2
COMMONWEALTH OF AUSTRALIA
Patents Act 1952-1969

CONVENTION APPLICATION FOR A PATENT

HOECHST AKTIENGESELLSCHAFT,
of 45 Bruningstrasse, D-6230 Frankfurt/Main 80,
Federal Republic of Germany

hereby apply for the grant of a Patent for an invention entitled: "N-BICYCLOHEPTYL- AND N-BICYCLOHEPTYL-IMIDAZOLES, A PROCESS FOR THEIR PREPARATION, THEIR USE AND PHARMACEUTICAL PRODUCTS"

which is described in the accompanying complete specification. This application is a Convention application and is based on the application numbered P34 10 498.4 for a patent or similar protective measure in the Federal Republic of Germany on 22nd March 1984

address for service is Messrs. Edwd. Waters & Sons, Patent Attorneys, Our
50 Queen Street, Melbourne, Victoria, Australia.

DATED this 20th day of March 1985.

HOECHST AKTIENGESELLSCHAFT
by James Murray

To: THE COMMISSIONER OF PATENTS

COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952-69

COMPLET E SPECIFICATION
COMMONWEALTH OF AUSTRALIA
Patents Act 1952
DECLARATION IN SUPPORT OF A CONVENTION APPLICATION UNDER PART XVI.
FOR A PATENT.

In support of the Convention application made under Part XVI. of the Patents Act 1952 by HOECHST AKTIENGESELLSCHAFT of 45, Brüningstrasse, D-6230 Frankfurt/Main 80, Federal Republic of Germany for a patent for an invention entitled:
"N-BICYCLOHEPTYL- AND N-BICYCLOHEPTENYL-IMIDAZOLES, A PROCESS FOR THEIR PREPARATION, THEIR USE AND PHARMACEUTICAL PRODUCTS"

We, Bernhard Beck, 4 Drosselweg, D-6246 Glashütten/Taunus,
Franz Lapice, 2 Sandweg, D-6233 Kelkheim (Taunus);
Federal Republic of Germany

do solemnly and sincerely declare as follows:

1. We are authorized by HOECHST AKTIENGESELLSCHAFT the applicant for the patent to make this declaration on its behalf.

2. The basic application as defined by Section 141 of the Act was made in the Federal Republic of Germany
under No. P 34 10 498.4 on March 22, 1984
by HOECHST AKTIENGESELLSCHAFT

3. a) Herbert Siegel, 10 Am Schieferberg, D-6233 Kelkheim (Taunus)
b) Ernold Granzer, 24 Falkensteiner Straße, D-6233 Kelkheim (Taunus)
a) and b) Federal Republic of Germany

We are the actual inventor(s) of the invention and the facts upon which HOECHST AKTIENGESELLSCHAFT
is entitled to make the application are as follows:

The said HOECHST AKTIENGESELLSCHAFT
is the assignee of the said Herbert Siegel and Ernold Granzer

4. The basic application referred to in paragraph 2 of this Declaration was the first application made in a Convention country in respect of the invention the subject of the application.

DECLARED at Frankfurt/Main, Federal Republic of Germany
this 26th day of February 1985

To the Commissioner of Patents
Useful in the treatment of hyperlipidemia

Claim

1. N-Bicycloheptyl- and N-bicycloheptenyl-imidazoles of the formula

\[
R_1^1-C-R_2^2
\]

in which \(R_1\) and \(R_2\) are identical or different and denote alkyl having 1 to 10 carbon atoms, cycloalkyl having 4 to 10 carbon atoms, phenyl which is optionally mono- or disubstituted by halogen, \((C_1-C_4)\)-alkyl, \((C_1-C_4)\)-alkoxy, trifluoromethyl, hydroxyl, amino, \((C_1-C_4)\)-alkylamino or \((C_1-C_4)\)-dialkylamino, the substituents in the case of disubstitution being identical or different, naphthyl or phenylalkyl having 1 to 4 alkyl carbon atoms, or \(R_1\) and \(R_2\) together represent a \((CH_2)_m\) bridge which is optionally substituted by phenyl, \(m\) denoting a number from 3 to 10,

\(A\) represents a single or double bond,

\[\ldots/2\]
(11) AU-A-40209/85

-2-

B denotes a single bond or, if \( n \) represents 0 or 1, also

\(-\text{CHOH}-\) group or, if \( n \) represents 1, the \(-\text{CHOH}-\) group, and

\( n \) represents 0, 1, 2, 3 or 4,

and their physiologically tolerated acid addition salts.

THF at room temperature and under atmospheric pressure, in
the presence of 0.5 g of Pd/c (5%), until one equivalent
of hydrogen has been absorbed. The catalyst is then fil-
tered off, the solution is evaporated, and the residue is
COMPLETE SPECIFICATION

Application Number: Lodged:

Priority:

Related Art:

Name of Applicant: HOECHST AKTIENGESELLSCHAFT

Address of Applicant: 45 Bruningstrasse, D-6230 Frankfurt/Main 80, Federal Republic of Germany

Actual Inventor: HERBERT SIEGEL and ERNOLD GRÄNZER

Address for Service: EDWD. WATERS & SONS, 50 QUEEN STREET, MELBOURNE, AUSTRALIA, 3000.

Complete Specification for the invention entitled:

N-BICYCLOHEPTYL- AND N-BICYCLOHEPTENYL-IMIDAZOLES, A PROCESS FOR THEIR PREPARATION, THEIR USE AND PHARMACEUTICAL PRODUCTS

The following statement is a full description of this invention, including the best method of performing it known to:
The invention relates to N-bicycloheptyl- and N-bicycloheptenyl-imidazoles, a process for their preparation, pharmaceutical products containing these compounds, and their use as medicaments, in particular for the treatment of hyperlipidemia.

It has already been described that imidazoles which are substituted on the nitrogen atom by a straight-chain or branched alkyl radical or by the benzyl radical have a hypolipidemic effect (see J. Med. Chem. 18, 833 (1975)). However, in order to achieve therapeutically satisfactory results, high doses of the compounds described in this publication are necessary. Imidazolmethyl-substituted bicycles having an antithromboembolic effect are described in German Offenlegungsschrift 2,944,663.

