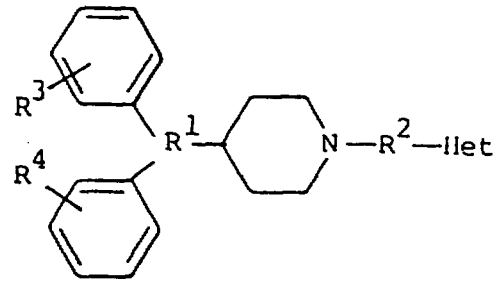
Description

The invention is concerned with novel N-substituted diphenylpiperidines of the formula



I

wherein
R^1 is CH, C=CH or CH-CH_2
R^2 is C_{1-12}-alkylene or CO-$(CH_2)_n$; n is 0 to 11,
R^3 and R^4 are hydrogen, halogen or C_{1-7}-alkoxy,
Het is pyridyl, pyrimidinyl or imidazolyl,
and salts thereof with pharmaceutically usable acids.

The invention is further concerned with a process for the manufacture of these compounds, novel intermediates which occur in this process as well as medicaments based on the said compounds.

In the scope of the invention "lower-alkoxy" signifies a straight-chain or branched group with 1-7 C atoms such as methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, t-butoxy, pentoxy and hexyloxy. "Alkylene" preferably denotes a straight-chain or branched group with 1-12, especially 4-10, C atoms such as methylene, ethylene, propylene, butylene, pentylene, hexylene, heptylene, octylene, nonylene, decylene or dodecylene. "Halogen" denotes chlorine, bromine, iodine and fluorine. "Het" preferably denotes 3-pyridyl, 5-pyrimidinyl or 1-imidazolyl.

Examples of salts of the compounds of formula I are those with pharmaceutically usable inorganic acids, e.g. hydrohalic acids such as hydrochloric acid, hydrobromic acid or hydroiodic acid, sulphuric acid, phosphoric acid or nitric acid, or with organic acids such as tartaric acid, citric acid, fumaric acid, camphorsulphonic acid, methanesulphonic acid, toluenesulphonic acid, salicylic acid, ascorbic acid, maleic acid or mandelic acid. Preferred salts are the hydrohalides, especially the hydrochlorides, and the maleates, fumarates and methanesulphonates.

Preferred compounds of formula I are those in which R^1 is C=CH and/or in which R^2 is C_{1-12}-, especially C_{4-10}-alkylene and/or in which R^3 and R^4 are hydrogen and/or in which Het is pyridyl.

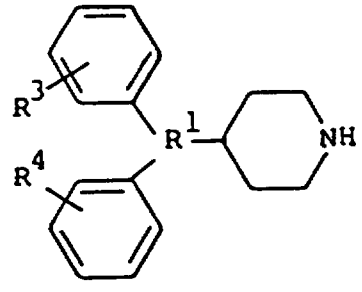
Examples of such compounds are:

3-[7-(4-(2,2-Diphenylethenyl)-1-piperidinyl]heptyl]-pyridine (1:1)-(E)-2-butenedioate hemihydrate,
3-[6-[4-(2,2-diphenylethenyl)-1-piperidinyl]hexyl]-pyridine (1:1)-(E)-2-butenedioate,
3-[5-[4-(2,2-diphenylethenyl)-1-piperidinyl]pentyl]-pyridine (1:1)-(E)-2-butenedioate and especially
3-[8-[4-(2,2-diphenylethenyl)-1-piperidinyl]-octyl]-pyridine and
3-[10-[4-(2,2-diphenylethenyl)-1-piperidinyl]decyl]-pyridine.

Further examples of compounds of formula I are:

3-[8-[4-[2,2-Bis(3-fluorophenyl)ethenyl]-1--piperidinyl]octyl]pyridine
3-[8-[4-[2,2-bis(2-fluorophenyl)ethenyl]-1--piperidinyl]octyl]pyridine
1-[6-[4-[2,2-bis(4-fluorophenyl)ethenyl]-1--piperidinyl]hexyl]-1H-imidazole
3-[8-[4-[2,2-bis(2-methoxyphenyl)ethenyl]-1--piperidinyl]octyl]pyridine
1-[6-[4-[2,2-bis(4-methoxyphenyl)ethenyl]-1--piperidinyl]hexyl]-1H-imidazole
5-[6-[4-[2,2-bis-(3-fluorophenyl)ethenyl]-1--piperidinyl]hexyl]pyrimidine.

The compounds of formula I and their salts can be manufactured by reacting a compound of the formula



II

with a halogenide of the formula Hal-R^2-Het, wherein R^1 to R^4 and Het have the above significance, if desired, reducing an obtained compound of formula I,

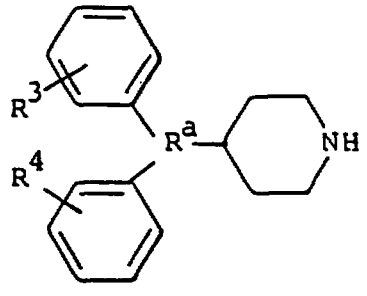
wherein R^2 contains a carbonyl group, to the corresponding compound of formula I, wherein R^2 is alkylene, and, if desired, isolating an obtained free base of formula I in the form of a salt with a pharmaceutically usable acid.

