11627/88

APPLICATION ACCEPTED AND AMENDMENTS

ACCEPTED 11-4-90

598634

FORM 1

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

APPLICATION FOR A STANDARD PATENT

Heinrich Mack Nachf., of D-7918 Illertissen, FEDERAL REPUBLIC OF GERMANY, hereby apply for the grant of a standard patent for an invention entitled:

Oxime-ethers of 2,6-dioxobicyclo-[3.3.0]octanones for Treatment of Heart and Circulation Diseases

which is described in the accompanying complete specification.

Details of basic application(s):-

Basic Applic. No:	Country:	Application Date:
P 3704604.7	FEDERAL REPUBLIC OF GERMANY	13 February 1987

The address for service is:-

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Patent Attorneys
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DATED this TENTH day of FEBRUARY 1988

Heinrich Mack Nachf.

By: M.J. Anderson

Registered Patent Attorney

TO: THE COMMISSIONER OF PATENTS
OUR REF: 49536
S&F CODE: 60030

5845/1

LODGED AT SUB-OFFICE
11 FEB 1988
Sydney

FEE STAMP TO VALUE OF $ 260 ATTACHED
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PATENT OFFICE 100 LODGED AT PATENT OFFICE ONE HUNDRED DOLLARS 11 FEB 1988 Sydney

PATENT OFFICE 60 LODGED AT PATENT OFFICE SIXTY DOLLARS 11 FEB 1988 Sydney AUSTRALIA

~~PC 7159~~

SPRUSON & FERGUSON

COMMONWEALTH OF AUSTRALIA
PATENTS ACT 1952

DECLARATION IN SUPPORT OF A CONVENTION APPLICATION FOR A PATENT

In support of the Convention Application made for a patent for an invention entitled:

Oxime-ethers of 2,6-dioxobicyclo-[3.3.0]octanones for Treatment of Heart and Circulation Diseases

I/~~We~~, Allen J. Spiegel on behalf of Heinrich Mack Nachf.
[full name of declarant(s)]

of D-7918 Illertissen, Federal Republic of Germany
[full address of declarant(s) - not post office box]

.....

.....

do solemnly and sincerely declare as follows:-

1. I am/~~We are~~ authorised by Heinrich Mack Nachf., 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 Federal Republic of Germany on 13 February 1987 by Heinrich Mack Nachf.

3. Peter Stoss; and Matyas Leitold, of Mozartstrasse 15, 7918 Illertissen; and Klaufluegelweg 21, 7950 Biberach, both in Federal Republic of Germany [respectively], are the actual inventors of the invention and the facts upon which the applicant is entitled to make the application are as follows:

   Heinrich Mack Nachf. is entitled by Contract of Emplyment between the inventors as employees and Heinrich Mack Nachf. as employer, as a person who would be entitled to have the patent assigned to it if a patent were granted upon an application made by the inventors.

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 New York, New York this 2nd day of March 19 88

Heinrich Mack Nachf.

.....
Signature of Declarant

ALLEN J. SPIEGEL
ASSISTANT DIRECTOR FOR
FOREIGN PATENTS

TO: THE COMMISSIONER OF PATENTS
AUSTRALIA

JTA:121W

(12) PATENT ABRIDGMENT (11) Document No. AU-B-11627/88
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 598634

(54) Title
OXIME-ETHERS OF 2,6-DIOXOBICYCLO-(3.3.0)OCTANONES FOR TREATMENT OF HEART AND CIRCULATION DISEASES

International Patent Classification(s)
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(71) Applicant(s)
HEINRICH MACK NACHF

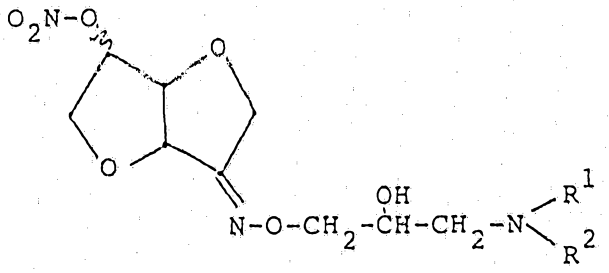
(72) Inventor(s)
PETER STOSS; MATYAS LEITOLD

(74) Attorney or Agent
SPRUSON & FERGUSON

(57) PHARMACEUTICALS FOR THE TREATMENT OF CARDIC OR CIRCULATORY BLOOD DISEASE.

CLAIM

1. Oxime ethers of 2,6-di-oxabicyclo[3.3.0]octanones of the formula I,



I

in which
R^1 and R^2 are the same or different and are selected from
(a) hydrogen,
(b) a straight-chain or branched alkyl group with 1-6 C-atoms,
(c) a ω-theophyllin-7-yl-alkyl group,

.../2

(d) a ~~unsubstituted or substituted~~ 2,3-dihydrobenzo[1.4]dioxin-2-yl-methyl group,

(e) a benzyl group, or

(f) R^1 and R^2, when taken together with the nitrogen atom to which they are attached, are piperazine, optionally substituted by alkyl, phenyl or alkoxyphenyl; theophyllin-7-yl; or theobromin-1-yl; and the salts of inorganic or organic acids; and wherein said substituents do not detract from the prophylactic or therapeutic activity of the compounds claimed.

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S & F Ref: 49536

FORM 10

COMMONWEALTH OF AUSTRALIA

PATENTS ACT 1952

COMPLETE SPECIFICATION

(ORIGINAL)

FOR OFFICE USE:

Class Int Class

Complete Specification Lodged:
Accepted:
Published:

Priority:

Related Art:

This document contains the amendments made under Section [illegible]

[illegible]

Name and Address of Applicant: Heinrich Mack Nachf.
D-7918 Illertissen

FEDERAL REPUBLIC OF GERMANY

Address for Service: Spruson & Ferguson, Patent Attorneys
Level 33 St Martins Tower, 31 Market Street
Sydney, New South Wales, 2000, Australia

Complete Specification for the invention entitled:

Oxime-ethers of 2,6-dioxobicyclo-[3.3.0]octanones for Treatment of Heart and Circulation Diseases

The following statement is a full description of this invention, including the best method of performing it known to me/us

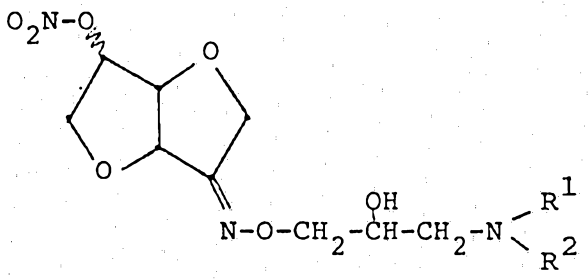
5845/3

P.C. 7159

OXIME ETHERS OF 2,6-DIOXABICYCLO[3.3.0[OCTANONES

Abstract

Oxime ethers of 2,6-dioxabicyclo[3.3.0]octanones of the formula I



have pharmacological activity and are especially applicable as drugs for the prophylaxis and therapy of cardiac and circulatory diseases.