Where the bicycles mentioned in this publication are bicycloheptanes, they are unsubstituted in the 7-position.

It has been found, surprisingly, that N-bicycloheptyl- and N-bicycloheptenyl-imidazoles substituted in the 7-position have a much greater hypolipidemic effect than imidazole derivatives hitherto described.

Thus the invention relates to new N-bicycloheptyl- and N-bicycloheptenyl-imidazoles of the formula I

\[
\begin{align*}
\text{R}^1 \quad &\text{C} \quad \text{R}^2 \\
&\text{B-(CH}_2\text{)}_n \quad \text{N} \\
&\text{C} \\
\end{align*}
\]

in which \( \text{R}^1 \) and \( \text{R}^2 \) are identical or different and denote alkyl having 1 to 10 carbon atoms, cycloalkyl having 4 to 10 carbon atoms, phenyl which is optionally mono- or disubstituted by halogen, \((\text{C}_1-\text{C}_6)\)-alkyl, \((\text{C}_1-\text{C}_4)\)-alkoxy, trifluoromethyl, hydroxyl, amino, \((\text{C}_1-\text{C}_4)\)-alkylamino or \((\text{C}_1-\text{C}_4)\)-dialkylamino, the substituents in the
case of disubstitution being identical or different, naphthalyl or phenylalkyl having 1 to 4 alkyl carbon atoms, or R¹ and R² together represent a \((\text{CH}_2\)\)ₙ bridge which is optionally substituted by phenyl, \(\text{m}\) denoting a number from 3 to 10.

A represents a single or double bond, 
B denotes a single bond or, if \(n\) represents 0 or 1, also the \(-\text{C}-\) group or, if \(n\) represents 1, the \(-\text{CHOH}-\) group, and \(n\) represents 0, 1, 2, 3 or 4,

and to their physiologically tolerated acid addition salts.

Alkyl is to be understood to be both straight-chain and branched alkyl.

The wavy line in formula I and in the formulae which follow indicates that the substituents can be in either the endo- or exo-position on the bicycle.

Preferred compounds of the formula I are those in which R¹ and R² are identical or different and denote phenyl and-phenyl which is monosubstituted by halogen, in particular fluorine or chlorine. A preferably represents a single bond, \(n\) particularly denotes 0 or 1, and B a single bond or the \(-\text{CO}-\) group.

The process for the preparation of compounds of the formula I and their salts comprises

a) converting an alcohol of the formula II

\[
\begin{align*}
\text{R}^1 & - \text{C} - \text{R}^2 \\
\text{A} & \quad \text{(CH}_2\text{)}_n\text{OH} \\
\text{B} & \quad \text{(CH}_2\text{)}_n\text{Y}
\end{align*}
\]

in which A, R¹, R² and \(n\) have the meanings indicated for formula I, by methods known per se into a compound of the formula III

\[
\begin{align*}
\text{R}^1 & - \text{C} - \text{R}^2 \\
\text{A} & \quad \text{(CH}_2\text{)}_n\text{Y}
\end{align*}
\]

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temperature for 10 hours. Water is added, the mixture is extracted with methylene chloride, and the organic phase is washed once with water, dried and the solvent is removed in vacuo. 4.2 g of imidazole derivative are obtained as a pale yellow oil from the precipitated and
in which A, R₁, R₂ and n have the meanings indicated for formula I, and Y denotes a leaving group, such as, for example, hydrogen, in particular chlorine or bromine, or a sulfonic acid derivative, such as (C₁₋₄-alkyl-SO₂-O⁻ or Cl(⁻)SO₂-O⁻), and reacting the latter with imidazole or an imidazole salt of the formula IV

\[ Z - \begin{array}{c} \text{IV} \\ \text{N} \end{array} \]

in which Z denotes hydrogen or alkali metal, to give a compound of the formula I in which R₁, R₂, A and n have the meanings indicated, and B represents a single bond, and, where appropriate, hydrogenating the double bond in a resulting compound in which A represents a double bond, the hydrogenation being carried out either on an intermediate or on a compound of the formula I (A = double bond), or

b) reacting a halide of the formula V

\[ \begin{array}{c} \text{V} \\ R^1 - \text{C} - \text{R}^2 \end{array} \]

in which A, R₁ and R₂ have the meanings indicated for formula I, n represents 0 or 1, and halogen represents bromine or chlorine, with imidazole or an imidazole salt of the formula IV, to give a compound of the formula I in which A, R₁ and R₂ have the meanings indicated, B is the -O- group, and n is 0 or 1, and, where appropriate, reducing the latter to give a compound in which B denotes the CHOH group and, if desired, converting with an acid the compounds obtained by a) or b) into the physiologically tolerated acid addition salts.

In process a), the alcohols of the formula II are converted into the halogen compound III (Y = halogen), for example with an inorganic halide, such as, for example, POCl₃, PCl₃, PBr₃, P(C₆H₅)₃/CCL₄ or SOCl₂, or they

NMR: 7.0-7.4, m, 10H; 1.3-3.2, m, 8H.

c) 7-Diphenylmethylenebicyclo[2.2.1]heptan-2-one

17.5 g (55 mmol) of the bicycloheptane derivative from b) are dissolved in 170 ml of DMSO. 7.8 g (139.3 mmol) of KOH in 30 ml of DMSO are added in portions and the mixture is stirred for 1 hour.
are converted into the sulfonic esters with a sulfonyl halide. Suitable sulfonyl halides are the customarily used halides, such as mesyl chloride, tosyl chloride or p-chlorobenzensulfonyl chloride. The substitution of halide or sulfonic ester is advantageously carried out with imidazole in the presence of an acid-binding additive, such as an aliphatic or aromatic amine, or with the sodium salt of imidazole, in a polar solvent, such as DMF, DMSO, THF or alcohol, at temperatures between 0 and 100°C.