The reaction of a compound of formula II with a halogenide Hal-R^2-Het can be carried out in a manner known per se, e.g. in a solvent in the presence of a base. When R^2 contains a carbonyl group an aprotic solvent, e.g. tetrahydrofuran (THF), benzene or toluene, is preferably used. As the base there is used in this case e.g. pyridine or triethylamine and the reaction temperature is conveniently about 0°C to the reflux temperature, especially 0°C. When R^2 is alkylene there is used as the solvent e.g. dimethylformamide (DMF), dimethyl sulphoxide or an alkanol such as ethanol and as the base e.g. anhydrous sodium carbonate, a sodium alkoxide such as sodium methoxide or an aqueous alkali metal hydroxide such as sodium hydroxide and the reaction temperature is conveniently about 0°C to about 100°C, especially about 50-75°C.

The facultative reduction of a compound of formula I can be carried out in a manner known per se, e.g. in a solvent such as THF or a hydrocarbon, e.g. toluene or benzene, with a hydride such as lithium aluminium hydride or sodium bis(2-methoxyethoxy)aluminium hydride at a temperature of about 0°C to the reflux temperature, preferably at room temperature.

The salts of the compounds of formula I are preferably manufactured in a solvent, e.g. ethanol, acetone or acetonitrile, by reacting the free base with the corresponding anhydrous acid.

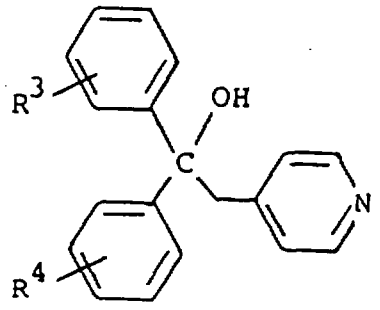
Among the compounds of formula II those of the formula



II-a

wherein R^a is C=CH or $CH=CH_2$ and R^3 and R^4 have the above significance,

are novel and as such are part of the invention. They can [be prepared] in a manner known per se by hydrogenating a pyridine derivative of the formula



III

wherein R^3 and R^4 have the above significance, to the corresponding piperidine derivative, followed by dehydration of the latter to the corresponding compound of formula II-a, wherein R^a is C=CH, and, if desired, hydrogenation to the compound of formula II-a, wherein R^a is $CH-CH_2$.

The hydrogenation of a compound of formula III can be carried out in a manner known per se, e.g. in a solvent such as glacial acetic acid in the presence of a hydrogenation catalyst, e.g. platinum oxide, with hydrogen, e.g. under a pressure up to about 6.8 bar, preferably about 3.4 bar, and at a temperature in the range of about 0 to about 100°C, preferably about 25-50°C.

The dehydration of the obtained piperidine derivative can be performed in the presence of trifluoroacetic acid or with an acid such as toluenesulphonic acid in a hydrocarbon such as toluene or benzene at a temperature in the range of about 0°C to about 50°C, preferably at about 25°C.

The facultative hydrogenation of a compound of formula II-a can be carried out in a solvent, e.g. an alkanol such as ethanol, using a catalyst such as 10% Pd/C in the presence of hydrogen under normal pressure and at a temperature of 25°C.

The compounds of formulae II, wherein R^1 is CH, III and Hal-R^2-Het are known or can be prepared according to methods known per se. Thus, the halogenides Hal-R^2-Het, wherein R^2 is alkylene, can be prepared by halogenating the corresponding alcohols, e.g. with thionyl chloride, in a solvent such as a halogenated hydrocarbon, e.g.

methylene chloride, or a hydrocarbon such as benzene or toluene, at a temperature in the range of about 0° to the reflux temperature, preferably at the reflux temperature.

The compounds of formula I and their pharmaceutically usable acid addition salts have insulin lowering activity and can therefore be used as medicaments for the treatment of obesity. This activity can be demonstrated according to methods known per se, e.g. as described in US Patent 4 500 540, by comparing the insulin secretion before and after perfusing isolated rat pancreas with the test compound. The results are given in Table I as the inhibition index, an inhibition index of more than 1 signifying the complete inhibition of the insulin secretion.

The results of the glucose clearance are also given in Table I. In this test the glucose level is determined on the one hand immediately before the administration of glucose to Sprague-Dawley rats and on the other hand 30, 60 and 90 minutes after glucose administration. Active compounds increase the glucose level in comparison to the controls. Since the glucose level achieves a maximum 30 minutes after administration of the glucose, the difference between the glucose level in the case of controls and in the case of treated rats 30 minutes after administration is used as the index of activity. The results are given in % of the controls, with substances having an index of more than 100% being active.

Table I

Free base of formula I of Examples 1-25	Perfusion of the pancreas Concentration (mM)	Inhibition index	Glucose clearance (% of control)
1	100	6.0	105
2	50	7.6	99
5	100	14.1	109
7	100	5.3	120
8	100	1.7	101
9	100	0.6	113
10	100	24.1	97
11	100	19.1	106
12	100	16.3	136
13	100	10.1	101
14	100	2.6	144
15	50	35	118
16	50	38	127
17	50	2.0	125
19	100	3.0	147
20	100	10.4	104
21	50	1.4	100
22	50	2.7	107
23	50		100
24	50	2.5	120
25	50	1.1	101

The activity of the products of formula I against obesity was determined in Zucker rats according to the method described in US Patent 4 500 540. The results are given in Table II for the free base of Example 16 and in Table III for the free base of further Examples.

