

The present invention relates to compounds which may be used in contrast media for radiography.

Iodobenzene compounds containing several iodine atoms on the benzene ring, usually 3 iodine atoms per benzene ring, and various other substituents have been used for a long time as contrast media. These other substituents are pharmacologically acceptable groups which enable the compounds to be administered to man and to animals. Generally speaking, these substituents are chosen, on the one hand, in order to confer on the compounds adequate solubility in water so that these compounds can be administered in aqueous solution and, on the other hand, in order to confer on these compounds a tolerability which is suitable for the human body.

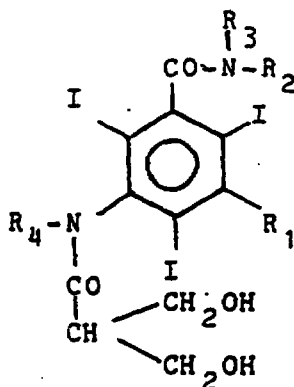
For this purpose, non-ionic structures have been proposed, that is to say iodobenzene derivatives possessing non-ionic substituents.

Thus, in the Patent FR-A-2 053 037, carbamoyl iodobenzene compounds containing a total of at least one N-hydroxy alkyl group and at least two hydroxyl groups were proposed.

A compound illustrative of this class is metrizamide which, however, has proved to be of limited stability.

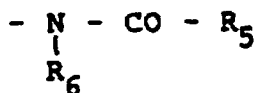
In European Patent Application 89 401 509.8, non-ionic compounds were proposed which are well tolerated by the human body and which exhibit good stability in aqueous solution.

These compounds correspond to the formula:



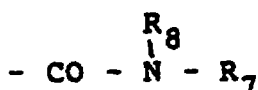
in which

R₁ represents a group of formula



R₅ representing a C₁-C₄ alkyl group, a C₁-C₄ hydroxyalkyl group or a C₁-C₄ polyhydroxyalkyl group,

R₆ representing a hydrogen atom, a C₁-C₄ alkyl group, a C₁-C₄ hydroxyalkyl group or a C₁-C₄ polyhydroxyalkyl group,
5 or a group of formula



R₇ representing a C₁-C₄ hydroxyalkyl group or a C₁-C₄ polyhydroxyalkyl group

10 R₈ representing a hydrogen atom or a C₁-C₄ alkyl group

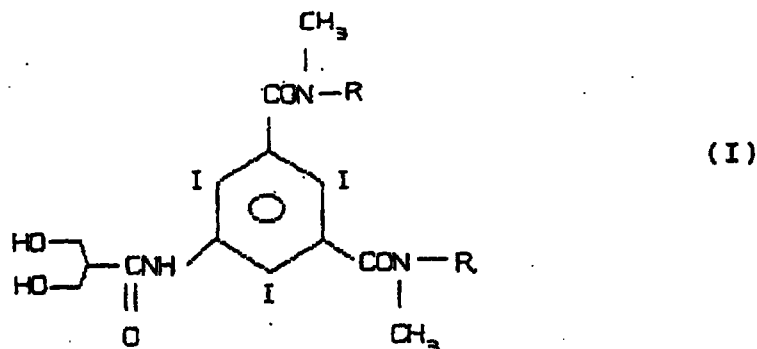
R₂ represents a hydrogen atom, a C₁-C₄ hydroxyalkyl group or a C₁-C₄ polyhydroxyalkyl group,

R₃ represents a hydrogen atom or a C₁-C₄ alkyl group, and

15 R₄ represents a hydrogen atom, a C₁-C₄ alkyl group, a C₁-C₄ hydroxyalkyl group or a C₁-C₄ polyhydroxyalkyl group.

The aim of the present invention is to provide novel compounds belonging to the family of the compounds of formula I, which are characterized by both good stability and good solubility in aqueous medium.
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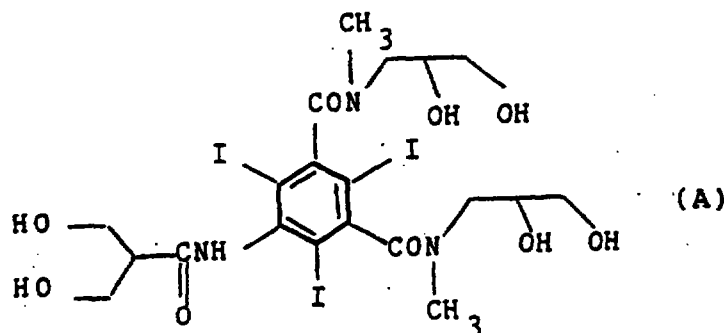
The compounds according to the invention correspond to the following general formula:



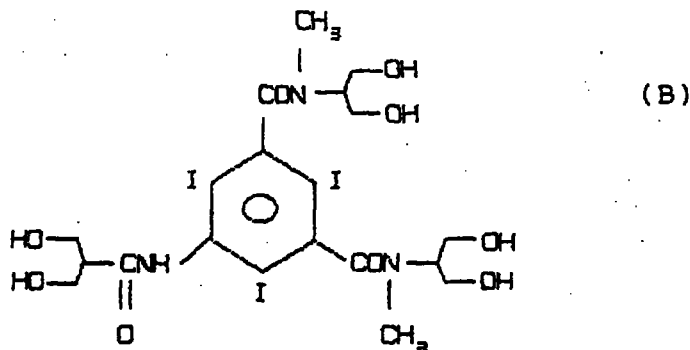
in which R represents the 2,3-dihydroxypropyl group or

the 1,3-dihydroxy-2-propyl group.

One of the compounds according to the invention is 5-[3-hydroxy-2-(hydroxymethyl)propionamido]-N,N'-dimethyl-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide, that is to say the compound of formula



The other compound according to the invention is 5-[3-hydroxy-2-(hydroxymethyl)propionamido]-N,N'-dimethyl-N,N'-bis(1,3-dihydroxy-2-propyl)-2,4,6-triiodoisophthalamide corresponding to the formula below:



10 These formulae cover not only the racemates but also all of the stereoisomers associated with the presence of asymmetric carbon and with the prevention of rotation of certain bonds owing to the steric hindrance contributed by the iodine atoms.

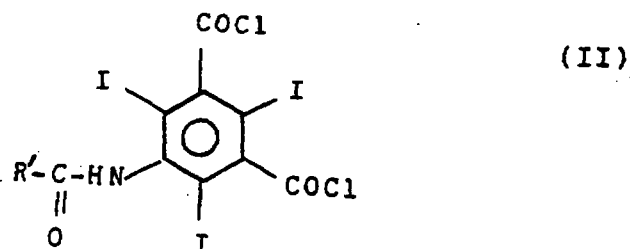
15 Unexpectedly, the compound of formula A is characterized by a better solubility in aqueous medium than the compound of Example 1 of the European patent application mentioned above, namely 5-[3-hydroxy-2-(hydroxymethyl)-N-(2,3-dihydroxypropyl)propionamido]-N',N''-bis(2-hydroxyethyl)-2,4,6-triiodoisophthalamide.

20 Furthermore, the compounds according to the invention possess the advantage, compared with the

compound of Example 1 of the patent application mentioned above, of being more readily accessible insofar as they do not require a final N-alkylation step which poses problems of purification on the industrial scale.

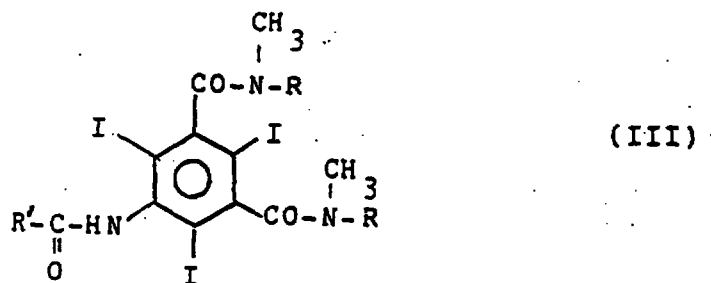
5 The compounds according to the invention may be obtained according to a process consisting in:

a) reacting a diacyl chloride of formula:



R' denoting a $-\text{CH}-(\text{CH}_2\text{OH})_2$ group in which the hydroxyl groups are protected,

10 with an amine chosen from 1-(N-methylamino)propane-2,3-diol and 2-(N-methylamino)propane-1,3-diol, so as to obtain a compound of formula



and b) removing the protecting groups of the group R'.

15 The compounds of formula II are described in FR-A-2 632 304.

The present invention also relates to contrast media which comprise at least the compounds according to the invention.

20 These contrast media are used in man and in animals for radiological purposes.

The preferred pharmaceutical form of the contrast media according to the invention consists of aqueous solutions of the compound.

25 The aqueous solutions generally contain a total of 5 to 100 g of compound according to the invention per

100 ml and the injectable quantity of such solutions may generally vary from 1 to 1000 ml.

