

--6398M Description of the industrial invention having title:

FM/st **"A PROCESS FOR THE PREPARATION OF (S)-N,N'-BIS[2-HYDROXY-1-(HYDROXYMETHYL)ETHYL]-5-[(2-HYDROXY-1-OXOPROPYL)AMINO]-2,4,6-TRIIODO-1,3-BENZENEDICARBOXAMIDE"**

In the name of: **BRACCO S.p.A.**

MI2000A 002601

Seating in: Milan

Seal of the Chamber of Commerce
Industry, Trade and Handicraft,
December 1, 2000 - Milan

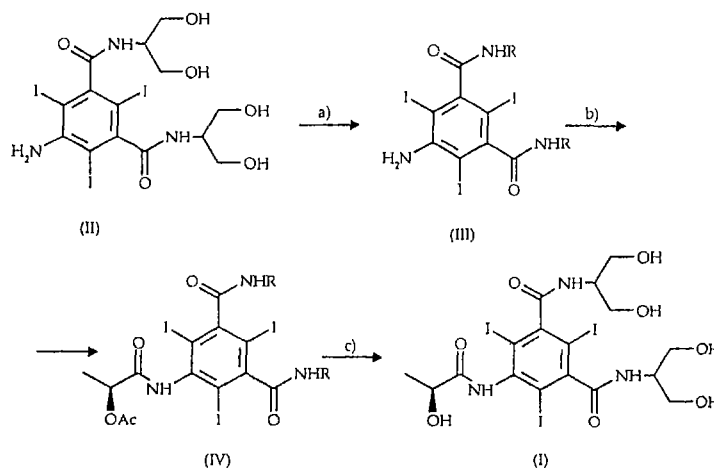
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The present invention relates to a process for the preparation of (S)-N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2-hydroxy-1-oxopropyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (I), starting from 5-amino-N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]2,4,6-triiodo-1,3-benzenedicarboxamide according to Scheme 1.

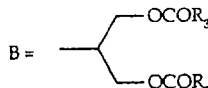
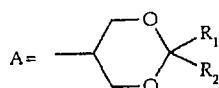


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Scheme 1



wherein R is a group of formula A or B



wherein R₁ and R₂, which are the same or different, are hydrogen, a C₁÷C₄ alkyl or an OR₄ group, wherein R₄ is a straight or branched C₁÷C₄ alkyl

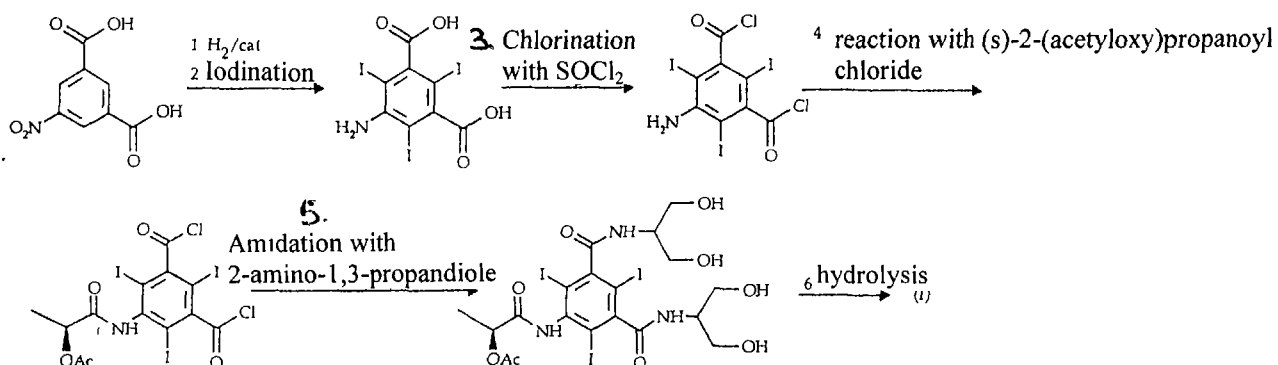


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group;

R_3 is a straight or branched $C_1 \div C_4$ alkyl group.

The compound of formula (I), which is known as Iopamidol, is one of the most widely employed non-ionic radiographic contrast agents in the world and it was first described in GB1472050, where its synthesis by the process outlined in the following Scheme has been reported:

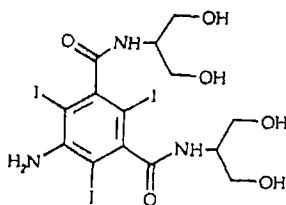


The above process, although quite effective, can be improved from the industrial point of view, especially as regards the environment protection, in particular avoiding the use of thionyl chloride, which is normally used in large amounts.