P.C. 7159

OXIME ETHERS OF 2,6-DIOXABICYCLO[3.3.0[OCTANONES

The majority of the β-receptor blockers therapeutically applied these days are aryloxypropanolamines. Additionally, some are arylethanolamines. Common to both types is an aryl group, i.e. an aromatic system. According to the current opinion of researchers, this aromatic system is a pre-requisite for achieving the desired therapeutic effect (see for example E. Schroder, C. Rufer, R. Schmiechen, Pharmazeutische Chemie, Thieme Verlag 1982, p. 682 ff).

In initial attempts to break through this princple, a possibility was indicated by compounds, in which the aromatic system was "extended outwards" by means of a conjugated double bond. Examples can be found in the following documents: U.S. Patent 4,469,706, DE-OS 2 651 084 and EP 31 266.

Subsequently, substances with purely aliphatic basic structures were also manufactured, including substituted oxime ethers, for example J. Med. Chem. 23, 620 (1980); J. Med. Chem. 27, 1291 (1984); J. Med. Chem. 28, 153 (1985); J. Med. Chem. 28, 896 (1985); DE-OS 2 658 762; DE-OS 2 658 938; EP 37 777; EP 87 378. However, such compounds have had no therapeutic impact so far.

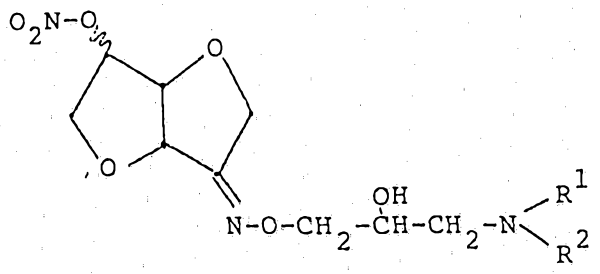
None of the prior art substances have a bicyclic basic structure, let alone one with hetero atoms in the

bicyclic ring system. Also, the derivatives known from the literature have no further functional groups in the molecule which could modify or contribute to the overall therapeutic effect. Such added effect was not expected. In the literature, many examples can be found for failed attempts to combine two or more so-called "pharmacophoric groups" in one molecule. In the majority of cases this procedure, occasionally referred to as "chemical hybridisation" or "intramolecular combination", results in the loss of all pharmacological efficacy. The presence of different groups, which are considered pharmacologically active, in one and the same molecule seems to lead mainly to an extinction of activity (see for example B. J. Nicolaus, "Symbiotic Approach to Drug ~~Design~~ Research", in "Decision Making in Drug Design", Edit. F. Gross, Raven Press, 1983, p. 173 ff.).

It can therefore be regarded as surprising, that this prejudice does not apply to the compounds according to the present invention. These distinguish themselves by a basic structure (2,6-dioxabicyclo-[3.3.0]octanone) hitherto not utilized in this field of indication, and additionally by the presence of both a nitrate ester group and an N-substituted 3-amino-2-hydroxypropyl-oxime ether function. Despite this chemical hybridization, the invention allowes for the creation of pharmaceutically active substances with novel structures, extending the range of application of known compound classes and exploiting new areas of pharmaceutical indication. Completely unexpectedly, the present compounds exhibit a pharmacological efficacy profile that generally can not be matched by other prior art substances.

AUSTRALIAN PATENT OFFICE LS

The present invention is concerned with new oxime ethers of 2,6-di-oxabicyclo[3.3.0]octanones of the formula I



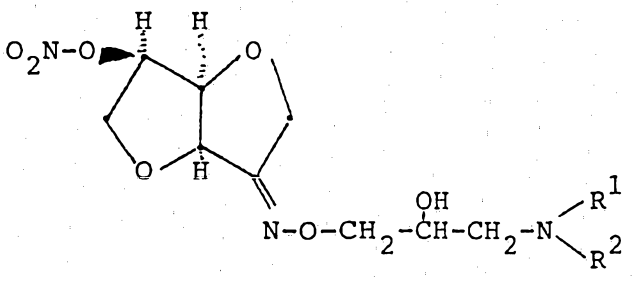
I

in which
R^1 and R^2 are the same or different and are selected from (a) hydrogen, (b) a straight-chain or branched alkyl group with 1-6 C-atoms, preferably with 3-4 C-atoms, (c) a ω-theophyllin-7-yl-alkyl group, wherein the alkyl group preferably contains 2-3 C-atoms, (d) a ~~unsubstituted or substituted~~ 2,3-dihydrobenzo[1.4]dioxin-2-yl-methyl group, and (e) a benzyl group, or (f) R^1 and R^2, when taken together with the nitrogen atom to which they are attached, are an unsubstituted or substituted piperazine ring, wherein the substituent may be either alkylphenyl or alkoxyphenyl, especially methylphenyl and methoxyphenyl; theophyllin-7-yl or theobromin-1-yl; and salts of inorganic or organic acids, preferably or pharmaceutically acceptable acids and wherein said substituents do not detract from the prophylactic or therapeutic activity of the compounds claimed.

Throughout the specification and claims the expression 'substituents which do not detract from the prophylactic or therapeutic activity of the compounds claimed' refers to 'substituents on the 2,3-dihydrobenzo[1.4]-dioxin-2-yl-methyl group' which do not prevent the claimed compounds from exhibiting their prophylactic or therapeutic use as drugs in cardiac and circularly diseases.

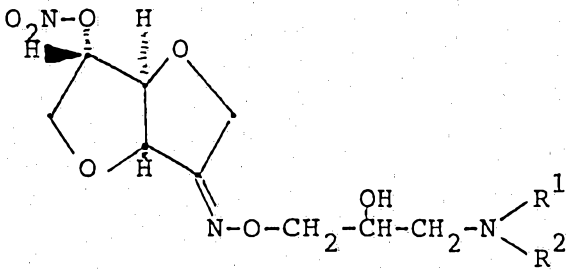
In formula I, the $O-NO_2$ group can be positioned both endo- and exocyclic to the ring system, as expressed in the formula by means of a corrugated line (≈)

The oxime ethers of 2,6-dioxabicyclo [3.3.0] octanones of the formula I of the present invention consist of the endo-isomers of the formula I a



I a

in which R^1 and R^2 have the meaning indicated above, and the exo-isomers of the formula I b,



I b

in which R^1 and R^2 have the meaning indicated above.

Due to the known oxime ether isomerisation, the compounds of formula I according to the present invention can also occur in the stereo-isomeric E- and/or Z-forms.

The N-substituted 3-amino-2-propanol side-chain present in the compounds of general formula I contains a chiral centre. Substances of this type can therefore exist both as racemates and in the form of pure optical antipodes as R- and S-enantiomers. The basic structures of 2,6-dioxabicyclo[3.3.0]octanones are also chiral molecules. For this reason, the compounds of formula I according to the present invention exist as diastereo-isomers.

AUSTRALIAN PATENT OFFICE

Both the mixtures of diastereo-isomers and the separated, configuratively uniform components, in the stereo-isomeric E- as well as Z-forms, are the subject of this invention.

2,6-Dioxabicyclo[3.3.0]oxtanones belong to a hitherto rarely investigated class of substances. Ketone derivatives are mentioned only once in the prior art namely in DE-OS 3 602 067.