The aqueous solutions of the compounds according to the invention may also contain certain additives such as:

- sodium chloride at concentrations between 0.1 and 10 mM

- disodium EDTA at concentrations between 0.1 and 2 mM

- sodium citrate at concentrations between 0.1 and 10 mM

- heparin at doses between 10 and 100 units per 100 ml of solution.

These compositions may be administered by all routes conventionally used for iodinated non-ionic contrast media. Thus, they may be administered via the enteral or parenteral route (intravenous or intra-arterial route, opacification of the cavities) and in particular into the subarachnoid space.

An example of a composition according to the present invention will be given below.

Composition

Compound A according to the invention 65 g

Water for injectable preparation

QS 100 ml

The examples which follow illustrate the preparation of the compounds according to the invention.

EXAMPLE 1

Preparation of 5-[3-hydroxy-2-(hydroxymethyl)propionamido]-N,N'-dimethyl-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide.

a) Preparation of [2-isopropyl-1,3-dioxane-5-carboxamido]-N,N'-dimethyl-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide.

74 g (98 mmol) of 5-[2-isopropyl-1,3-dioxane-5-carboxamido]-2,4,6-triiodoisophthaloyl dichloride are suspended in 300 ml of isopropanol containing 41 ml (294 mmol) of triethylamine. 31 g (295 mmol) of N-methylaminopropane-2,3-diol are added dropwise. Stirring is

maintained for 12 h at room temperature. The triethylamine hydrochloride is removed by filtration.

The filtrate is evaporated to dryness and the residue is taken up in water and eluted from OH⁻ resin
5 IRA 67.

After evaporation, the product is purified by passage through silanized silica (Kieselgel 60 Merck) with water as eluent.

After evaporation to dryness, 60 g of a white
10 powder are recovered in a yield of 68.5 %.

Iodine determination: 96.4 %

HPLC purity: 97 % Hypersil CB 25 cm 5 μ m
NaH₂PO₄ 0.01 M 60
Methanol 40

15 TLC SiO₂, Rf. 0.12
0.25
0.30 0.36

Eluent CHCl₃ 55, MeOH 30, NH₃H₂O 10

NMR (DMSO) ¹H 200 MHz

20 0.9 ppm (doublet) CH₃ (6H); 2.8 ppm (singlet) N-CH₃ (3H);
3 ppm (singlet) N-CH₃ (3H); 3.3 ppm (multiplet) N-CH₂ and
CH (5H); 3.5-3.9 ppm (multiplet) CH₂ and CH (8H); 4.3 ppm
(quartet) CH (3H); 4.6 ppm (triplet) OH (2H); 4.7 ppm
(doublet) OH (2H); 10.2 ppm (broad multiplet) NH (1H).

25 b) Preparation of 5-[3-hydroxy-2-(hydroxymethyl)-
propionamido]-N,N'-dimethyl-N,N'-bis(2,3-dihydroxy-
propyl)-2,4,6-triiodoisophthalamide.

45 g (50.6 mmol) of the compound described in a)
are dissolved in 101 ml (10 eq.) of 5 N hydrochloric
30 acid. Stirring is maintained for 12 h at room tempera-
ture. The solution is filtered and evaporated to dryness.
The solid obtained is taken up in 100 cm³ of ethyl ether
and then filtered off and eluted from silanized silica
(Kieselgel 60 Merck) with water. After evaporation to
35 dryness, 38 g of a white powder are recovered.

Yield = 90 %

Iodine determination = 98.3 %

HPLC purity $\geq$ 98 % Hypersil C8 25 cm 5 μ
NaH₂PO₄ 0.01 M 95

MeOH

5

TLC SiO₂, Rf. 0.56

0.63

0.67

5 Eluent CHCl₃ 55, MeOH 30, NH₃•H₂O 10

NMR (DMSO) ¹H 200 MHz

2.7 ppm (multiplet) CH (1H); 2.85 ppm (broad singlet) N-CH₃ (3H); 3.08 ppm (poorly resolved doublet) N-CH₃ (3H); 3.10-3.35 ppm (multiplet) N-CH₂; 3.45 ppm (quartet) CH₂ (4H); 3.6-4 ppm (multiplet) OH (6H); 9.9 ppm (multiplet) NH (1H).

EXAMPLE 2

Preparation of 5-[3-hydroxy-2-(hydroxymethyl-propionamido)-N,N'-dimethyl-N,N'-bis(1,3-dihydroxy-2-propyl)-2,4,6-triiodoisophthalamide]

a) Preparation of (2-isopropyl-1,3-dioxane-6-carboxamido)-N,N'-dimethyl-N,N'-bis(1,3-dihydroxy-2-propyl)-2,4,6-triiodoisophthalamide.