The alcohols of the formula II are either described in the literature or are prepared in analogy to described methods. For the preparation of alcohols of the formula II in which n is 1, the procedure is advantageously as follows:

Bicycloheptene derivatives are obtained from \( R^1, R^2 \)-substituted pentafulvenes and appropriately substituted olefins, such as, for example, acrylic acid, acrylic esters, acrylonitrile, \( X \)-chloroacrylonitrile, methyl vinyl ketone and other electron-poor olefins, without a solvent or in the presence of a solvent, at temperatures of, advantageously, 20–80°C, in accordance with the method indicated in Ann. 566, pages 1 et seq. and 27 et seq. (1950). The bicycloheptene derivative of the formula VI

\[
\begin{align*}
R^1 - \text{C} - R^2 \\
\text{VI}
\end{align*}
\]

in which \( R^1 \) and \( R^2 \) have the meanings indicated, and \( X \) denotes hydrogen or a \( (C_1-C_4) \)-alkyl group, is obtained by reaction with acrylic acid or an appropriate acrylic ester. The reaction is many times faster than indicated in Ann. 566, 1 et seq. The reaction time is usually between a few hours and some days.

The fulvenes used to synthesize the bicycle are obtained by methods known from the literature (see Adv. in Alicyclic Chem. 2, 59 (1968)).

The compounds of the formula VI are particularly...
suitable for procedure a). They are converted into the corresponding alcohol using a reducing agent, for example a complex hydride, such as LiAlH₄.

An alcohol of the formula II in which \( n \) is 1 and \( A \) represents a single bond is obtained by hydrogenation by methods known per se.

In the preparation of the alcohols of the formula II in which \( n \) represents 0 and \( A \) represents a single bond, the starting material used is, for example, a ketone of the formula VII

\[
\text{VII} \quad R^1 - C - R^2
\]

which is reduced, for example, with LiAlH₄ to give the desired alcohol.

Compounds of the formula VIII

\[
\text{VIII} \quad R^1 - C - R^2
\]

in which \( X \) denotes the cation of an alkali metal or \((C_1-C_4)-alkyl\) are obtained by reaction of the same ketone VII with organometallic reagents, such as \((\text{EtO})_2\text{POCHNaCOX}\), or with a Wittig reagent such as, for example, \((C_6H_5)_2\text{POCHNaCOX}\)

or with a Wittig reagent such as, for example, \((\text{EtO})_2\text{POCHNaCOX}\). The reduction to give the alcohol is carried out as described above, for example. In the subsequent hydrogenation, only the double bond in the side-chain is hydrogenated.

In principle, the hydrogenation of the endocyclic double bond \((A=\text{double bond})\) is possible at any stage of the synthetic sequence. However, it is preferably carried out at the stage of the cyclo adduct (compound of the formula VII) or on the imidazole derivative I itself. The procedure is known per se, the catalyst used being, for
example 5 % Pd on charcoal. In this way, compounds accor-
ding to the invention, with A = single bond, are obtained.

The preparation of compounds of the formula I
which contain a keto or hydroxyl group in the imidazole-
substituted side-chain (B = CO or CHO) is carried out by
process b). The halide of the formula V used as starting
material is obtained by methods known from the literature.
The methyl ketone which is described in Ann. 566, 27
(1950), which is preferably used, was converted under
kinetic control into the silyl enol ether (see JOC 34,
2324 (1969)) and the latter was then brominated (see

The imidazole derivative according to the inven-
tion is obtained by reacting the corresponding halide,
preferably in a polar organic solvent, such as DMF, DMSO,
THF or low molecular weight alcohols, at a temperature
between 0°C and 100°C, preferably room temperature, with
at least twice the amount of imidazole or the Na salt of
imidazole. The resulting keto imidazole derivative (B =
CO) can, where appropriate, be reduced to the correspon-
ding alcohol (B = CHOH). Complex hydrides such as, for
example LiAlH₄ or NaBH₄, in a suitable solvent
are most suitable for the reduction.

Acid addition salts can be prepared from the
imidazole derivatives of the general formula (I), which
usually result as an oil. All acids which form physio-
logically tolerated salts are suitable for this. These
include both inorganic acids such as, for example, hydro-
chloric acid, nitric acid and sulfuric acid and mono- and
bifunctional organic acids, in particular carboxylic acids,
such as acetic acid, succinic acid, tartaric acid etc.
The compounds according to the invention, of the
formula I, have valuable pharmacological properties, in
particular; they exhibit a very strong and favorable effect
on the serum lipoproteins. Thus the invention also relates
to pharmaceutical products based on these compounds, and
to their use as medicaments, in particular for affecting
the serum lipoproteins.

It is generally accepted that hyperlipoproteinemia

<table>
<thead>
<tr>
<th>No.</th>
<th>R¹</th>
<th>R²</th>
<th>A</th>
<th>B</th>
<th>Config.</th>
<th>n</th>
<th>phys. data</th>
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</thead>
</table>

- 21 -
is an essential risk factor for the development of arteriosclerotic vascular changes, in particular coronary heart disease. Thus, extreme importance attaches to the reduction in raised serum lipoproteins for the prophylaxis and reduction of arteriosclerotic changes. However, very particular classes of serum lipoproteins are important in this context, since the low density (LDL) and very low density lipoproteins (VLDL) represent a risk factor for atherogenesis, while the high density lipoproteins (HDL) exert a protective function with respect to arteriosclerotic vascular changes. Accordingly, hypolipidemic agents should lower VLDL-cholesterol and LDL-cholesterol in the serum but, at the same time, where possible leave the HDL-cholesterol concentration unaffected or even raise it, so that the antiatherogenic index HDL increases.

The compounds according to the invention have valuable therapeutic properties. Thus, they lower, in particular, the concentration of LDL and VLDL but they lower the HDL fraction only at excessive doses which have already reduced the LDL-cholesterol concentration by more than about 50%, so that the result in the therapeutically utilizable range is a great reduction in the LDL fraction without any effect on the HDL fraction. Thus, these compounds represent a considerable advance compared with the comparison compound clofibrate which, apart from LDL, always brings about a very great reduction in HDL, as is evident from the data described below. Thus they can be used for the prophylaxis and regression of arteriosclerotic changes since they eliminate a causal risk factor. This includes not only primary hyperlipidemia, but also certain types of secondary hyperlipidemia as occur with, for example, diabetes. The increase in the relative liver weight caused by the compounds at effective doses is zero or only slight, while clofibrate, which is used as a standard hypolipidemic agent, leads to a great increase in the relative liver weight.