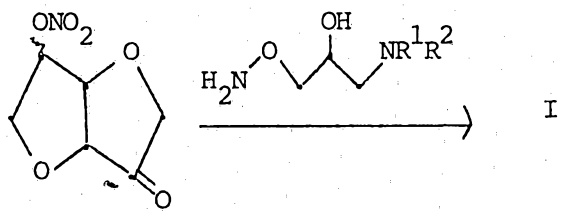
Apart from the bicyclo nomenclature used here, the compounds of the present invention can also be described under the nomenclature for fused ring systems, as hexahydro-furo [3.2-b]furanes.

Among the salts covered by the subject of the invention are those formed with inorganic and organic acids, preferably, however, those formed with pharmaceutically acceptable acids. Examples of these are, hydrochlorides, hydrobromides, nitrates, sulfates, phosphates, acetates, oxalates, maleates, fumarates, tartrates, lactates, maleinates, malonates, citrates, salicylates, methane sulfonates, benzene sulfonates, toluene sulfonates and naphthalene sulfonates.

These or other salts of the present novel compounds, as for example picrates may serve for the purification of the free bases by converting the free base into a salt, isolating the salt, if necessary, recrystallizing or otherwise purifying the salt, and subsequently releasing the base from the salt.

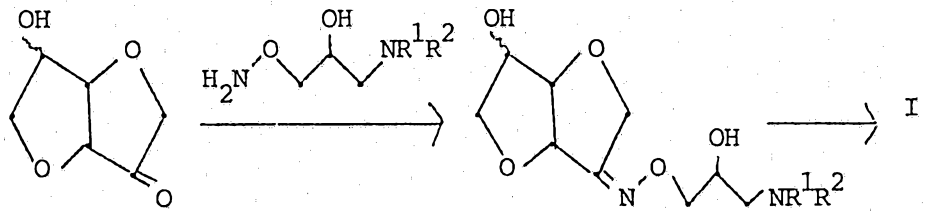
The compounds of the formula I may be prepared by one of the following routes:

a)



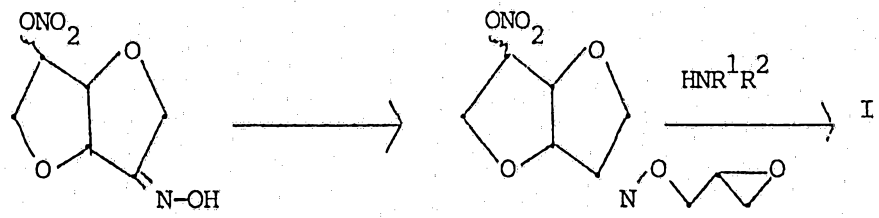
II III I

b)

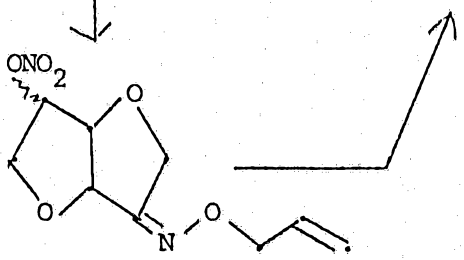


IV III V I

c)

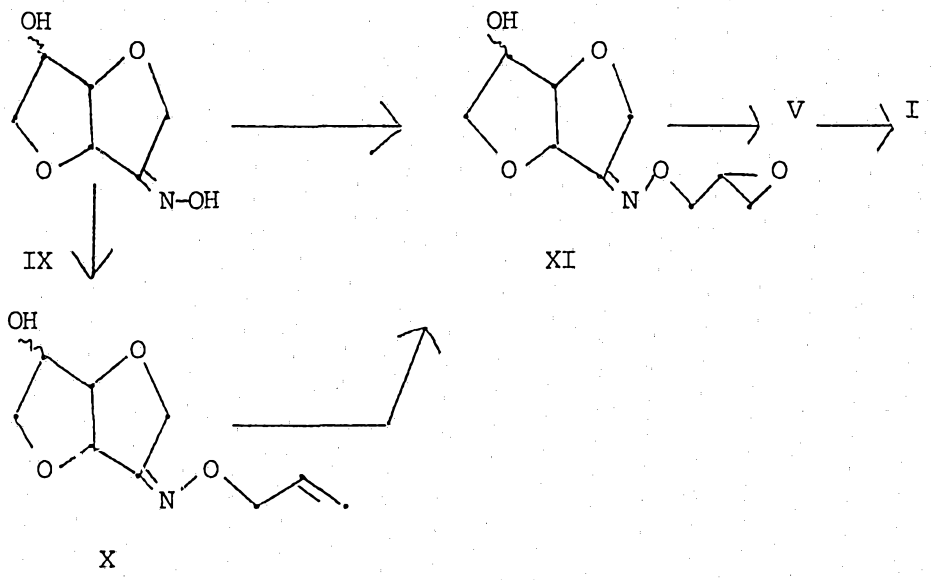


VI VIII



VII

d)



X

According to route a) 4-oxo-2,6-dioxabicyclo[3.3.0]-octan-8-endo/exo-ol-nitrate (DE-OS 3 602 067) of the formula IX is reacted in a well-known manner with an O-substituted hydroxylamine derivative of the formula III, in which R^1 and R^2 have the meaning indicated above. Such preparative methods are extensively described in the literature and are familiar to persons skilled in the art. Some of the compounds of the general formula III are known (DE-OS 2 651 083), others are new intermediates for the synthesis of the compound I of this invention.

In addition, the compound I of this invention can be prepared via route B). This starts by using a corresponding hydroxy-ketone IV (Chem. Ber. 96, 3195 (1963)), which is reacted with the same hydroxylamine derivatives III as in route a). The reaction products V formed hereby are subsequently converted to the nitrate ester I in the usual way. This synthesis is also based on a method familiar to a skilled person.

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A further possibility for the manufacture of the compounds I of the invention is stated in route c). Here, a 4-hydroximino-2,6-dioxabicyclo[3.3.0]octan-8-endo/exo-ol-nitrate of the formula VI (DE-OS 3 602 067) is converted either directly or via the intermediate step of O-allyl-oxime VII into the O-(2,3-epoxypropyl)-oxime VIII and this is subsequently reacted with amines HNR^1R^2, in which R^1 and R^2 have the meaning indicated above. All steps of this synthesis can be carried out using similar methods found in the literature.

Finally, the compounds I of the invention may be obtained via route d). This is based on hydroxy oximes IX, which are obtainable from the compounds IV in the usual way. The resulting product XI may be prepared either directly or via the intermediate step of O-allyl-oxime X. The synthesis is continued as in route c), with amines HNR^1R^2, thus forming V. This is subsequently converted into the nitrate ester in the usual way. This route also employs well-known reactions and can be readily used by a skilled person without further explanations.