1.46 g (13.9 mmol) of N-methylaminopropane-1,3-diol (synthesized according to European Patent Application EP-A-025 083 filed by EPROVA A.G.) is dissolved in a mixture composed of 20 cm³ of N,N-dimethylacetamide and 2 cm³ (14.4 mmol) of triethylamine. 3.5 g (4.65 mmol) of 5-(2-isopropyl-1,3-dioxane-5-carboxamido)-2,4,6-triiodoisophthaloyl dichloride are added portionwise. Stirring is maintained for 3 hours at 30°C and then for 12 hours at room temperature. The triethylamine hydrochloride is removed by filtration.

The filtrate is evaporated to dryness and the residue is crystallized in a mixture composed of 20 cm³ of isopropanol and 200 cm³ of ethyl ether.

After filtration and drying, 3.6 g of a white powder are recovered in a yield of 87 %.

TLC SiO₂ Rf 0.16

0.28

Eluent: toluene 60 - methyl ethyl ketone 35 - formic acid 25.

NMR (DMSO) ¹H: 200 MHz.

0.9 ppm (doublet) CH₃ (6H); 1.7 ppm (multiplet) CH (1H);
2.7 ppm (singlet) N-CH₃ (3H) Z-isomer; 2.99 ppm (singlet)
N-CH₃ (3H) E-isomer; 3.4-4 ppm (multiplet) CH, CH₂ (15
H); 4.8 ppm (multiplet) CH₂OH (4H); 10.2 ppm (multiplet)
5 NH (1H).

b) Preparation of 5-[3-hydroxy-2-(hydroxymethyl-
propionamido]-N,N'-dimethyl-N,N'-bis(1,3-dihydroxy-2-
propyl)-2,4,6-triiodoisophthalamide.

3 g (3.4 mmol) of the compound described in a)
10 are dissolved in 10 cm³ (15 eq) of 5 N hydrochloric acid.
Stirring is maintained for 3 hours at 45°C and then for
12 hours at room temperature. The solution is evaporated
to dryness. The residue obtained is taken up in 50 cm³ of
ethyl ether, filtered off and then dissolved in 50 cm³ of
15 water, before being eluted from an H⁺ resin (IRN 77) and
an OH⁻ resin (IRA 68).

After evaporation to dryness, 1.7 g of a white
powder are recovered in a yield of 60.7 %.

Iodine purity: 98.4 %
20 TLC SiO₂ Rf 0.26
0.33
0.45

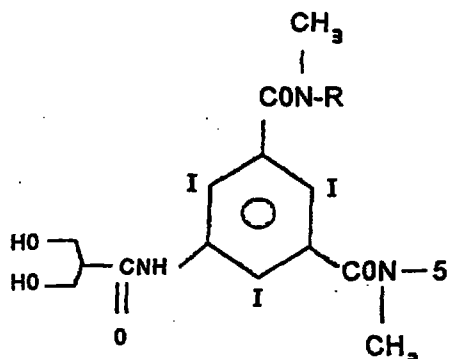
Eluent: butanol 50, water 25, acetic acid 11.

NMR (DMSO) ¹H 200 MHz.
25 2.7 ppm (broad singlet) N-CH₃ (3H), Z-isomer; 3 ppm
(broad singlet- N-CH₃ (3H), E-isomer; 3.3-4.05 ppm
(poorly resolved multiplet) CH, CH₂OH (15 H); 4.45 ppm
(poorly resolved multiplet) CH₂OH (6 H); 9.8 ppm
(multiplet) NH (1H).

30 NMR (DMSO) ¹³C 200 MHz.
170.6 ppm (2 C); 172 ppm (1 C); 149 ppm (C_{Ar}-C);
145 ppm (C_{Al}-NH); 100-98-90 ppm (C_{Ar}-I); 61-57-52 ppm
(C-H); 59.1-59.9 ppm (CH₂-OH); 32.8-30.1 ppm (CH₃-N).