The effect of the compounds listed was investigated on the serum lipoproteins in male Wistar rats which
were treated with the compounds listed, suspended in poly-
ethylene glycol 400, by gavage for 7 days. In addition,
a control group received only the solvent polyethylene
glycol 400, and, in most experiments, there was a group of
5 rats which received the standard hypolipidemic agent
clofibrate. As a rule, 10 animals were used in each group,
their blood being sampled from the orbital plexus after
shallow ether anesthesia at the end of the treatment. The
serum lipoproteins from the rat serum obtained were frac-
tionated into the following density classes in a prepara-
tive ultracentrifuge:

- VLDL < 1.006
- LDL 1.006 to 1.04
- HDL 1.04 to 1.21

Since, in contrast to humans, the serum lipo-
proteins of the rat contain about 4/5 HDL-cholesterol and
only 1/5 LDL-cholesterol, and only very small amounts of
VLDL (conversely, about 4/5 LDL and VLDL and only 1/5 HDL
in humans), fractionation of the rat serum into lipoprotein
classes is absolutely necessary for assessment of a hypo-
lipidemic effect in the rat. This is because simply re-
ducing the serum total cholesterol content in the rat
would merely indicate the undesired reduction in the anti-
atherogenic HDL class which predominates in the rat. A
desired reduction of LDL with, at the same time, a des-
ired increase in HDL would, however, have no (substantial)
effect on the total cholesterol content of rat serum.

The cholesterol contained in the lipoprotein frac-
tions isolated in the ultracentrifuge was determined com-
pletely enzymatically by the CHOD-PAP method using the
Boehringer-Mannheim assay combination, and the figures
have been converted into µg/ml serum. Table I below shows
the percentage change in the lipoprotein cholesterol in
the treated group compared with a control group kept under
the same conditions. As is evident from Table I, clofi-
brate brings about a greater reduction in the HDL than in
the LDL fraction, while the new compounds exert a strong
and selectively reducing effect on the atherogenic lipo-
protein fractions (VLDL and LDL), and leave the protective
HDL fraction essentially unaffected.

were added dropwise. After one hour, 27.5 g (0.1 mol)
of ketone obtained according to Example 5c), in dimethoxy-
ethane, were added dropwise, and the mixture was then
stirred at 50°C for 7 hours and worked up with metho-

Percentage changes in the lipoproteins in rat serum after oral administration of the compounds for 7 days

<table>
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<tr>
<th>Example No.</th>
<th>Dose (mg/kg/day)</th>
<th>% change in cholesterol, relative to the control groups</th>
<th>% change in the serum lipoprotein fractions</th>
<th>% change in the relative liver weight</th>
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Formula:

\[ H_5C_6-C-C_6H_5 \]
Particularly suitable therapeutic preparations of the compounds of the formula I are tablets, coated tablets, capsules, suppositories and syrups. In these, the new compounds can be used either alone or mixed with pharmaco-logically acceptable vehicles. An oral administration form is preferred. For this purpose, the active compounds are preferably mixed with auxiliaries known per se, and converted, by methods known per se, into suitable administration forms, such as tablets, hard gelatine capsules, aqueous or oily suspensions or aqueous or oily solutions. Examples of inert vehicles which can be used are magnesium carbonate, lactose or corn starch, with the addition of other substances such as, for example, magnesium stearate. This can entail the preparation being carried out as dry or as moist granules. Particularly suitable oily vehicles or solvents are vegetable and animal oils such as, for example, sunflower oil or fish liver oil. A suitable daily dose is about 20 mg to 1 g, preferably 50 to 100 mg. A dosage unit preferably contains 10 to 25 mg.

For the treatment of disturbances of lipid metabolism, apart from the customary fillers and vehicles, the formulations can also contain an antihypertensive agent such as, for example, a saluretic, reserpine, hydralazine, guanethidine, α-methyldopa, clonidine or a β-sympathico-lytic agent, a compound having antithrombotic activity, such as, for example, acetylsalicylic acid, sulfipyrazone, ticlopidine and heparinoids, or an agent having antihyperuricemic activity, an oral antidiabetic, a geriatric agent or an agent effecting an increase in blood flow.

The examples which follow illustrate the preparation of the compounds:

Unless otherwise specified, the NMR spectra were recorded in DCCl₃. The chemical shifts are expressed in δ values.

Example 1

exo,endo-2-(1-Imidazolomethyl)-7-isopentylidenebicyclo[2.2.1]heptane

a) Methyl exo,endo-7-isopentylidenebicyclo[2.2.1]-hept-5-eno-2-carboxylate
23.3 g (0.175 mol) of 6,6-diethylfulvene are mixed with 2.4 g (0.280 mol) of methyl acrylate, a spatula tip of hydroquinone is added, and the mixture is heated at 60°C for 30 h. After removal of the excess acrylate in vacuo, 30.7 g of methyl exo,endo-7-isopentylidenebicyclo[2.2.1]hept-5-ene-2-carboxylate are obtained as an oil. NMR: 6.0–6.5, 2H; 3.6 and 3.7 s, exo and endo CO₂CH₃; 1.2–3.5 m, 9H; 0.9, t, 2 CH₃

b) Methyl exo,endo-7-isopentylidenebicyclo[2.2.1]-10 heptane-2-carboxylate

30.6 g (0.138 mol) of ester from a) are dissolved in 100 ml of THF. After addition of 2 g of Pd/C, hydrogenation is carried out at room temperature and under atmospheric pressure until one equivalent of hydrogen has been absorbed. After filtering off the catalyst with suction, the filtrate is distilled at 0.2 mm Hg. 20.1 g of methyl exo,endo-7-isopentylidenebicyclo[2.2.1]heptane-2-carboxylate of boiling point 76°C are obtained. NMR: 3.6 and 3.7, s, exo and endo CO₂CH₃; 0.7–3.0, m,

