium hydroxide solution and is thereafter worked up as described in Example 1. 2.7 g. of almost pure 1 - veratryl - 4 - methyl - 5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0.] - undeca - 1,3,6,8,10 - pentene are obtained, m.p. 150 to 154°C. This product is preferably purified as described in Example 5.

Example 7

A mixture of 3.86 g. (0.01 moles) of 3-(2-veratroyl - 4,5 - dimethoxyphenyl) - pentan - 2-one, 0.60 g. (0.0125 moles) of pure hydrazine hydrate, 30 ml. of abs. ethanol and 10 ml. of benzene is refluxed for 10 hours; thereafter 20 ml. of the solvent mixture are distilled off. The residue is kept in a refrigerator for one day, after which the separated light cream-coloured compound of the formula IV is filtered off and washed with 5 ml. of methanol. Yield: 2.7 g. (72%), m.p. 164—167°C. The product is recrystallized from an 18-fold quantity of isopropanol or a 30-fold quantity of methanol with a recovery of 80%. The purified product melts at 168°C, and does not show melting point depression in admixture with the compound prepared in Example 6. The above reaction is preferably carried out in aqueous alcoholic medium, or in the presence of traces of an alkali metal hydroxide.

WHAT WE CLAIM IS:—

1. 1 - Veratryl - 4 - methyl - 5 - ethyl - 7,8 - dimethoxy - 2,3 - diazabicyclo - [5.4.0] - undeca - 1,3,6,8,10 - pentene having the formula I:

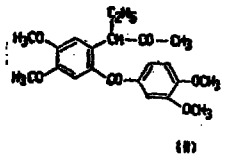


(I)

and acid addition salts thereof.

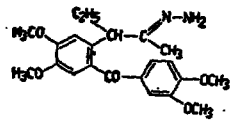
2. Pharmaceutical products containing the compound of formula I as claimed in claim 1 and/or one or more physiologically compatible acid addition salts thereof, in association with a pharmaceutical carrier or excipient.

3. A process for preparing the compound of formula I as claimed in claim 1 which comprises reacting 3 - (2 - veratroyl - 4,5 - dimethoxyphenyl)-pentan-2-one of the formula II



(II)

with hydrazine or hydrazine hydrate and reacting the obtained 3 - (2 - veratroyl - 4,5 - dimethoxyphenyl) - pentan - 2 - one monohydrazone of the formula III



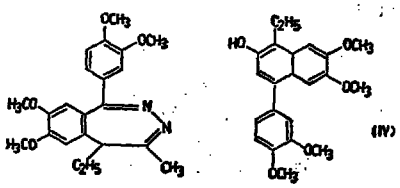
(III)

with an acid.

4. A process as claimed in claim 3 wherein the compound of formula I by reaction with a mineral acid.

5. A process for preparing the compound of formula I as claimed in claim 1 which comprises reacting a 1-veratryl-3-methyl-4-ethyl-6,7 - dimethoxy-isobenzopyrilium salt with hydrazine or hydrazine hydrate, and liberating the cmopound of formula I by reaction with an acid binding agent.

6. A process for preparing the compound of formula I as claimed in claim 1 which comprising reacting 3 - (2 - veratroyl - 4,5 - dimethoxyphenyl) - pentan - 2 - one with hydrazine or hydrazine hydrate in a mixture of one or more C_{1-4} alcohols and benzene, allowing the mixture to stand at 0 to 5°C at least one hour, decomposing the separated 1-ethyl-4-veratryl - 6,7 - dimethoxy - 2 - naphthol adduct of the formula IV



(IV)

with an acid, and liberating the compound of formula I by treating the mixture with an alkali.

7. A process as claimed in any of claims 3 to 6 in which the compound of formula I is transformed to an acid addition salt by reacting it with a pharmaceutically acceptable acid.

8. A process as claimed in any of claims 3 to 6 wherein a salt of the compound of formula I is converted to the free base by treating it with an acid binding agent.

9. A process as claimed in claim 6, in which the decomposition of the compound of formula IV is carried out directly in the reaction mixture.

10. A process as claimed in claim 6, in which the decomposition of the compound of formula IV is carried out after isolation.

11. A process as claimed in any of claims 3 to 10 substantially as herein described.

12. A process for preparing the compound of formula I as claimed in claim 1 substantially as herein described in the Examples.

13. The compound of formula I, as defined in claim 1, and acid addition salts thereof, whenever prepared by a process as claimed in any of claims 3 to 12.

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