Table II

Dose (mg/kg)	Body weight gain (g)	Carcass lipid difference (g)	Food intake (% of control)	Circulating insulin (% of control)
9	+9		91	83
17	-16		89	76
24	-32		82	47
34	-55		83	33
28	-88	-62	81	47

Table III

Example	Dose (mg/kg)	Body weight gain (g)	Food intake (% of control)	Relative body weight/gain index
16	38	-49	73	92
16	58	-76	70	94
21	49	-12	100	17

The compounds of formula I can be administered as medicaments, e.g. in the form of pharmaceutical preparations which contain them together with a compatible organic or inorganic inert carrier. Water, gelatine, lactose, starch, magnesium stearate, talc, vegetable oils, gums or polyalkylene glycols are examples of such carriers. The pharmaceutical preparations can be suitable for enteral, e.g oral, or parenteral administration and can be made up in solid form, e.g. as tablets, dragees, suppositories or capsules, or in liquid form, e.g. as solutions, suspensions or emulsions. The pharmaceutical preparations can be sterilized and/or can contain adjuvants such as preserving, stabilizing, wetting or emulsifying agents, salts for producing an osmotic pressure or buffers. They may also contain other therapeutically active substances.

The pharmaceutical dosage amounts can comprise about 250 to 500 mg of a compound of formula I or of a pharmaceutically usable acid addition salt thereof. Oral dosage amounts can amount to about 5 to about 30 mg/kg/day.

The following Examples illustrate the invention.

A. Preparation of the alcohols Het-R^2-OH

a) A mixture of 6.40 l of 1,3-diaminopropane and 15 g of lithium wire was heated to 65°C in an oil bath. An additional 153 g of lithium wire were added portionwise. 1.56 kg of potassium t-butoxide were added to the solution which was cooled to 20°C. The solution was stirred at 20°C for 15 minutes. 500 g of 3-octyn-1-ol in 100 ml of THF were added. The mixture was stirred at 20°C overnight and then poured into 12 l of ice-water while stirring. An additional 8 l of ice were added and the mixture was extracted three times with 8 l of methylene chloride. The combined extracts were washed with 8 l of water, 8 l of 1N hydrochloric acid and 4 l of sodium chloride solution and then dried. After removal of the solvent and distillation

there were obtained 338.2 g (68% yield) of 7-octyn-1-ol in the form of a colourless liquid, b.p. 104°C/16 mbar.

b) A mixture of 34.6 g of 7-octyn-1-ol, 26.4 ml of 3-bromopyridine, 115 ml of triethylamine and 350 ml of dichloromethane was stirred under a stream of argon. To the mixture were added 3.85 g of bistriphenylphosphine--palladium(II) chloride and 0.365 g of copper(I) iodide and then the mixture was heated under reflux overnight. The cooled reaction mixture was diluted with ether and the solids were filtered and washed with ether. The filtrates were extracted repeatedly with 1N hydrochloric acid and the combined aqueous layers were made strongly basic with excess sodium hydroxide. The mixture was extracted with dichloromethane, dried and evaporated, whereby there were obtained 51 g (91%) of crude 8-(3-pyridyl)-7-octyn-1-ol. By catalytic hydrogenation in 1000 ml of ethanol using 5 g of 10% Pd/C there were obtained, after distillation, 36 g (72%) of 3-pyridineoctanol, b.p. 145-152°C/0.4 mbar. Analysis, calculated for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76; found: C, 75.13; H, 10.21; N, 6.66.

c) By substituting 7-octyn-1-ol by 3-butyn-1-ol and 5-hexyn-1-ol there were obtained:

1) 5-pyrimidinebutanol, b.p. 175-180°C/0.4 mbar. Analysis, calculated for $C_8H_{12}N_2O$: C, 63.13; H, 7.95; N, 18.41; found: C, 62.83; H, 7.98; N, 18.63, and, respectively,

2) 5-pyrimidinehexanol, b.p. 170-175°C/0.8 mbar. Analysis, calculated for $C_{10}H_{16}N_2O$: C, 66.63; H, 8.95; N, 15.54; found: C, 66.62; H, 9.15; N, 15.59.

B. Preparation of the halogenide Hal-R^2-Het (R^2 = alkylene)

To a solution of 0.03 mol of the alcohol from A. in 40 ml of methylene chloride was added dropwise a solution of 0.04 mol of thionyl chloride in 10 ml of methylene chloride. The resulting solution was heated under reflux for 1 hour, then cooled and washed with saturated potassium carbonate solution. The organic layers were dried and evaporated at 25°C. The resulting oil was used in the next step without further purification.

In this manner, from 145.8 g of 3-pyridineoctanol there were obtained 191.3 g of 3-(8-chlorooctyl)pyridine in the form of an oil.

C. Preparation of the halogenide Hal-R^2-Het [R^2 = $CO-(CH_2)_n$]

Solid pyridinecarboxylic acid was added to thionyl chloride (20 ml) cooled in ice. The mixture was stirred at 25°C for 15 minutes and then evaporated to dryness several times from toluene. The resulting crude acid chloride hydrochloride was used in the next step without further purification.