All compounds of the formulae V, VII, VIII, IX, X and XI are not known in the prior art and are therefore novel intermediates for preparation of the compounds I of the invention. The following compounds, for example, may be intermediates:

VII: 4-(O-Allyl-oximino)-2,6-dioxacicyclo[3.3.0]-octan- 8-endo-ol-nitrate

4-(O-Allyl-oximino)-2,6-dioxabicyclo[3.3.0]-octan- 8-exo-ol-nitrate

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VIII: 4-[O-(2,3-Epoxypropyl)-oximino]-2,6-dioxa-bicyclo[3.3.0]octan-8-endo-ol-nitrate
4-[O-(2,3-Epoxypropyl)-oximino]-2,6-dioxa-bicyclo[3.3.0]octan-8-exo-ol-nitrate

IX: 4-Hydroximino-2,6-dioxabicyclo[3.3.0]octan-8-endo-ol
4-Hydroximino-2,6-dioxabicyclo[3.3.0]-octan-8-exo-ol

X: 4-(O-Allyl-oximino)-2,6-dioxabicyclo[3.3.0]-octan-8-endo-ol
4-(O-Allyl-oximino)-2,6-dioxabicyclo[3.3.0]-octan-8-exo-ol

XI: 4-[O-(2,3-Epoxypropyl)-oximinol]-2,6-dioxa-bicyclo[3.3.0]octan-8-endo-ol
4-[O-(2,3-Epoxypropyl)-oximino]-2,6-dioxa-bicyclo[3.3.0]octan-8-exo-ol

The following derivatives of 4-[O-(3-amino-2-hydroxypropyl)-oximino]-2,6-dioxabicyclo[3.3.0]octan-8-endo- and exo-ols serve as examples for the intermediate products V, whereby only the 3-amino substitutents are given for each:

3-Isopropylamino
3-tert. Butylamino
3-[4-(2-Methyl-phenyl)-piperazinyl]
3-[4-(2-Methoxy-phenyl)-piperazinyl]
~~3-(2-Benzo[1,4]dioxinyl-methylamino)~~ 3-(2,3-dihydro benzo[1.4]dioxin-2-yl-methylamino
3-Theophyllin-7-yl
3-Theobromin-1-yl
3-[2-(7-Theophyllinyl)-ethylamino]
3-[3-(7-Theophyllinyl)-propylamino].

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Surprisingly, the compounds according to the present invention distinguish themselves by a wide pharmacological spectrum of activity and can therefore be regarded as valuable medicinal agents. They have cardiac relieving, cardiovascular effects, without inducing a reflectoral increase in the heart rate. They have a hypotensive and spasmolytic effect. In addition, they also have β_1-receptor blocking properties.

In the following, the many pharmacological effects are illustrated using the compounds of Examples 1 and 3.

In the determination of the orientating toxicity of the compounds of examples 1 and 3, mice withstood 500 mg/kg perorally without exhibiting clinical symptoms and without fatalities.

On isolated aorta strips from rats and rabbits, both substances exhibited dose-dependent inhibition of potassium chloride-induced contractions.

ED_{50}-values (mM/L):	Rat	Rabbit
Example 1	0.024	0.0059
Example 2	0.472	4

Table 1 Inhibition of Isoprenaline tachycardia in narcotised, despinalised rats after prophylactic, intravenous or intraduodenal application

Substance	n	Dose mg/kg	ED_{50} mg/kg	95% Confidence Limits
Example 1 i.v.	9	5.0 - 20.0	11.0	10.23 - 16.24
Example 1 i.d.	9	40.0 - 160.0	82.63	75.86 - 98.76
Example 3 i.v.	9	2.5 - 10.0	4.60	3.84 - 7.48
Example 3 i.d.	9	40.0 - 160.0	74.57	66.73 - 83.33

Table 2 Influence on the T-wave elevation in the ECG of narcotised rats, which was induced by intravenous bolus injection of Lypressin. The substances were administered perorally 15 minutes and at various times before the Lypressin injection

Substance	n/Time	Dose mg/kg	ED_{50} mg/kg	95% Confidence Limits	Length of action at ED_{50}-Dose (min.)
Example 1	10	20.0 - 80.0	53.76	45.56 - 63.43	240
Example 3	10	20.0 - 80.0	50.82	37.62 - 68.65	240

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Table 3 Cardiovascular effects of the compound of example 3 after intravenous administration to narcotised rats (Pentobarbital) with opened thorax and artificial respiration.

MAP = mean arterial blood pressure
TPVR = total peripheral vascular resistence
PAP = blood pressure in the A. pulmonalis
LVP = left ventricular blood pressure
CO = cardiac minute volume
SV = cardiac output
BAF = blood flow in the A femoralis
HR = cardiac frequency
LV dp/dt = maximum left ventricular pressure increase rate
LVEDP = left ventricular end diastolic pressure

Substance	n	Parameters		Previous Value	Efficacy of the substance	Changes	Maximum efficacy (min)	Length of action (min)
Example 3 1.0 mg/kg i.v.	4	MAP	(mmHg)	117 ± 5	81 ± 5**	36 ± 20	1.2 ± 0.0	111 ± 15
		TPVR	(mmHg/ml)	142 ± 9	99 ± 6**	-43 ± 4	1.0 ± 1.0	13 ± 8
		BAF	(ml/min)	73 ± 16	40 ± 11**	-34 ± 5	1.3 ± 0.3	109
		PAP	(mmHg)	22 ± 3	17 ± 2	-5 ± 2	3.0 ± 0.1	50 ± 18
		LVP	(mmHg)	130 ± 12	92 ± 12**	-38 ± 2	1.7 ± 0.4	103 ± 28
		LVEDP	(mmHg)	3.8 ± 1.0	3.1 ± 1.0	0.7 ± 0.7	9.3 ± 8	51 ± 28
		HR	(beats/min)	140 ± 8	127 ± 4	-13 ± 10	7 ± 3	> 114
		CO	(l/min)	0.83 ± 0.04	0.74 ± 0.08	-0.09 ± 0.02	5 ± 2	113 ± 21
		SV	(ml/min)	6.0 ± 0.4	6.3 ± 0.6	+0.3 ± 0.5	2 ± 1	31 ± 24
		LV dp/dt	(mmHg/s)	2558 ± 141	1747 ± 84*	-811 ± 116	6.8 ± 5	107 ± 12

Significant difference compared to the previous value $p < 0.05$*, $p < 0.01$**

Table 4 Cardiovascular effects of example 3 after i.d. administration to narcotised rats (Pentobarbital) with opened thorax and artificial respiration.

MAP = mean arterial blood pressure
TPVR = total peripheral vascular resistence
PAP = blood pressure in the A. pulmonalis
LVP = left ventricular blood pressure
CO = cardiac minute volume
SV = cardiac output
BAF = blood flow in the A femoralis
HR = cardiac frequency
LV dp/dt = maximum left ventricular pressure increase rate
LVEDP = left ventricular end diastolic pressure

Substance	n	Parameters		Previous Value	Efficacy of the substance	Changes	Maximum efficacy (min)	Length of action (min)
		MAP	(mmHg)	116 ± 7	91 ± 12**	-25 ± 4	58 ± 12	> 167
		TPVR	(mmHg/ml)	155 ± 8	132 ± 10**	-23 ± 3	39 ± 5	> 136
Example 3		BAF	(ml/min)	70 ± 4	47 ± 23*	-23 ± 5	42 ± 8	> 167
30 mg/kg	4	PAP	(mmHg)	22.8 ± 6	18.5 ± 7*	-4.3 ± 5	33 ± 11	111 ± 16
i.d.		LVP	(mmHg)	133 ± 9	95 ± 10**	-38 ± 11	65 ± 17	> 153
		LVEDP	(mmHg)	3.8 ± 1	1.5 ± 2*	-2.3 ± 0.9	38 ± 27	77 ± 8
		HR	(beats/min)	142 ± 5	119 ± 7	-23 ± 4	78 ± 44	> 167
		CO	(l/min)	0.75 ± 0.03	0.66 ± 0.05	-0.09 ± 0.02	62 ± 8	> 167
		SV	(ml/min)	5.3 ± 0.4	5.8 ± 0.3	+0.5 ± 0.07	33 ± 3	> 167
		LV dp/dt	(mmHg/s)	2345 ± 100	1466 ± 189**	-879 ± 90	76 ± 10	> 132

Significant difference compared to the previous value $p < 0.05$*, $p < 0.01$**

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Table 5 Influence on the systolic arterial pressure (SAP) and the heart rate (HR) of concious normotensive beagle dogs. Substance was administered perorally.