CLAIMS for the Contracting States AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE, GR

1. Compounds corresponding to the general formula:



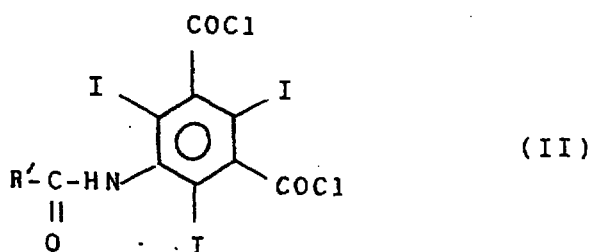
in which R is chosen from 2,3-dihydroxypropyl and 1,3-dihydroxy-2-propyl groups.

2. 5-[3-Hydroxy-2-(hydroxymethyl)propionamido]-N,N'-dimethyl-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoiso-phthalamide.

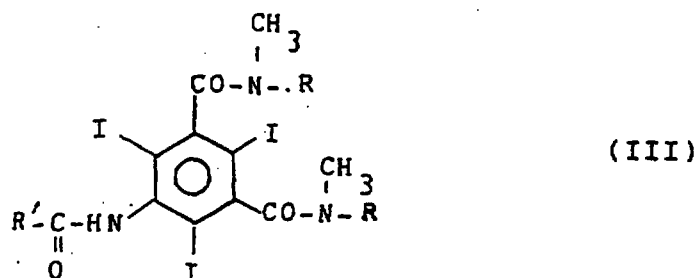
3. 5-[3-Hydroxy-2-(hydroxymethyl)propionamido]-N,N'-dimethyl-N,N'-bis(1,3-dihydroxy-2-propyl)-2,4,6-triiodo-isophthalamide.

4. Process for the preparation of a compound according to Claim 1, consisting in

a) reacting a diacyl chloride of formula:



15 R' denoting a $-\text{CH}-(\text{CH}_2\text{OH})_2$ group in which the hydroxyl groups are protected, with an amine chosen from 1-(N-methylamino)-propane-2,3-diol and 2-(N-methylamino)-propane-1,3-diol, so as to obtain a compound of formula



and

b) removing the protecting groups of the group R'.

5. Contrast medium, characterized in that it contains at least one compound according to Claim 1.

5 6. Contrast medium, characterized in that it contains at least the compound of Claim 2.

7. Contrast medium, characterized in that it contains at least the compound of Claim 3.

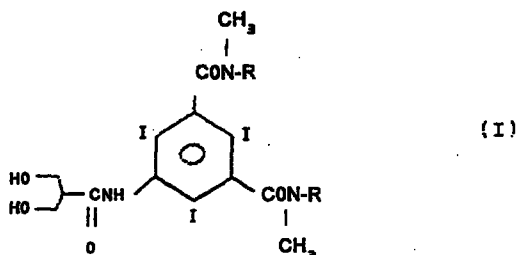
8. Contrast medium according to Claim 6, characterized in that it consists of an aqueous solution of the compound.

9. Contrast medium according to Claim 7, characterized in that it consists of an aqueous solution of the compound.

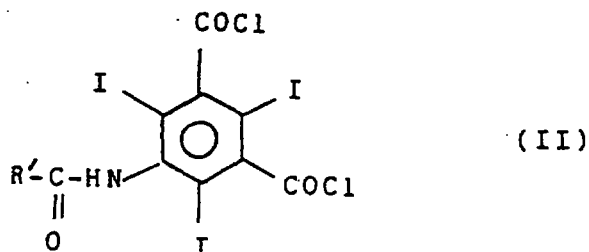


CLAIMS for the Contracting States: ES

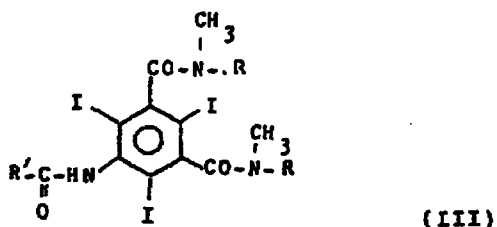
1. Process for the preparation of a compound corresponding to the general formula:



in which R is chosen from 2,3-dihydroxypropyl and 1,3-dihydroxy-2-propyl groups, consisting in
5 a) reacting a diacyl chloride of formula:



R' denoting a $-\text{CH}-(\text{CH}_2\text{OH})_2$ group in which the hydroxyl groups are protected,
with an amine chosen from 1-(N-methylamino)-propane-2,3-diol and 2-(N-methylamino)-propane-1,3-diol, so as to
10 obtain a compound of formula



and b) removing the protecting groups of the group R'.

2. Process for the preparation of a contrast medium, characterized in that a compound of formula I as defined
15 in Claim 1 is placed in a form which may be administered.

3. Process according to Claim 2, characterized in

that the compound is placed in the form of an aqueous solution.