D. Preparation of the compounds of formula III

a) A solution of 252.5 g of 4-picoline and 2.50 l of THF was cooled to below 20°C and treated at 15-20°C with 1.315 l of a solution of 1.85M phenyllithium in 70:30 cyclohexane:ether. The mixture was stirred at 15-20°C for 30 minutes and then cooled to -5-0°C. At this temperature there was added a solution of 494.2 g of benzophenone in 1.50 l of THF. The mixture was then stirred at room temperature for 3 hours. After the addition of 1.0 l of deionized water and 2.0 l of THF the mixture was warmed in order to dissolve the solids. The aqueous phase was separated and extracted with 2.0 l of THF. The combined organic solutions were dried. The solvent was evaporated. The resulting solid was mixed with 1.60 l of hexane at the reflux temperature. The suspension was stored at 4°C overnight and then filtered. The solids were washed with 1.0 l of petroleum ether and dried, there being obtained 699.6 g (94% yield) of α,α-diphenyl-4-pyridineethanol, m.p. 154-155°C.

b) α,α-Bis(3-methoxyphenyl)-4-pyridineethanol, m.p. 134-135°C, was prepared in a similar manner.

E. Hydrogenation of the compounds of formula III

a) 40 g of α,α-diphenyl-4-pyridineethanol were hydrogenated under 3.4 bar in 500 ml of glacial acetic acid using 4.0 g of platinum oxide. After filtration and evaporation the solid residue was dissolved in a hot mixture of water and toluene. An excess of sodium hydroxide solution was then added and the resulting mixture was cooled and filtered. The crude product was recrystallized from toluene, there being obtained 32.5 g (80%) of α,α-diphenyl-4-piperidineethanol, m.p. 153-154°C. The hydrochloride was crystallized from methanol, m.p. 271°C (dec.).

b) Analogously, from α,α-bis(4-fluorophenyl)-4--pyridineethanol there was obtained α,α-bis(4-fluorophenyl)-4-piperidineethanol, m.p. 161-163°C.

c) In a similar manner, a solution of 63 g of α,α--bis(3-methoxyphenyl)-4-pyridineethanol in 400 ml of acetic acid was hydrogenated using 2 g of platinum oxide to give 62.5 g of α,α-bis(3-methoxyphenyl)-4--piperidineethanol, m.p. 111-113°C.

d) In a variant of procedure a), 260 g of α,α--diphenyl-4-pyridineethanol in 3.0 l of ethanol were hydrogenated to give 190.65 g (72%) of α,α-diphenyl-4--piperidineethanol in the presence of 26 g of 5% Rh/C as the catalyst.

F. Preparation of the compounds of formula II-a

a) 20 g of α,α-diphenyl-4-piperidineethanol were dissolved in 40 ml of anhydrous trifluoroacetic acid and stirred for 15 minutes. Volatile substances were removed under a vacuum and the residue was separated between toluene and 2N sodium hydroxide solution. The organic layers were dried and evaporated and the residue was crystallized from hexane to give 17.2 g (92%) of 4-(2,2--diphenylethenyl)piperidine, m.p. 98-99°C.

b) Analogously, from 25 g of α,α-bis(4-fluorophenyl)--4-piperidineethanol, 0.25 molar methylbenzene solvate, and 50 ml of trifluoroacetic acid there were obtained 19.6 g (83%) of the hexane solvate of 4-[2,2-bis(4-fluorophenyl)ethenyl]-piperidine, m.p. 84-86°C.

c) Analogously, a solution of 15 g of α,α-bis(3--methoxyphenyl)-4-piperidineethanol in 30 ml of trifluoroacetic acid was converted into 4-[2,2-bis(3-methoxyphenyl)ethenyl]piperidine, m.p. of the hydrobromide 135.5-137°C.

d) 15.2 g of 4-(2,2-diphenylethenyl)piperidine in 500 ml of ethanol were hydrogenated using 1.5 g of 10% Pd/C. After filtration and evaporation the resulting oil solidified into a low-melting wax. The 4-(2,2-diphenylethyl)piperidine hydrochloride, m.p. 178-179°C, was recrystallized from 2-propanol/ether.

e) 4-[2,2-bis(4-fluorophenyl)ethyl]piperidine hydrochloride was obtained as a colourless oil in a similiar manner.

G. Manufacture of the compounds of formula I

Example 1

A mixture of 2.0 g of 4-diphenylmethylpiperidine in 5 ml of DMF and 4.2 ml of triethylamine was treated at 0°C with a solution of 5 ml of DMF and the acid chloride obtained from 2.0 g of 3-pyridinebutyric acid. After 15 minutes the mixture was diluted with chloromethane, filtered and evaporated to dryness. The residue was partitioned between toluene and 1N sodium hydroxide and the organic layer was washed with sodium chloride solution, dried and evaporated, there being obtained 3.3 g

of crude oil. This was purified by chromatography on silica gel using 98:2 ethyl acetate/triethylamine. The colourless oil obtained was dried at 70°C under a vacuum, there being obtained 2.8 g (86%) of 4-diphenylmethyl-1-[1--oxo-4-(3-pyridyl)butyl]piperidine, 0.1 molar ethyl acetate solvate. Analysis, calculated for $C_{27}H_{30}N_2O.0.1C_4H_8O_2$: C, 80.79; H, 7.62; N, 6.88
found: C, 80.91; H, 7.57; N, 6.81.

Example 2

Analogously to Example 1, from 7.9 g of 4-(2,2--diphenylethenyl)-piperidine and the acid chloride prepared from 6.6 g of 3-pyridinebutyric acid there were obtained, after crystallization of the toluene extracts from dichloromethane/ether, 9.1 g (74%) of 4-(2,2--diphenylethenyl-1-[1-oxo-4-(3-pyridyl)butyl]piperidine, m.p. 91-93°C.