20 19H.

c) exo,endo-2-Hydroxymethyl-7-isopentylidenebicyclo[2.2.1]heptane

1.9 g (50 mmol) of LiAlH₄ in 100 ml of absolute ether are initially introduced. Then, under gentle reflux, 20.0 g (90 mmol) of ester from b) in 50 ml of absolute ether are added dropwise, and the mixture is then stirred under reflux for one hour. It is hydrolyzed with dilute hydrochloric acid, and the ether phase is separated off, washed with water and dried over sodium sulfate. After removal of the ether in vacuo, 15.7 g of the alcohol remain as an oil. NMR: 3.6 and 3.2 d, exo and endo CH₂; 1.2–2.8, m, 13H; 0.9, t, 2 CH₃.

d) exo,endo-7-Isopentylidenebicyclo[2.2.1]heptane-

35 2-methyl (p-chlorophenyl)sulfonate

9.0 g (90 mmol) of triethylamine are added dropwise to 15.6 g (81 mmol) of alcohol from c) and 18.8 g (89 mmol) of p-chlorobenzenesulfonyl chloride in 100 ml of methylene chloride at room temperature. After 16 hours,
water is added, and the organic phase is separated off, washed once with water and dried. After evaporation in a rotary evaporator, 26.6 g of exo,endo-7-isopentylidene-bicyclo[2.2.1]heptane-2-methyl (p-chlorophenyl)sulfonate remain.

NMR: 7.4-8.1, m, 4H; 4.0, q and 3.6, d, exo and endo.

CH\(_2\)-OSO\(_2\)-C\(_6\)H\(_5\); 3.4, m, 19H

Example e) exo,endo-2-(1-imidazolomethyl)-7-isopentylidene-bicyclo[2.2.1]heptane

6.4 g (72 mmol) of sodium imidazolide in 80 ml of DMF are initially introduced, and 25.2 g (71 mmol) of sulfonic ester from d) in 50 ml of DMF are added dropwise at room temperature. The reaction mixture is stirred at 60°C for 16 h, then cooled and water is added. The mixture is extracted three times with 150 ml of methylene chloride each time, and the organic phase is dried and evaporated. After purification of the residue by column chromatography on silica gel using cyclohexane/ethyl acetate (2:1), 6 g of the title compound are obtained as a pale yellow, solidifying oil.

Formula:

\[
\begin{align*}
\text{H}_5\text{O}_2\text{-C-}2\text{H}_5 \\
\begin{tikzpicture}
\node[draw] (a) at (0,0) {H};
\node[draw] (b) at (1,0) {C};
\node[draw] (c) at (1,1) {C};
\node[draw] (d) at (2,0) {CH\(_2\)};
\node[draw] (e) at (2,1) {N};
\node[draw] (f) at (2,2) {N};
\draw (a) -- (b) -- (c) -- (d) -- (e) -- (f);
\end{tikzpicture}
\end{align*}
\]

NMR: 7.4, s, 1H; 6.9, d, 2H; 3.9, d and 3.6, q, exo and endo CH\(_2\)-imidazole; 0.5-2.7 m, 19 H.

Example 2

endo-2-(1-imidazolomethyl)-7-cyclohexylidenebicyclo[2.2.1]heptane

4 g (15.8 mmol) of endo-2-(1-imidazolomethyl)-7-cyclohexylidenebicyclo[2.2.1]hept-5-ene (prepared in analogy to Example 1a), c), d), e) from 6,6-pentamethylenefulvene, methyl acrylate and sodium imidazolide; melting point 48°C, see Example 10) are hydrogenated in 50 ml of
THF at room temperature and under atmospheric pressure, in
the presence of 0.5 g of Pd/c (5%), until one equivalent
of hydrogen has been absorbed. The catalyst is then fil-
tered off, the solution is evaporated, and the residue is
recrystallized from isopropyl ether. 3.3 g of imidazole
derivative of melting point 95°C are obtained.

Formula:

\[
\text{(CH}_2\text{)}_5\text{NMe}_2
\]

NMR: 7.5, s, 1H; 6.9, d, 2H; 3.9, d and 3.6, q, exo and
endo CH \text{2-imidazole}; 0.5-2.7, m, 19H.

**Example 3**

exo-2-(1-Imidazolomethyl)-7-diphenylmethylenebicyclo[2.2.1]-
heptane

a) exo and endo 7-Diphenylmethylenebicyclo[2.2.1]-
hept-5-ene-2-carboxylic acid

50 g (0.218 mol) of 6,6-diphenylfulvene and 31.3 g
(0.435 mol) of acrylic acid are intimately mixed and
allowed to stand at room temperature for 14 days until
decolorized. By fractional recrystallization of the solid
white crude product with ethanol, first 35.3 g of the endo
acid of melting point 190°C are obtained. Evaporation
of the mother liquor and recrystallization of the residue
from cyclohexane provides 8.4 g of the exo acid of melting
point 146°C.

**NMR (endo acid):**

7.4-7.0, m, 10H; 6.48, q, 1H;
6.28, q, 1H;
3.7-3.9, m, 1H; 3.35-3.55, m, 1H;
3.2, dt, 1H, 2.22 o, 1H; 1.64, q, 1H.

**NMR (exo acid):**

7.0-7.4, m, 10H; 6.42 t, 2H;
3.54-3.64, m, 1H; 3.40-3.52, m, 1H;
2.20-2.55, m, 2H; 1.60, q, 1H.
b) Methyl exo-7-diphenylmethylenecyclo[2.2.1]hept-5-ene-2-carboxylate

7.4 g (24.3 mmol) of the exo acid from a) are dissolved in 50 ml of absolute methanol, and 0.5 g of concentrated sulfuric acid is added. The mixture is stirred at 40°C for 2 hours, allowed to stand at room temperature overnight, then water is added and the mixture is extracted with methylene chloride. After drying and evaporation of the organic phase, 7.8 g of methyl ester remain as a yellowish oil.