An advantageous process for the preparation of the compound of formula (I) has now been found.

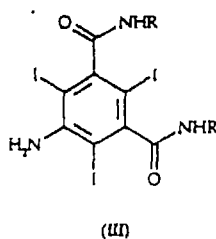
The process of the invention comprises:

a) protecting the hydroxy groups of compound (II)

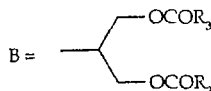
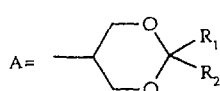


(II)

with a suitable protecting agent, to give the compounds of formula (III),



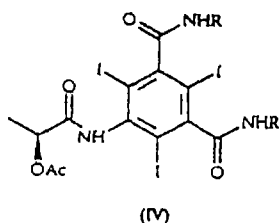
wherein R is a group of formula A or B



wherein R₁ and R₂, which are the same or different, are hydrogen, a C₁-C₄ alkyl or a OR₄ group, wherein R₄ is a straight or branched C₁-C₄ alkyl group;

R₃ is a straight or branched C₁-C₄ alkyl group;

b) acylating the amino group in position 5 of the compound of formula (III), by reaction with at least one mol of (*S*)-2-(acetyloxy)propanoyl chloride to give the compounds of formula (IV)



wherein R is as defined above;

c) hydrolysis of the protecting groups present on the hydroxy groups of the compound of formula (IV).

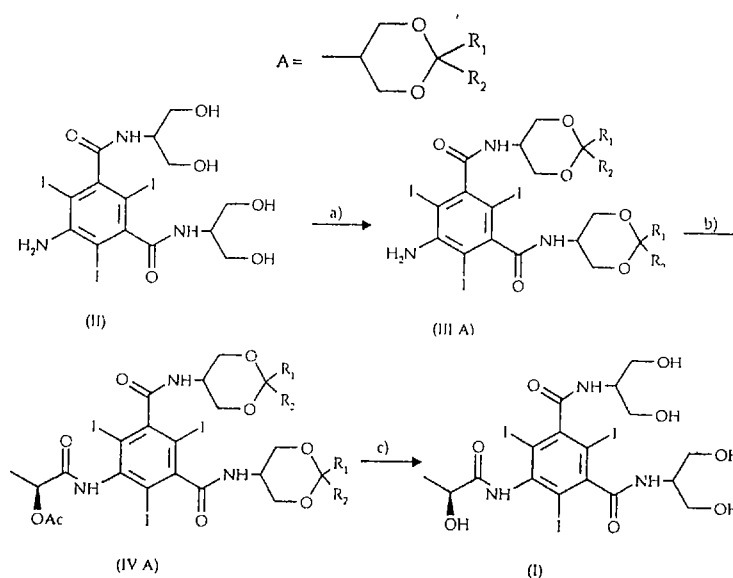
The preparation of the compound of formula (II), which is an intermediate for the preparation of (III), can be carried out by known methods, as disclosed in GB 1472050, CH 627653 or US 5,278,311.

Preferred methods for the preparation of the compound of formula (II) are those disclosed in GB 1472050 and CH 627653, not providing the use of chlorinating agents such as thionyl chloride, which causes environmental problems.

The preparation of (III) is carried out by reaction of compound (II) with a reactant such as an aldehyde or a ketone, even in the corresponding acetal or ketal forms, an anhydride or an orthoester to selectively protect the hydroxy groups.

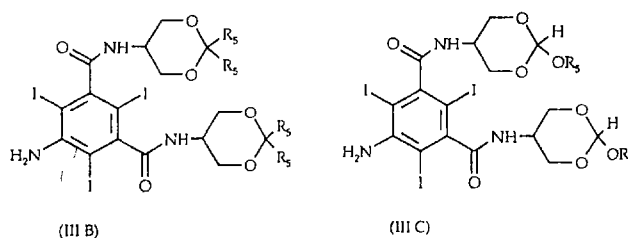
When R represents a group of formula A, the preparation of compound (I) is carried out according to Scheme 2,

Scheme 2

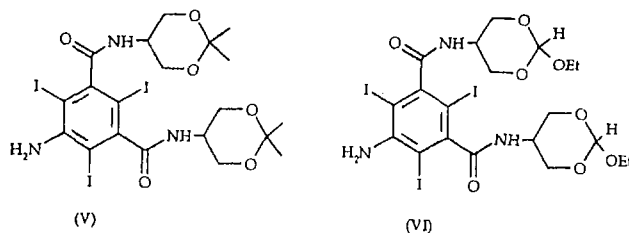


wherein step a) is carried out as described above.