Example 3

Analogously to Example 1, from 9.0 g of 4-[2,2-bis(4--fluorophenyl)ethenyl]piperidine, 0.15 molar hexane solvate, and the acid chloride obtained from 6.6 g of 3-pyridinebutyric acid there were obtained, after crystallization of the toluene extract from ether, 8.7 g (65%) of 4-[2,2-bis[4-fluorophenyl)ethenyl]1-[1-oxo-4-(3-pyridyl)-butyl]piperidine, m.p. 100-102°C.

Example 4

Analogously to Example 1, from 5.27 g of 4-(2,2--diphenylethenyl)piperidine and the acid chloride obtained from 6.5 g of 3-pyridinepentanoic acid there were obtained 8.0 g (94%) of crude 4-(2,2-diphenylethenyl)-1-[1-oxo-5--(3-pyridyl)pentyl]piperidine, m.p. 82-84°C after crystallization from ether.

Example 5

Analogously to Example 1, from 5.3 g of 4-(2,2--diphenylethyl)piperidine and the acid chloride obtained from 5.0 g of 3-pyridinebutyric acid there were obtained 6.3 g (76%) of 4-(2,2-diphenylethyl)-1-[1-oxo-4-(3--pyridyl)butyl]piperidine, m.p. 98-100°C after crystallization from methylene chloride/ether.

Example 6

Analogously to Example 1, from 8.3 g of 4-[2,2-bis(4--fluorophenyl)ethyl]piperidine and the acid chloride obtained from 6.1 g of 3-pyridinebutyric acid there were obtained 10.5 g (85%) of 4-[2,2-bis(4-fluorophenyl)ethyl]-

-1-[1-oxo-4-(3-pyridyl)butyl]piperidine, m.p. 108-110°C after crystallization from methylene chloride/ether.

Example 7

A solution of 7.8 g of the product of Example 1 in 100 ml of toluene was treated dropwise while stirring with 12 ml of a 3.5M solution of sodium bis(2-methoxyethoxy)-aluminium hydride in toluene. After 30 minutes the mixture was treated dropwise with an excess of sodium hydride and extracted with toluene. The organic layers were washed with sodium chloride solution, dried and evaporated, there being obtained 6.9 g (90%) of crude free base in the form of an oil. A solution of 5.9 g of this base in 50 ml of hot ethanol was treated with 1.8 g of maleic acid and the solution was then diluted with 150 ml of ether. The resulting solid was recrystallized as described above and there were obtained 6.7 g (87%) of 3-[4-[4-(diphenyl-methyl)-1-piperidinyl]butyl]pyridine (1:1)-(Z)-2-butene-dioate, m.p. 140-141°C.

Example 8

Analogously to Example 7, from 5.0 g of the product of Example 2 and 7.2 ml of a 3.5M solution of sodium bis(2-methoxyethoxy)aluminium hydride in toluene there were obtained 4.4 g of 3-[4-[4-(2,2-diphenylethenyl)-1--piperidinyl]butyl]pyridine, m.p. 54-56°C. This was dissolved in 50 ml of hot ethanol and treated with 1.28 g of fumaric acid. After dilution with 50 ml of ether there were obtained 4.1 g (67%) of fumarate, m.p. 163-165°C.

Example 9

Analogously to Example 7, from 13.0 g of the product of Example 3 and 34 ml of a 3.4M solution of sodium bis(2-methoxyethoxy)aluminium hydride in toluene there were obtained 8.9 g of free base as an oil. A solution of the base in 50 ml of hot methanol was treated with 2.3 g of fumaric acid and the methanol was distilled off with the addition of ethyl acetate. The resulting solid was recrystallized from methanol/ethyl acetate and there were obtained 8.9 g (56%) of pure 3-[4-[4-[2,2-bis(4-fluoro-phenyl)ethenyl]-1-piperidinyl]butyl]pyridine (1:1)-(E)-2--butenedioate, m.p. 183-184°C (decomposition).

Example 10

Analogously to Example 7, from 7.4 g of the product of Example 4 and 10.0 ml of a 3.5M solution of sodium bis(2--methoxyethoxy)aluminium hydride in toluene there were obtained 7.4 g of free base in the form of an oil. The free base was treated as in Example 9 and there were

obtained 8.4 g (92%) of 3-[5-[4-(2,2-diphenylethenyl)-1--piperidinyl]pentyl]pyridine (1:1)-(E)-2-butenedioate, m.p. 160-161°C (decomposition).

Example 11

Analogously to Example 7, from 6.1 g of the product of Example 5 and 9 ml of a 3.5M solution of sodium bis(2--methoxyethoxy)aluminium hydride in toluene there were obtained 5.4 g (90%) of the free base 3-[4-[4-(2,2--diphenylethyl)-1-piperidinyl]-butyl]pyridine of m.p. 62-64°C after crystallization from hexane. A solution of 5.25 g of the free base and 1.53 g of fumaric acid in 30 ml of hot methanol was diluted with 50 ml of ether and cooled. There were obtained 6.4 g (96%) of the fumarate, m.p. 146-148°C.

Example 12

In a similar manner analogously to Example 7, from 11.6 g of the product of Example 6 and 30 ml of a 3.4M solution of sodium bis(2-methoxyethoxy)aluminium hydride there were obtained 7.4 g (65%) of free base in the form of an oil. A solution of 7.4 g of the free base and 2.0 g of fumaric acid in 50 ml of methanol was diluted with ethyl acetate and cooled. After filtration and recrystallization from THF/ether there were obtained 7.1 g (76%) of 3-[4-[4-[2,2-bis(4-fluorophenyl)ethyl]-1-piperidinyl]-butyl]pyridine (1:1)-(E)-2-butenedioate, m.p. 155-156°C (decomposition).