Substance	n	Dose mg/kg	Measuring Parameters	Influence of the substances on blood pressure and heart rate at different times (h)					
				0	0.5	1	2	3	4
Example 3	4	5.0	SAP (mmHg)	137 ± 7	109 ± 4	106 ± 2	116 ± 5	122 ± 4	128 ± 7
			Changes (mmHg)		-28 ± 6**	-31 ± 5**	-21 ± 2*	-15 ± 4*	-9 ± 3
			HR (Schl/M)	95 ± 8	82 ± 7	75 ± 5	70 ± 6	76 ± 4	81 ± 4
			Changes (Schl/M)		-13 ± 2*	-20 ± 5*	-24 ± 6*	-19 ± 5*	-14 ± 4*
Example 1	4	10.0	SAP (mmHg)	134 ± 3	98 ± 3***	102 ± 4****	114 ± 3***	118 ± 3*	115 ± 3*
			Changes (mmHg)		-36 ± 2	-32 ± 2	-20 ± 1	-16 ± 2	-19 ± 3
			HR (Schl/M)	88 ± 3	73 ± 3	72 ± 5	74 ± 6	78 ± 4	79 ± 5
			Changes (Schl/M)		-15 ± 3*	-16 ± 4*	-14 ± 2*	-10 ± 3*	-9 ± 2*

Significant difference compared to initial value $p < 0.05$*, $p < 0.01$**, $p < 0.001$***

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Table 6 Reduction of the arterial mean pressure in narcotised rabbits. The substance was administered i.d.

Substance	n	Dose mg/kg	ED_{30} (mmHg) mg/kg	95% Confidence Limits
Example 1	9	8.0 - 32.0	24.23	14.06 - 41.76
Example 3	9	8.0 - 32.0	22.82	16.03 - 32.49

The invention is also concerned with the application of compounds of the formula I and their salts as medicinal agents, especially for the treatment and prophylaxis of cardiac and circulatory diseases. The drug formulation contains at least one compound of the formula I, if desired in the form of one of the compound's physiologically tolerable acid addition salts, as active substance and can be administered either alone or mixed with suitable carrier substances. Such drugs could contain the compounds of the invention or the salts thereof in a weight content of 0.1 to 99.9%. The dosage can be chosen as desired and may lie in the range of 1 mg to 500 mg.

All formulations known to those skilled in the art are suitable. Examples of suitable pharmaceutical application forms are suppositories, powders, granulates, tablets, capsules, suspensions, liquids, parenterals and transdermal systems. Solid, semi-solid or liquid carrier materials or dilution media can be used in the manufacture of pharmaceutical dosage forms. Included herein are correcting agents, binding agents, lubricants, emulsifiers etc. Examples of such agents are: starch, such as potato and cereal starches, sugar such as lactose, sucrose, glucose, mannitol, sorbitol, celluloses such as crystalline cellulose, methyl cellulose, calcium carboxymethyl cellulose, sodium carboxymethyl cellulose and hydroxypropyl cellulose, inorganic materials such as potassium phosphate, calcium sulfate, calcium carbonate and talc, gelatin, gum arabic, polyvinyl pyrrolidone, surfactant substances such as fatty acid glycerides, fatty acid-sorbitane esters, fatty acid esters of sucrose polyglycerin and others.

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Some examples of drug formulations using the compounds of the invention are listed as follows:

Tablets:

Composition	mg/tablet
Compound of the invention	3
Microcrystalline cellulose	25
Lactose	17
Carboxymethyl cellulose calcium	4.5
Magnesium stearate	0.5

The above listed ingredients are sieved, carefully and sufficiently mixed, and pressed on a suitable tablet press.

Capsules:

Composition	mg/capsule
Compound of the invention	10
Lactose	40
Microcrystalline cellulose	30
Talc	10

The above listed ingredients are sieved, carefully and sufficiently mixed and filled into hard gelatin capsules on a suitable capsule filling machine.

The following examples serve to illustrate the invention. Unless otherwise stated, the compounds illustrated in the examples are diastereoisomeric mixtures.

Example 1

4-(2-Hydroxy-3-isopropylamino-propyl)-oximino-2,6-dioxabicyclo[3.3.0]octan-8-endo-ol-nitrate

a) O-(2-Hydroxy-3-isopropylamino-propyl)-acetohydroximic acid ethyl ester: 15.9 g of O-(2,3-epoxypropyl)-acetohydroximic acid ethyl ester (DE 2 651 085) are heated with 17.7 g of isopropylamine in 100 ml

of ethanol for 4 hours under reflux. The solvent and the excess isopropylamine are subsequently removed using a rotary evaporator and the oily residue is distilled under vacuum. Boiling point 71 - 73° C/0.2 mm; yield 17.5 g.

$C_{10}H_{22}N_2O_3$ (218.29).

b) O-(2-Hydroxy-3-isopropylamino-propyl)-hydroxylamine-dihydrochloride: 21.2 g of the intermediate product a) are heated with 150 ml of 2 N-HCl for 15 min. under reflux. The solution is evaporated to dryness under reduced pressure and the residue is recrystallized using ethanol. Melting point 166 - 167°C; yield 20.5 g (cf. DE-OS 2 651 083).

$C_6H_{16}N_2O_2$. 2 HCl (221.13).

c) 22.1 g of the compound b) are added to a solution of 13.8 g of anhydrous potassium carbonate in 1 l of dry methanol and stirred for 5 min at room temperature, in order to release the base. 18.9 g of 4-Oxo-2,6-dioxabicyclo [3.3.0]octan-8-endo-ol-nitrate (DE-OS 3 602 067) are added and the mixture is stirred overnight. After filtering off the inorganic salts and removing the solvent the product is recrystallized several times using isopropanol. Yield 21.7 g; melting point 78 - 80°C; $[\alpha]_D^{20}$ + 172.6 (c = 0.701, acetone).

$C_{12}H_{21}N_3O_7$ (319.32).

Example 2

4-(2-Hydroxy-3-isopropylamino-propyl)-oximino-2,6-dioxabicyclo[3.3.0]octan-8-exo-ol-nitrate

The base is released from 22.1 g of O-(2-hydroxy-3-isopropylamino-propyl)-hydroxylamine dihydrochloride (example 1 b), by dissolving in 1 l of methanol, using the stoichiometrical amount of anhydrous potassium

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carbonate. 18.9 g of 4-Oxo-2,6-dioxabicyclo[3.3.0]-octan-8-exo-ol-nitrate (DE-OS 3 602 067) are added to this and the whole is stirred overnight at room temperature. After treating in the normal way, the raw base is precipitated as the semioxalate, which is recrystallized using methanol. Yield 26.2 g; melting point 156°C (decomposition); $[\alpha]_D^{20}$ + 6.80 (c = 0.741, methanol).