NMR: 6.9-7.4, m, 10 H; 6.2-6.4, m, 2H; 3.2-3.8, m, 2H; 3.4, s, 3H of CO₂CH₃; 2.1-2.6, m, 2H; 1.2-1.8, m, 1H.

c) Methyl exo-7-diphenylmethylenecyclo[2.2.1]heptane-2-carboxylate

7.4 g (23.3 mmol) of ester from b) are dissolved in 100 ml of THF, and hydrogenation is carried out at room temperature and under atmospheric pressure, in the presence of 5% Pd on charcoal, until one equivalent of hydrogen has been absorbed. The catalyst is filtered off, and the solution is evaporated. 8.2 g of methyl exo-7-diphenylmethylenecyclo[2.2.1]heptane-2-carboxylate remain as an oily residue.

NMR: 7.0-7.5, m, 10H; 3.4, s, 3H of CO₂CH₃; 1.0-2.8, m, 9H.

d) exo-2-Hydroxymethyl-7-diphenylmethylenecyclo[2.2.1]heptane

7.9 g (24.8 mmol) of ester from c) in 50 ml of dry ether are added dropwise to 1.0 g (27.1 mmol) of lithium aluminum hydride in 35 ml of dry ether. The mixture is stirred under reflux for 2 hours, then dilute hydrochloric acid is added, and the organic phase is separated off, washed once with water, dried and the solvent is removed under waterpump vacuum. 7.1 g of the alcohol are obtained as an oil.

NMR: 6.7-7.4, m, 10H; 3.3, q, 2H, CH₂OH; 0.9-2.5, m, 9H.

e) exo-7-Diphenylmethylenecyclo[2.2.1]heptane-2-methyl (p-chlorophenyl)sulfonate

7.0 g (24.1 mmol) of alcohol from d) and 5.7 g (26.6 mmol) of p-chlorobenzenesulfonyl chloride in 50 ml
of methylene chloride are initially introduced. 2.7 g (26.6 mmol) of triethylamine are added dropwise to this
at room temperature. After standing overnight, water is
added, and the organic phase is separated off, washed once
with water, dried and evaporated. 11.8 g of sulfonic
ester remain as an oil.
NMR: 6.9-7.9, m, 14H; 3.8, q, 2H; CH2-OSO2-Cl;
0.9-2.5, m, 9H.

f) exo-2-(1-Imidazolomethyl)-7-diphenylmethylene-
bicyclo[2.2.1]heptane
10.9 g (23.5 mmol) of sulfonic ester from e) in
25 ml of DMF are added to 2.3 g (25.8 mmol) of sodium
imidazolide in 50 ml of DMF. The mixture is stirred at
50°C for 5 hours, allowed to stand overnight, then water
is added and the mixture is extracted three times with
150 ml of methylene chloride each time. The methylene
chloride phase is washed once with water, dried and evapo-
rated. The residue (7.2 g) is induced to crystallize
with cyclohexane/ethyl acetate. 3.0 g of imidazole deriv-
ative of melting point 170°C are obtained.

Example 4
endo-2-(O( Ketto-β-imidazoloethyl)-7-diphenylmethylene-
bicyclo[2.2.1]heptane
13.3 g (35 mmol) of endo-2-(bromoacetyl)-7-di-
phenylmethylenebicyclo[2.2.1]heptane (prepared in analogy
to Ann. 566, 27 and Synthesis 1976, 194; the resulting
crude product is used for the subsequent reaction) in 30 ml
of DMF are added dropwise to 6.0 g (88 mmol) of imidazole
in 150 ml of DMF, and the mixture is stirred at room
temperature for 10 hours. Water is added, the mixture is extracted with methylene chloride, and the organic phase is washed once with water, dried and the solvent is removed in vacuo. 4.2 g of imidazole derivative are obtained as a pale yellow oil from the residue by column chromatography on silica gel.

Formula:

\[
\text{H}_5\text{C}_6\text{-C...C}_6\text{H} \quad \text{H} \quad \text{C-CH}_2\text{N} \quad \text{N}
\]

NMR: 6.0-7.4, m, 1H; 6.6, d, 2H, 4.5, s, 2H; 1.0-3.0, m, 9H.

Example 5

exo,endo-2-(1-imidazoyl)-7-diphenylmethylenebicyclo[2.2.1]heptane

a) exo,endo-2-chloro-2-cyano-7-diphenylmethylenebicyclo[2.2.1]hept-5-ene

46 g (0.2 mol) of 6,6-diphenylfulvene and 17.6 g (0.2 mol) of \( \alpha \)-chloroacrylonitrile are dissolved in 120 ml of toluene, and the solution is stirred at 80°C for 20 hours. The solvent is removed under waterpump vacuum, and the residue is recrystallized from isopropanol. 37.2 g of exo,endo-2-chloro-2-cyano-7-diphenylmethylenebicyclo[2.2.1]hept-5-ene are obtained as colorless crystals of melting point 135°C.

NMR: 7.0-7.4, m, 10H; 6.3-6.8, m, 2H; 3.8-4.0, m, 1H; 3.4-3.7, m, 1H; 2.9, q, 1H; 1.8, d, 1H.

b) exo,endo-2-chloro-2-cyano-7-diphenylmethylenebicyclo[2.2.1]heptane

17.5 g (55 mmol) of the bicycloheptene derivative from a) are hydrogenated in the presence of 1 g of Pd/C, at room temperature and under atmospheric pressure, until 1235 ml of hydrogen have been absorbed. After filtering off the catalyst and removal of the solvent, 17.6 g of bicycloheptane derivative remain as a solid of melting point 84-87°C.
R0
C L 3 ,P CIL 3
PB
r 3  P
(C 6 H 5 3 /CCI 4
or
SodL 2
or
they

NMR: 7.0-7.4, m, 10H; 1.3-3.2, m, 8H.

7-Diphenyl(methylenebicyclo[2.2.1]heptan-2-one

17.5 g (55 mmol) of the bicycloheptane derivative from b) are dissolved in 170 ml of DMSO. 7.8 g (139.3 mmol) of KOH in 30 ml of water are added to this. The mixture is then stirred at room temperature for 3 hours. After addition of 800 ml of water, the mixture is extracted with methylene chloride, and the organic phase is dried and evaporated. The residue is recrystallized from isopropyl ether. 13.7 g of ketone of melting point 88°C are obtained.