Example 13

A mixture of 4.0 g of 4-(2,2-diphenylethenyl)-piperidinyl, 4.64 g of 3-(3-bromopropyl)-pyridine hydrobromide, 8.25 ml of 4N sodium hydroxide and 50 ml of DMF was stirred at 25°C for 3 hours. Volatile materials were removed and the residue was partitioned between ethyl acetate and 1N sodium hydroxide. The organic layers were dried and evaporated and the residue (5.8 g) was chromatographed on silica gel using 96:2:2 ethyl acetate-methanol--triethylamine. The fractions obtained were combined and evaporated, there being obtained 4.9 g (85%) of free base in the form of an oil. A solution of 4.9 g of the free base in methanol was treated as in Example 9 and there were obtained 4.3 g (66%) of 3-[3-[4-(2,2-diphenyl-ethenyl)-1-piperidinyl]-propyl]pyridine (1:1)-(E)-2--butenedioate, m.p. 154-156°C (decomposition).

Example 14

A mixture of 4.64 g of 4-(2,2-diphenylethenyl)-piperidine, 3.7 g of 3-(6-chlorohexyl)pyridine, 2.64 g of

sodium iodide and 50 ml of DMF was stirred at 50°C for 18 hours. The solvent was evaporated and the residue was partitioned between 1N sodium hydroxide and ethyl acetate. The resulting oil (7.4 g) was chromatographed on silica gel using 98:2 ethyl acetate-triethylamine. After evaporation of the fractions obtained there were obtained 3.9 g (52%) of free base in the form of an oil. A solution of 3.9 g of the free base in 25 ml of hot methanol was treated with 1.07 g of fumaric acid as in Example 9 and there were obtained 4.0 g (82%) of 3-[6-[4-(2,2-diphenylethenyl)-1-piperidinyl]hexyl]pyridine (1:1)-(E)-2-butenedioate, m.p. 170-172°C (decomposition).

Example 15

Analogously to Example 14, from 3.9 g of 4-(2,2-diphenylethenyl)piperidine and 3.1 g of 3-(7-chloroheptyl)pyridine there were obtained 4.0 g (62%) of free base in the form of an oil. After crystallization of the fumarate from ethanol/ethyl acetate there was obtained pure 3-[7-[4-(2,2-diphenylethenyl)-1-piperidinyl]heptyl]-pyridine (1:1)-(E)-2-butenedioate hemihydrate, m.p. 96-99°C (decomposition).

Example 16

Analogously to Example 14, from 8.64 g of 4-(2,2-diphenylethenyl)piperidine and 7.4 g of 3-(8-chlorooctyl)pyridine there were obtained 11.0 g (74%) of 3-[8-[4-(2,2-diphenylethenyl)-1-piperidinyl]octyl]pyridine, m.p. 54-55°C after recrystallization from hexane. The fumarate was crystallized from ethanol/acetone, m.p. 128-129°C.

Example 17

A mixture of 7.4 g of 3-(6-chlorohexyl)pyridine, 10.3 g of 4-[2,2-bis(4-fluorophenyl)ethyl]piperidine, 5.6 g of sodium iodide and 100 ml of DMF was stirred at 50°C for 18 hours and at 100°C for 1 hour. The solvent was evaporated and the residue was partitioned between ethyl acetate and 1N sodium hydroxide. The organic layers were dried and evaporated and the product (10.5 g) was chromatographed on silica gel using 50:50:2 hexane/ethyl acetate/triethylamine. The fractions obtained were combined and evaporated, there being obtained 8.5 g (53%) of free base in the form of an oil. A solution of 8.5 g of the free base in methanol was treated as in Example 9 and there were obtained 7.5 g (72%) of 3-[6-[4-[2,2-bis(4-fluorophenyl)ethyl]-1-piperidinyl]hexyl]pyridine (1:1)-(E)-2-butenedioate, m.p. 140-141°C.

Example 18

7.3 g of 3-[8-[4-(2,2-diphenylethenyl)-1-piperidinyl]-octyl]pyridine were hydrogenated under normal conditions using 100 ml of ethanol and 1.5 g of 10% Pd/C as the catalyst. After filtration and evaporation the residue was crystallized from hexane and there were obtained 6.0 g (82%) of 3-[8-[4-(2,2-diphenylethyl)-1-piperidinyl]octyl]-pyridine, m.p. 68-70°C. The fumarate was crystallized from acetone, m.p. 110-111°C.

Example 19

Analogously to Example 14, from 4.64 g of 4-(2,2--diphenylethenyl)piperidine and 3.0 g of 5-(4-chloro-butyl)pyrimidine (prepared from 5-pyrimidinebutanol) there were obtained 3.6 g (52%) of free base in the form of an oil. After crystallization of the fumarate from methanol/ethyl acetate there were obtained 3.0 g of 5-[4-[4-(2,2--diphenylethenyl)-1-piperidinyl]butyl]pyrimidine (1:1)--(E)-2-butenedioate, m.p. 181-182°C.