$C_{12}H_{21}N_3O_7 \cdot 0.5\ C_2H_2O_4$ (364.34).

Example 3

4-(3-tert.-Butylamino-2-hydroxy-propyl)-oximino-2,6-dioxabicyclo[3.3.0]octan-8-endo-ol-nitrate

a) O-(3-tert.-Butylamino-2-hydroxy-propyl)-acetohydroximic acid ethyl ester: 31.8 g of O-(2,3-epoxypropyl)-acetohydroximic acid ethyl ester are heated with 43.9 g of tert. butylamine in 300 ml of ethanol for 4 hours under reflux. The solvent and the excess tert.-butylamine are subsequently removed on a rotary evaporator and the oily residue is distilled under vacuum. Boiling point 83 - 84° C/0.2 mm; yield 40.6 g (cf. DE-OS 2 651 083).

b) O-(3-tert.-butylamino-2-hydroxy-propyl)-hydroxylamine-dihydrochloride: 40.6 g of the intermediate product a) are heated with 150 ml of 2 N HCl for 15 min under reflux. The solution is evaporated to dryness under reduced pressure and the residue recrystallized using ethanol. Melting point 194 - 195°C; yield 36.9 g (cf. DE-OS 2 651 083):

$C_7H_{18}N_2O_2 \cdot 2\ HCl$ (235.15).

c) 16.2 g of the base released from compound b) are dissolved in 1 l of methanol. After adding 18.9 g of 4-oxo-2,6-dioxabicyclo[3.3.0]octan-8-endo-ol-

nitrate, it is stirred overnight at room temperature. Normal treatment and precipitation of the raw base as semioxolate produces colorless crystals, which are recrystallized using isopropanol. Yield 22.0 g; melting point 155 - 160°C (dec.); $[\alpha]_D^{20}$ + 163.6 (c = 0.583, methanol).

$C_{13}H_{23}N_3O_7 \cdot 0.5\ C_2H_2O_4$ (378.37).

Example 4

4-(3-tert.-Butylamino-2-hydroxy-propyl)-oximino-2,6-dioxabicyclo[3.3.0]octan-8-exo-ol-nitrate

16.2 g of O-(3-tert.butylamino-3-hydroxy-propyl)-hydroxyl-amine (example 3 b), are dissolved in 1 l of methanol. 18.9 g of 4-Oxo-2,6-dioxabicyclo[3.3.0]-octan-8-exo-ol-nitrate are added and the whole is stirred overnight at room temperature. After treating in the normal way, the raw base is precipitated as the semioxalate and this is recrystallized using methanol. Yield 23.3 g; melting point 179°C (dec.); $[\alpha]_D^{20}$ + 6.50 (D = 0.655, methanol).

$C_{13}H_{23}N_3O_7 \cdot 0.5\ C_2H_2O_4$ (378,37).

Example 5

4-〈3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-hydroxy-propyl〉-oximino-2,6-dioxabicyclo[3.3.0]octan-8-endo-ol-nitrate

a) O-〈3-[4-(2-Methoxyphenyl)-1-piperazinyl]-2-hydroxy-propyl〉-acetohydroximic acid ethyl ester: analogous to example 1 a) from 15.9 g of O-(2,3-epoxy-propyl)-acetohydroximic acid ethyl ester and 19.2 g of 1-(2-methoxyphenyl)piperazine. Melting point 73 - 74°C (using diisopropyl ether). Yield 23.3 g.

$C_{18}H_{29}N_3O_4$ (351.45).

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b) O- ⟨3-[4-(2-Methoxyphenyl)-1-piperazinyl]-2-hydroxy-propyl⟩-hydroxylamine-trihydrochloride: from 35.1 g of the aforementioned compound by heating with 2 N HCl, analogous to example 1 b). Yield 21.9 g; melting point 154 - 157°C (dec.) (cf. DE-OS 2 651 083).

$C_{14}H_{23}N_3O_3 \cdot 3\ HCl \cdot H_2O$ (408.75).

c) By reacting 28.1 g of base from compound b) with 18.9 g of 4-oxo-2,6-dioxabicyclo[3.3.0]octan-8-endo-ol-nitrate. Oxalate: yield 31.4 g; melting point 63 - 67°C (using isopropanol); $[\alpha]_D^{20}$ + 125.5 (c = 1.0, methanol).

$C_{20}H_{28}N_4O_8 \cdot C_2H_2O_4 \cdot 0{,}5\ H_2O$ (551.51).

Example 6

4- ⟨3-[4-(2-Methoxyphenyl)-1-piperazinyl]-2-hydroxy-propyl⟩-oximino-2,6-dioxabicyclo[3.3.0]octan-8-exo-ol-nitrate

By reacting 28.1 g of O- 3-[4-(2-methoxyphenyl)-1-piperazinyl]-2-hydroxy-propyl -hydroxylamine (base) with 18.9 g of 4-oxo-2,6-dioxabicyclo[3.3.0]octan-8-exo-olnitrate. Oxalate: melting point 90 - 93°C (using ethyl acetate); yield 29.0 g; $[\alpha]_D^{20}$ + 45.5 (c = 1.0, methanol).

$C_{20}H_{28}N_4O_8 \cdot C_2H_2O_4$ (542.51).

Example 7

4- ⟨3-[4-(2-Methylphenyl)-1-piperazinyl]-2-hydroxy-propyl⟩-oximino-2,6-dioxabicyclo[3.3.0]octan-8-endo-ol-nitrate

a) O- ⟨3- 4-(2-methylphenyl)-1-piperazinyl]-2-hydroxy-propyl⟩-acetohydroximic acid ethyl ester: from 15.9 g of O-(2,3-epoxypropyl)acetohydroximic acid ethyl ester and 17.6 g of 1-(2-methylphenyl)-piperazine. The

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oily product is purified by means of column chromatography on silica gel (mobile phase petroleum ether 50 - 70°C/tetrahydrofuran (THF)/methanol, 80/20/2). Yield 30 g.

$C_{18}H_{29}N_3O_3$ (335.45).

b) O-〈3-[4-(2-Methylphenyl)-1-piperazinyl]-2-hydroxy-propyl〉-hydroxylamine-trihydrochloride: from the aforementioned compound by means of hydrolysis with 2 N-HCl. Melting point 159 - 161°C (dec.) (using methanol).

$C_{14}OH_{23}N_3O_2 \cdot 3\ HCl \cdot 3\ H_2O$ (428.79).

c) By usual reaction of the base from the aforementioned compound with 4-oxo-2,6-dioxabicyclo-[3.3.0]octan-8-endo-ol-nitrate. Oxalate: melting point 58 - 62°C (using isopropanol); $[\alpha]_D^{20}$ + 116.50 (c = 1.0, methanol).

$C_{20}H_{28}N_4O_7 \cdot C_2H_2O_4$ (526.51).