NMR: 7.0-7.4, m, 10H; 3.1-3.4, in, 2H; 1.5-2.5, m, 6H.

d) exo,endo-7-Diphenylmethylenecyclo[2.2.1]heptan-2-ol

12.0 g (44 mmol) of the ketone from c) are dissolved in a mixture of 50 ml of ethanol and 30 ml of tetrahydrofuran, and reduced with 1.2 g (33 mmol) of NaBH₄ at room temperature for 5 hours. After addition of water, the mixture is extracted with methylene chloride. The organic phase is dried and evaporated. 11.8 g of the alcohol are obtained as an oil.

NMR: 7.0-7.4, m, 10H; 3.5-4.5, in, exo- and endo-2-H; 1.0-2.8, m, 8H.

e) exo,endo-7-Diphenylmethylenecyclo[2.2.1]heptan-2-ol methanesulfonate

4.8 g (48.0 mmol) of triethylamine are slowly added to 11.5 g (42.8 mmol) of the alcohol from d) and 5.4 g (47.0 mmol) of methanesulfonyl chloride in 100 ml of methylene chloride, and the mixture is stirred at room temperature for 16 h. After addition of 500 ml of water, the organic phase is separated off, dried and evaporated. 14.7 g of sulfonic ester are obtained as an oil.

NMR: 7.0-7.4, m, 10H; 4.8-5.2, m, exo- and endo-2-H; 2.9, s, CH₃; 1.0-3.1, m, 8H.

f) exo,endo-2-(1-Imidazolyl)-7-diphenylmethylenecyclo[2.2.1]heptane

A solution of Na imidazole in 50 ml of DMF is prepared from 3.1 g (45.7 mmol) of imidazole and 1.4 g (45.7 mmol) of 80% sodium hydride. 14.7 g (41.5 mmol)
The compounds of the formula VI are particularly

-19-
of the sulfonic ester from e) in 50 ml of DMF is added
dropwise to this solution, and the mixture is stirred at
100°C for 7 days. After addition of water, the mixture
is extracted with methylene chloride. The organic phase
5 is dried and evaporated. The oily residue (12.7 g) is
chromatographed on silica gel (mobile phase: cyclohexane
ethyl acetate, 3:1). 1.2 g of the desired imidazole deri-

vative is eluted as an oil from which, with hydrogen
chloride in ether, 1.0 g of the corresponding salt, of

10 melting point 160°C, is obtained.

Formula:

\[
\text{H}_5 \text{C}_6 - \text{C} - \text{C}_6 \text{H}_5
\]

NMR: 8.8-9.0, s, 1H; 6.5-7.5, m, 13H; 5.4-5.7, m, 1H;
1.0-2.8, m, 8H.

The following compounds of the formula I are pre-
pared in an analogous manner (Examples 6 to 23).
The procedure is known per se, the catalyst used being, for

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It is generally accepted that hyperlipoproteinemia

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For compounds 16, 17, 19 and 20, it is also possible for $R_2$ to be unsubstituted and $R_1$ to be phenyl-substituted by chlorine or fluorine.

* was obtained by reduction of the compound from Example 4 with NaBH₄, in a manner known per se.

Example 24
exo-2-Carbonylimidazolyl-7-diphenylmethylenebicyclo[2.2.1]-heptane

a) exo-7-Diphenylmethylenebicyclo[2.2.1]heptane-2-carboxylic acid

8 g (26.5 mmol) of exo-7-diphenylmethylenebicyclo[2.2.1]hept-5-ene-2-carboxylic acid were dissolved in 80 ml of tetrahydrofuran and hydrogenated under atmospheric...
pressure and at room temperature, in the presence of 1 g of Pd/C, until one equivalent of hydrogen had been absorbed. After filtering off the catalyst and evaporation of the solution, 8.1 g of the hydrogenated acid remained as an oil.

NMR: 11.2, 1H; 6.9-7.4, m, 10 H; 3.5-3.8, m, 2H; 1.0-3.2, m, 7 H.

b) exo-2-Carbonylimidazolyl-7-diphenylmethylenecyclo-

[2.2.1]heptane

8.1 g (26.5 mmol) of the acid from a) in 60 ml of tetrahydrofuran were initially introduced. 2 drops of pyridine were added, and 5.5 g (46 mmol) of thionyl chloride were added dropwise. The mixture was heated to reflux for two hours, the solvent was removed in vacuo, and 9.4 g of crude acid chloride were obtained. This was dissolved again in 50 ml of tetrahydrofuran and, at 0-5°C, 6.9 g (102 mmol) of imidazole in tetrahydrofuran were added dropwise, and the mixture was stirred at room temperature for 24 hours and worked up with water and methylene chloride. 8.8 g of oil were obtained and distilled in a Kugelrohr (250°C, 0.3 mbar). 4.5 g of pure imidazole derivative were thus obtained.

Example 25:

\[ \text{Ethyl E,2-7-diphenylmethylenecyclo[2.2.1]heptane-2-methylenecarboxylate} \]

3.0 g (0.1 mol) of 80% sodium hydride in 250 ml of dimethoxyethane were initially introduced, and 22.5 g (0.1 mol) of triethyl phosphonoacetate in dimethoxyethane were added dropwise of ketone obtained from ethane, were added and stirred at 50°C 5 methylene chloro-oil.

NMR: 7.0-7.4, m, 3.3, 1H; 1.0

10 (ethyliden-2-ol): 23 g (0.1 mol) sodium hydride in 100 ml of diisopropyl ether were added dropwise of hydride in 100 ml 70°C for 8 hours.

15 acid/methylene chloride

21.6 g of crude alcohol were isogel, cyclohexane NMR: 7.0-7.4, m, 20 m, 1H; 2.9, m, 1 c) exo,endo-2-(ethyl-2-ol)

6.8 g (25 ml of 1 g of Pd/C, pressure, until absorbed. After the solvent, 6.7 g of alk was added.

30 m, 12H.