Example 20

Analogously to Example 14, from 7.4 g of 4-(2,2--diphenylethenyl)piperidine and 5.9 g of 5-(6-chloro-hexyl)pyrimidine there were obtained 5.9 g (50%) of 5-[6--[4-(2,2-diphenylethenyl)-1-piperidinyl]hexyl]pyrimidine, m.p. 88-90°C after crystallization from hexane.

Example 21

Analogously to Example 1, from 7.9 g of 4-(2,2--diphenylethenyl)piperidine and the acid chloride prepared from 8.24 g of 3-pyridinenonanoic acid there were obtained 12.4 g (73.7%) of 4-(2,2-diphenylethenyl)-1-[1-oxo-9-(3--pyridyl)nonyl]piperidine, m.p. 82-83°C after crystallization from ether.

Example 22

Analogously to Example 7, from 6.5 g of the product of Example 21 and 7.7 ml of a 3.5M solution of sodium bis(2-methoxyethoxy)aluminium hydride in toluene there was obtained 3-[9-[4-(2,2-diphenylethenyl)-1-piperidinyl]--nonyl]pyridine, m.p. 51-53°C after crystallization from hexane. After evaporation of the hexane filtrates there were obtained 5.9 g of a product which, after dissolution in 25 ml of hot methanol, was treated with 1.47 g of fumaric acid. The methanol was distilled off with the addition of acetone and the resulting solids were recrystallized from methanol/acetone. There were obtained 6.7 g (85%) of 3-[9-[4-(2,2-diphenylethenyl)-1--piperidinyl]nonyl]pyridine fumarate, m.p. 125-127°C.

Example 23

Analogously to Example 14, from 6.59 g of 4-(2,2--diphenylethenyl)piperidine and 6.4 g of 3-(10-chlorodecyl)pyridine there were obtained 10.4 g (86%) of 3-[10--[4-(2,2-diphenylethenyl)-1-piperidinyl]decyl]pyridine, m.p. 63-65°C after crystallization from hexane. The fumarate was crystallized from acetone, m.p. 134-136°C.

Example 24

Analogously to Example 1, from 3.4 g of 4-(2,2--diphenylethenyl)piperidine and the acid chloride prepared from 2.73 g of 6-(1H-imidazol-1-yl)hexanoic acid there were obtained 4.7 g (84%) of 4-(2,2-diphenylethenyl)-1-[1--oxo-6-(1H-imidazol-1-yl)hexyl]piperidine, m.p. 98-100°C after crystallization from ethyl acetate/hexane.

Example 25

In a manner analogous to Example 7, from 2.5 g of 4-(2,2-diphenylethenyl)-1-[2-oxo-6-(1H-imidazol-1-yl)-hexyl]-piperidine and 3.4 ml of a 3.5M solution of sodium bis(2-methoxyethoxy)aluminium hydride in toluene there were obtained 1.7 g (70%) of 1-[6-[4-(2,2-diphenyl-ethenyl)-1-piperidinyl]hexyl]-1H-imidazole, m.p. 104-106°C after crystallization from ether/hexane.

Example 26

A mixture of 1.65 g of 4-[2,2-bis(3-methoxyphenyl)--ethenyl]piperidine, 1.13 g of 3-(8-chlorooctyl)pyridine, 0.75 g of sodium iodide and 0.53 g of anhydrous sodium carbonate in 10 ml of DMF was stirred at 75°C for 16 hours under argon. The solvent was removed in a vacuum and the residue was taken up in a mixture of ethyl acetate and a 1N sodium hydroxide solution. The separated aqueous layers were again extracted with 3 portions of ethyl acetate. The organic layers were washed with water and sodium chloride solution, then combined, dried, decolorized with active charcoal and evaporated, there being obtained 2.5 g of an oil. This was purified by HPLC (hexane:ethyl acetate: triethylamine, 34:17:1) and there were obtained 1.8 g of 3-[8-[4-[2,2-bis(3-methoxyphenyl)-ethenyl]-1-piperidinyl]-octyl]pyridine in the form of an oil.

A solution of 1.7 g of the obtained base in ethanol was treated with 418 mg of oxalic acid dihydrate. Then, the mixture was heated under reflux in order to dissolve the solids, filtered and diluted with 30 ml of ether. The mixture was cooled and the resulting solid was filtered. There were obtained 2.0 g of 3-[8-[4-[2,2-bis(3-methoxy-phenyl)ethenyl]-1-piperidinyl]octyl]pyridine (1:1)-ethane-dioate, 0.25 molar hydrate, m.p. 112-115°C.

Example 27

Tablets and capsules of the following composition were manufactured in a manner known per se:

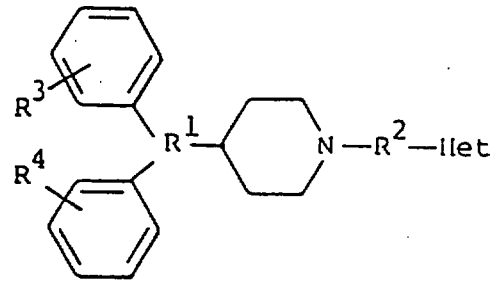
A. Ingredient:	mg/tablet:	
3-[8-[4-(2,2-Diphenylethenyl)--1-piperidinyl]octyl]pyridine	250	500
Lactose	100	200
Polyvinylpyrrolidone	10	20
Modified starch	10	20
Magnesium stearate	3	6

B. Ingredient:	mg/tablet:	
3-[8-[4-(2,2-Diphenylethenyl)--1-piperidinyl]octyl]pyridine	250	500
Lactose	75	150
Pregelatinized starch	15	30
Microcrystalline cellulose	75	150
Magnesium stearate	3	6