Example 8

4-〈3-[4-(2-methylphenyl)-1-piperazinyl]-2-hydroxy-propyl〉-oximino-2.6-dioxabicyclo[3.3.0]octan-8-exo-ol-nitrate

Preparation as in the previous examples, from ~~O-〈3-[4-(2-methylphenyl)-1-piperazinyl]-2-hydroxy-propyl〉-hydroxyl-amine~~ O-[3-(2,3-dihydrobenzo[1,4]-dioxin-2-yl-methylamino)-2-hydroxy-propyl]-hydroxyl-amine and 4-oxo-2,6-dioxabicyclo[3.3.0]-octan-8-exo-ol-nitrate. Oxalate: melting point 85 - 88°C (using isopropanol/ethanol 2:1); $[\alpha]_D^{20}$ + 49.0 (c = 1.0, methanol).

$C_{20}H_{28}N_4O_7 \cdot C_2H_2O_4$ (526.51).

Example 9

4-[3-~~(2-Benzo[1,4]dioxinyl~~-methylamino)-2-hydroxy-propyl]-oximino-2,6-dioxabicyclo[3.3.0]octan-8-endo-ol-nitrate

a) O-[3-(2-Benzo[1.4]dioxinyl-methylamino)-2-hydroxy-propyl]-acetohydroximic acid ethyl ester: from

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15.9 of O-(2,3-epoxy-propyl)-acetohydroximic acid 2-(aminomethyl)-2-3-dihydrobenzo[1.4]dioxin. The oily product was purified by means of column chromatography on silica gel (mobile phase petroleum ether 50 - 70°C/THF, 1:1). Yield 15.2 g.

$C_{16}H_{24}N_2O_5$ (324,38).

(b) O-[3-(2,3-Dihydrobenzo[1.4]dioxin-2-yl-methylamino)-2-hydroxy-propyl]-hydroxylamine-dihydrochloride: by hydrolysis of (a) with 2 NHCl. The substance is extremely hygroscopic.

$C_{12}H_{18}N_2O_4 \cdot 2\ HCl$ (327.22).

(c) By reaction of the base from the aforementioned compound with 4-oxo-2,6-dioxabicyclo[3.3.0]-octan-8-endo-ol-nitrate. Oxalate: melting point 72°C (using ethanol/methanol 4:1); $[\alpha]_D^{20}$ + 130.0 (c = 1.0, methanol).

$C_{18}H_{23}N_3O_9 \cdot C_2H_2O_4$ (515.44).

Example 10

4-[3-(2,3-Dihydrobenzo[1.4]dioxin-2-yl-methylamino)-2-hydroxy-propyl]-oximino-2,6-dioxabicyclo[3.3.0]octan-8-exo-ol-nitrate

Manufactured in the usual way from O-[3-(2,3-dihydrobenzo[1.4]dioxin-2-yl-methylamino)-2-hydroxy-propyl]-hydroxy-ylamine and 4-oxo-2,6-dioxabicyclo[3.3.0]octan-8-exo-ol-nitrate. Oxalate: melting point 176 - 177°C (using ethanol): $[\alpha]_D^{20}$ + 50.5 (c = 1.0, methanol).

$C_{18}H_{23}N_3O_9 \cdot C_2H_2O_4$ (515.44).

Example 11

4-[2-Hydroxy-3-(7-theophyllinyl)-propyl]-oximino-2,6-dioxabicyclo[3.3.0]-octan-8-exo-ol-nitrate

(a) O-[2-Hydroxy-3-(7-theophyllinyl)-propyl]-acetohydroximic acid ethyl ester: from 15.9 g O-(2,3-epoxypropyl)-aceto-hydroximic acid ethyl ester and 18.0

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g theophylline in ethanol. The colorless crystalline raw product was used directly in the next step.

$C_{14}H_{21}N_5O_5$ (339.35).

b) O-[2-hydroxy-3-(7-theophyllinyl)-propyl]-hydroxylamine-hydrochloride: from the aforementioned compound by means of hydrolysis with 2N HCl. Recrystallization using isopropanol produced hygroscopic crystals which were immediately processed further.

$C_{10}H_{15}N_5O_4$. HCl (305.72).

c) By reaction of the free base from b) with 4-oxo-2,6-dioxabicyclo[3.3.0]octan-8-exo-ol-nitrate. Hydrochloride: melting point: 140 - 143°C (dec.) (using chloroform); $[\alpha]_D^{20}$ + 60.0 (c = 1.0, methanol).

$C_{16}H_{20}N_6O_9$. HCl (476.83).

Example 12

4-[2-hydroxy-3-(1-theobrominyl)-propyl]-oximino-2,6-dioxabicyclo[3.3.0]octan-8-exo-ol-nitrate

a) O-[2-Hydroxy-3-(1-theobrominyl)-propyl]-acetohydroximic acid ethyl ester: from 15.9 g of O-(2,3-epoxypropyl)-acetohydroximic acid ethyl ester and 18.0 g of theobromine, a crystalline product is obtained which was processed further without purification.

$C_{14}H_{21}N_5O_5$ (339.35).

b) O-[2-Hydroxy-3(1-theobrominyl)-propyl]-hydroxylamine-hydrochloride: from the aforementioned compound by means of hydrolysis with 2 N-HCl. Using ethanol, a crystalline, hygroscopic substance was obtained which is incorporated into the next step in this form.

$C_{10}H_{15}N_5O_4$. HCl (305.72)

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c) By reaction of the base from b) with 4-oxo-2,6-dioxabicyclo[3.3.0]octan-8-exo-ol-nitrate. The substance crystallized with 0.25 mol 2-propanol. Melting point 99 - 100°C (using 2-propanol); $[\alpha]_D^{20}$ + 57.5 (c = 1.0, methanol).

$C_{16}H_{20}N_6O_9$ (440.38).

Example 13

4- 3-[N-Benzyl-N-(3-⟨7-theophyllinyl⟩-propyl)]-amino-2-hydroxy-propyl-oximino-2,6-dioxabicyclo-[3.3.0]octan-8-exo-ol-nitrate

a) O- 3-[N-Benzyl-N-⟨3-(7-theophyllinyl)-propylamino⟩-2-hydroxy-propyl]-acetohydroximic acid ethyl ester: from 15.9 g of O-(2,3-epoxypropyl)-acetohydroximic acid ethyl ester and 32.7 g of 7-(3-benzylamino-propyl)-theophylline. The oily raw product was reacted further without purification.

$C_{24}H_{35}N_6O_5$ (487.58).

b) O- 2-Hydroxy-3-[N-Benzyl-N-⟨3-(7-theophyllinyl)-propyl⟩]-amino-propyl-hydroxylamine-dihydrochloride: by hydrolysis of the aforementioned compound with 2 N-HCl. The crystalline raw product was directly reacted further.

$C_{20}H_{28}N_6O_4$. 2 HCl (489.40).

c) By reaction of the free base from b) with 4-oxo-2,6-dioxabicyclo[3.3.0]octan-8-exo-ol-nitrate. 1,5 hydrochloride . 0,5 H_2O: melting point 89°C (dec.) (using isopropanol); $[\alpha]_D^{20}$ + 45.0 (c = 1.0, methanol).

$C_{26}H_{33}N_7O_9$. 1.5 HCl . 0.5 H_2O (651.29).