The alcohol of the imidazole derivative 0.8 g of a color
were added dropwise. After one hour, 27.5 g (0.1 mol) of ketone obtained according to Example 5c), in dimethoxyethane, were added dropwise, and the mixture was then stirred at 50°C for 3 hours and worked up with water/methylene chloride. 35 g of product were obtained as an oil.

NMR: 7.0-7.4, m, 10 H; 5.6 and 5.8, m, 1H; 3.3, m, 1H; 1.0-3.0, m, 7H; 1.3, t, 3H.

b) E,Z-7-Diphenylmethylenebicyclo[2.2.1]heptane-2-10 (ethyliden-2-ol)

23 g (0.067 mol) of ester from a), in THF were added dropwise to 3.8 g (0.1 mol) of lithium aluminum hydride in 100 ml of THF, and the mixture was stirred at 70°C for 8 hours and worked up with dilute hydrochloric acid/methylene chloride. After removal of the solvent, 21.6 g of crude product remained, from which 12.5 g of alcohol were isolated by column chromatography (silica gel, cyclohexane/ethyl acetate = 5:1).

NMR: 7.0-7.4, m, 10H; 5.4-5.6, m, 1H; 4.1, d, 2H; 3.2, 20 m, 1H; 2.9, m, 1H; 1.1-2.6, m, 6H.

c) exo,endo-7-Diphenylmethylenebicyclo[2.2.1]heptane-2-(ethyl-2-ol)

6.8 g (22.5 mmol) of alcohol from b) were dissolved in 100 ml of THF and hydrogenated in the presence of 1 g of Pd/C, at room temperature and under atmospheric pressure, until one equivalent of hydrogen had been absorbed. After filtering off the catalyst and removal of the solvent, 6.7 g of oil remained.

NMR: 6.9-7.4, m, 10H; 3.3-3.8, m, 1H; 0.5-3.1, 30 m, 12H.

The alcohol from 25.c) was reacted further to give the imidazole derivative in analogy to Example 3 e,f.

0.8 g of a colorless oil was obtained.
NMR: 6.6-7.5, m, 13H; 3.6-4.0, m, 2H; 0.6-2.8, m, 11H.
CLAIMS

1. N-Benzylhept-5-ene-2-carboxylic acid (89 mmol) of p-chloro methylene dichloride.

THE CLAIMS DEFINED

1. Compounds of the formula I

\[
R_1 - \text{alkyl}
\]

in which \( R_1 \) and \( R_2 \) denote an alkyl having 4 to 10 carbon atoms, disubstituted by haloxy, trifluoromethyl, or \((\text{C}_1-\text{C}_4)\)-alkyl, \( n \) represents 0, 1, or 2, and \( n \) represents 0, 1, 2.

2. A process claimed in claim 1, comprising the conversion of an acid chloride into its thio ester derivative.
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. N-Bicycloheptyl- and N-bicycloheptenyl-imidazoles of the formula I

![Chemical Structure](image)

in which $R^1$ and $R^2$ are identical or different and denote alkyl having 1 to 10 carbon atoms, cycloalkyl having 4 to 10 carbon atoms, phenyl which is optionally mono- or disubstituted by halogen, ($C_1$-$C_4$)-alkyl, ($C_1$-$C_4$)-alkoxy, trifluoromethyl, hydroxyl, amino, ($C_1$-$C_4$)-alkylamino or ($C_1$-$C_4$)-dialkylamino, the substituents in the case of disubstitution being identical or different, naphthyl or phenylalkyl having 1 to 4 alkyl carbon atoms, or $R^1$ and $R^2$ together represent a $(CH_2)_m$ bridge which is optionally substituted by phenyl, $m$ denoting a number from 3 to 10,

$A$ represents a single or double bond,

$B$ denotes a single bond or, if $n$ represents 0 or 1, also $C-$ group or, if $n$ represents 1, the $-CHOH-$ group, and

$n$ represents 0, 1, 2, 3 or 4,

and their physiologically tolerated acid addition salts.

2. Compounds as claimed in claim 1, wherein $R^1$ and $R^2$ in formula I are identical or different and denote phenyl, 4-chlorophenyl or 4-fluorophenyl, $A$ denotes a single bond, $n$ represents 0 or 1, and $B$ denotes a single bond or the CO group.

3. A process for the preparation of compounds as claimed in claim 1, which comprises

a) converting an alcohol of the formula II
in which A, R¹, R² and n have the meanings indicated for formula I, by methods known per se into a compound of the formula III

in which A, R¹, R² and n have the meanings indicated for formula I, and Y denotes a leaving group, and reacting the latter with imidazole or an imidazole salt of the formula IV

in which Z denotes hydrogen or alkali metal, to give a compound of the formula I in which R¹, R², A and n have the meanings indicated, and B represents a single bond, and, where appropriate, hydrogenating the double bond in a resulting compound in which A represents a double bond, the hydrogenation being carried out either on an intermediate or on a compound of the formula I (A = double bond), or b) reacting a halide of the formula V
in which \( A, R_1 \) and \( R_2 \) have the meanings indicated for formula I, \( n \) represents 0 or 1, and halogen represents bromine or chlorine, with imidazole or an imidazole salt of the formula IV, to give a compound of the formula I in which \( A, R_1 \) and \( R_2 \) have the meanings indicated for formula I, \( B \) is the \(-C-\) group, and \( n \) is 0 or 1, and, where appropriate, reducing the latter to give a compound in which \( B \) denotes the \( \text{CHOH} \) group and, if desired, converting with an acid the compounds obtained by a) or b) into the physiologically tolerated acid addition salts.

4. A pharmaceutical product containing a compound as claimed in claim 1.

5. A process for the preparation of a pharmaceutical product containing a compound as claimed in claim 1, which comprises converting it into a suitable administration form by addition of auxiliaries.

6. The use of compounds as claimed in claim 1 for the treatment of disturbances of the serum lipoprotein spectrum.

7. A process for the treatment of disturbances of the serum lipoprotein spectrum, which comprises administration of an effective amount of a compound as claimed in claim 1.

DATED this 20th day of March 1985.

Hoechst Aktiengesellschaft

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END