B. Ingredient:	mg/capsule:	
3-[8-[4-(2,2-Diphenylethenyl)--1-piperidinyl]octyl]pyridine	250	500
Pregelatinized maize starch	20	40
Modified starch	10	20
Talc	10	20
Magnesium stearate	1	2

Claims

1. N-Substituted diphenylpiperidines of the formula



I

wherein
R^1 is CH, C=CH or CH-CH_2
R^2 is C_{1-12}-alkylene or CO-$(CH_2)_n$, n is 0 to 11,

Example 27

Tablets and capsules of the following composition were manufactured in a manner known per se:

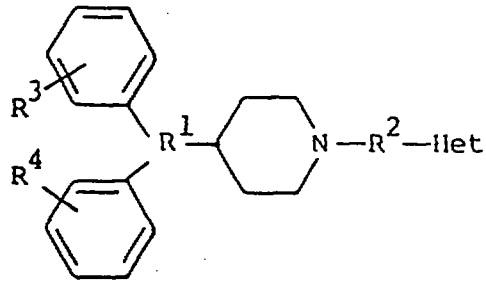
A. Ingredient:	mg/tablet:	
3-[8-[4-(2,2-Diphenylethenyl)--1-piperidinyl]octyl]pyridine	250	500
Lactose	100	200
Polyvinylpyrrolidone	10	20
Modified starch	10	20
Magnesium stearate	3	6

B. Ingredient:	mg/tablet:	
3-[8-[4-(2,2-Diphenylethenyl)--1-piperidinyl]octyl]pyridine	250	500
Lactose	75	150
Pregelatinized starch	15	30
Microcrystalline cellulose	75	150
Magnesium stearate	3	6

B. Ingredient:	mg/capsule:	
3-[8-[4-(2,2-Diphenylethenyl)--1-piperidinyl]octyl]pyridine	250	500
Pregelatinized maize starch	20	40
Modified starch	10	20
Talc	10	20
Magnesium stearate	1	2

Claims

1. N-Substituted diphenylpiperidines of the formula



I

wherein
R^1 is CH, C=CH or $CH-CH_2$
R^2 is C_{1-12}-alkylene or $CO-(CH_2)_n$, n is 0 to 11,

* C L M S *

R^3 and R^4 are hydrogen, halogen or C_{1-7}-alkoxy,
Het is pyridyl, pyrimidinyl or imidazolyl,
and salts thereof with pharmaceutically usable acids.

2. Compounds according to claim 1, wherein R^1 is C=CH.

3. Compounds according to claim 1 or 2, wherein R^2 is C_{1-12}, especially C_{4-10}-alkylene.

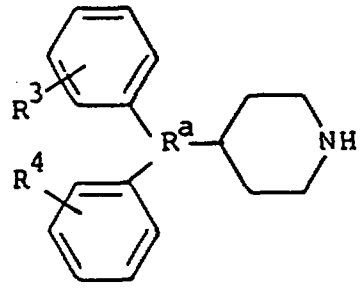
4. Compounds according to claim 1, 2 or 3, wherein R^3 and R^4 are hydrogen.

5. Compounds according to claim 1, 2, 3 or 4, wherein Het is pyridyl.

6. A compound from the following group:

3-[7-(4-(2,2-Diphenylethenyl)-1-piperidinyl]heptyl]-pyridine (1:1)-(E)-2-butenedioate hemihydrate,
3-[6-[4-(2,2-diphenylethenyl)-1-piperidinyl]hexyl]-pyridine (1:1)-(E)-2-butenedioate,
3-[5-[4-(2,2-diphenylethenyl)-1-piperidinyl]pentyl]-pyridine (1:1)-(E)-2-butenedioate and especially
3-[8-[4-(2,2-diphenylethenyl)-1-piperidinyl]-octyl]-pyridine and
3-[10-[4-(2,2-diphenylethenyl)-1-piperidinyl]decyl]-pyridine.

7. N-Unsubstituted diphenylpiperidines of the formula



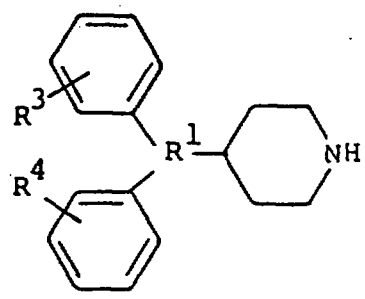
II-a

wherein R^a is C=CH or $CH=CH_2$ and R^3 and R^4 are as in claim 1.

8. A compound according to any one of claims 1-6 for use as a therapeutically active substance, especially for lowering the insulin level and for treating obesity.

9. A process for the manufacture of compounds according to any one of claims 1-6, characterized by reacting a compound of the formula

* C L M S *



II

with a halogenide of the formula Hal-R^2-Het, wherein R^1 to R^4 and Het are as in claim 1, if desired, reducing an obtained compound of formula I, wherein R^2 contains a carbonyl group, to the corresponding compound of formula I, wherein R^2 is C_{1-12}-alkylene, and, if desired, isolating an obtained free base of formula I in the form of a salt with a pharmaceutically usable acid.

10. A pharmaceutical preparation, especially for the treatment of obesity, based on a compound according to any one of claims 1-6.

11. The use of a compound according to any one of claims 1-6 in the manufacture of a preparation according to claim 10.

* C L M S *