Example 14

4- 2-Hydroxy-3-[3-(7-theophyllinyl)-propyl]-amino-propyl-oximino-2,6-dioxabicyclo[3.3.0]octan-8-exo-ol-nitrate

a) O- 3-[N- ⟨3-(7-theophyllinyl)-propyl⟩ -amino]-2-hydroxy-propyl-acetohydroximic acid ethyl ester: from 15.9 g of O-(2,3-epoxypropyl)-acetohydroximic acid ethyl ester and 23.7 g of 7-(3-aminopropyl)-theophylline. The oily raw product was reacted further without further purification.

$C_{17}H_{28}N_6O_5$ (396.45).

b) O-[2-Hydroxy-3- ⟨-3-(7-theophyllinyl)-propyl-amino⟩ -propyl]-hydroxylamine-dihydrochloride: by hydrolysis of a) with 2 N-HCl. The crystalline product obtained using ethanol was immediately processed further.

$C_{13}H_{22}N_6O_4 \cdot 2\ HCl$ (399.28).

c) By reaction the free base from b) with 4-oxo-2,6-dioxabicyclo[3.3.0]octan-8-exo-ol-nitrate. Hydrochloride . 0.5 H_2O: melting point 89 - 92°C (dissolved in chloroform, precipitated with ether); $[\alpha]_D^{20}$ + 49.0 (c = 1.0, methanol).

$C_{19}H_{27}N_7O_9 \cdot HCl \cdot 0.5\ H_2O$ (542.94).

Example 15

4- {2-Hydroxy-3-[2-(7-theophyllinyl)-ethyl]-amino-propyl} -oximino-2,6-dioxabicyclo[3.3.0]-octan-8-exo-ol-nitrate

a) O- {3-[N- 2-(7-theophyllinyl)-ethyl -amino]-2-hydroxy-propyl} -acetohydroximic acid ethyl ester: from 15.9 g of O-(2,3-epoxypropyl)-acetohydroximic acid ethyl ester and 22.3 g of 7-(2-aminoethyl)-theophylline. The oily raw product was processed further without purification.

$C_{16}H_{26}N_6O_5$ (382.42).

b) O-[2-Hydroxy-3-〈2-(7-theophyllinyl)-ethyl-amino〉-propyl]-hydroxylaminee-dihydrochloride. By hydrolysis of a) with 2N HCl. Using ethanol, a crystalline product was obtained which was processed further in this form.

$C_{12}H_{20}N_6O_4$. 2 HCl (385.25).

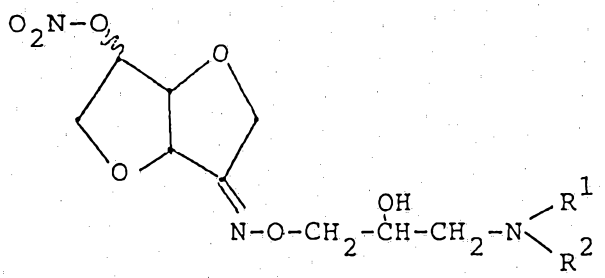
c) By reaction of the free base from b) with 4-oxo-2,6-dioxabicyclo[3.3.0]octan-8-exo-ol-nitrate. Semioxalate: melting point 174°C (using methanol) $[\alpha]_D^{20}$ + 52.5 (c = 1.0, water).

$C_{18}H_{25}N_7O_9$. 0.5 $C_2H_2O_4$ (528.46).

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The claims defining the invention are as follows:

1. Oxime ethers of 2,6-di-oxabicyclo[3.3.0]octanones of the formula I,



I

in which

R^1 and R^2 are the same or different and are selected from

(a) hydrogen,

(b) a straight-chain or branched alkyl group with 1-6 C-atoms,

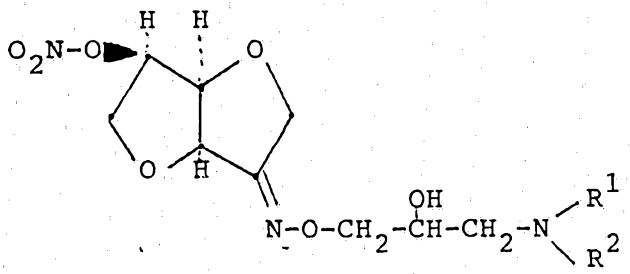
(c) a ω-theophyllin-7-yl-alkyl group,

(d) a ~~unsubstituted or substituted~~ 2,3-dihydrobenzo[1.4]dioxin-2-yl-methyl group,

(e) a benzyl group, or

(f) R^1 and R^2, when taken together with the nitrogen atom to which they are attached, are piperazine, optionally substituted by alkyl, phenyl or alkoxyphenyl; theophyllin-7-yl; or theobromin-1-yl; and the salts of inorganic or organic acids; and wherein said substituents do not detract from the prophylactic or therapeutic activity of the compounds claimed.

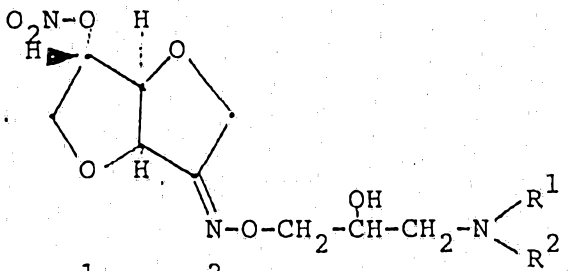
2. A compound according to claim 1, characterized in that said compound is in the endo-form of the formula I a,



I a

in which R^1 and R^2 are as defined in claim 1, and the salts thereof.

3. A compound according to claim 1, characterized in that said compound is in the exo-form of the formula I b,



I b

in which R^1 and R^2 are as defined in claim 1, and the salts thereof.

4. A compound according to claim 1, characterized by being in the form of a position isomer, a stereoisomer, an E- and/or Z- isomer, a diastereoisomers, or a mixture thereof, including the salts thereof.

5. A compound according to any one of claims 1 to 4, characterized in that at least one of R^1 and R^2 is a straight-chain or branched alkyl group of three or four carbon atoms.

6. A compound according to any one of claims 1 to 4 characterized in that R^1 and R^2 are taken together with the nitrogen atom to which they are attached to form an ω-theophyllin-7-yl-alkyl group having 2 or 3 carbon atoms in said alkyl group.

7. A compound according to any one of claims 1 to 4, characterized in that R^1 and R^2 are taken together with the nitrogen atom to which they are attached to form a piperazine ring substituted by methylphenyl or methylphenoxy.

8. A pharmaceutical composition for the treatment of a cardiac or a circulatory blood disease which comprises a compound according to claim 8 and a pharmaceutically acceptable carrier.

9. An oxime ether of 2,6-dioxabicyclo[3.3.0]-octanones of the formula I as defined in claim 1 and substantially as herein described with reference to any one of Examples 1 to 15.

10. A pharmaceutical composition for the treatment of a cardiac or a circulatory blood disease comprising an ether as defined in claim 9 and a pharmaceutically acceptable carrier, excipient and/or adjuvant.

11. A method of treating a cardiac or a circulatory blood disease in a patient in need of such treatment which method comprises administering to said patient a therapeutically effective amount of a compound as defined in any one of claims 1 to 8, or 9 or a composition as defined in claim 8 or claim 10.

12. A process for preparing an ether of formula I as defined in claim 1 which process is substantially as herein described with reference to any one of Examples 1 to 15.

DATED this TWENTY-SEVENTH day of FEBRUARY 1990
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