Preferred compounds of formula (III A) are those of general formula (III B) and (III C), wherein R₅ represents a straight or branched C₁-C₄ alkyl group;



Among the compounds of general formula (III B), particularly preferred is the compound of formula (V) 5-amino-*N,N'*-bis(2,2-dimethyl-1,3-dioxan-5-yl)-2,4,6-triiodo-1,3-benzenedicarboxamide, wherein R_5 is methyl; among the compounds of general formula (III C), the compound of formula (VI) 5-amino-*N,N'*-bis(2-ethoxy-1,3-dioxan-5-yl)-2,4,6-triiodo-1,3-benzenedicarboxamide in which R_5 is ethyl.



The reaction conditions in the preparation of the compounds of formula (III) depend on the protecting group employed. For the preparation of compounds of formula (III A) (Scheme 2), step a) is carried out employing from about 2 to 3 mol of the corresponding protecting agent per mol of compound (II), in the presence of an aprotic dipolar solvent or of a mixture of inert solvents.

In particular, in the preparation of the compounds of formula (III A) an acidic catalyst will be preferably used, in amounts of 0.1÷2 mol per mol of (II); suitable acids that can be employed in this step are strong acids, such as sulfuric, methanesulfonic, *p*-toluenesulfonic and hydrochloric acid, or carboxylic acids, such as formic, acetic, or propionic acid.

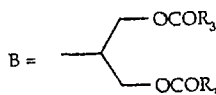
The preferred employed reagents among those used in step a) of the reaction of the compound of formula (III B) are dialkylketons of formula $(R_5)_2C=O$ or the corresponding ketals of formula $(R_5)_2C(OR_6)_2$, or dialkylketones $(R_5)_2C=O$ together with alkyl orthoformate of formula $HC(OR_4)_3$; in the case of compounds of formula (III C), alkyl orthoformate

HC(OR₅)₃ wherein R₅ and R₆, which are the same or different, are a C₁-C₄ straight alkyl group. Said reactants are generally used in amounts of at least two mol per mol of compound (II), under anhydrous conditions. The presence of water can indeed promote the hydrolytic degradation of the solvent.

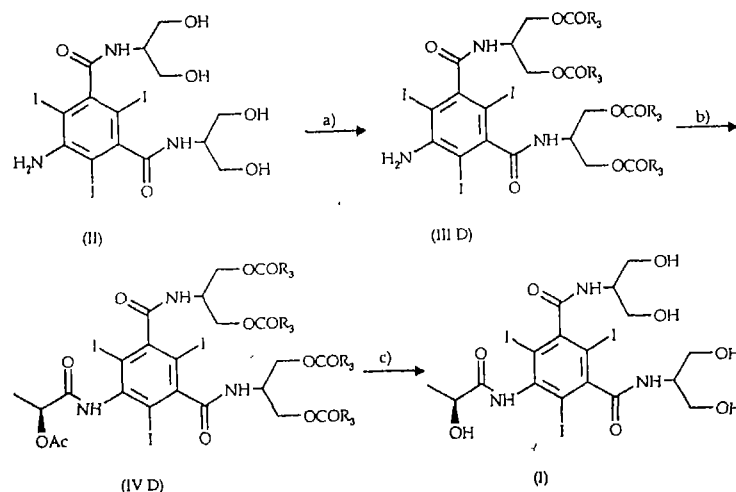
Step a) occurs at a temperature ranging from 5÷50°C and with a completion time from 5 minutes to 30 hours, depending on the reactant and the employed conditions.

Particularly preferred for the hydroxy protection is 2,2-dimethoxypropane or acetone in the presence of alkyl orthoformate to dry the reaction medium, so as to obtain the compound of formula (V), or in the presence of ethyl orthoformate so as to obtain the compound of formula (VI). The preparation of compound (V) is preferably carried out by dropping a solution of (II) into *N,N*-dimethylacetamide and 0.1 mol of sulphuric acid and 3 mol of 2,2-dimethoxypropane per mol of compound (II) at a temperature of 25°C. Analogously, the preferred preparation of compound (VI) is carried out by dropping a solution of (II) in *N,N*-dimethylacetamide and 0.1 mol of methansulphuric acid and 2.2 mol of triethyl orthoformate per mol of (II) at a temperature of 25°C. Upon completion of the formation reaction of (V) and (VI), and after neutralisation of the acid catalyst and concentration of the obtained solution to residue, the isolation of the two products is carried out by crystallisation from a 5% NaHCO₃ aqueous solution, and then from ethanol and from water.

When according to Scheme 1 R represents a group B, the preparation of compound (I) is carried out according to Scheme 3.

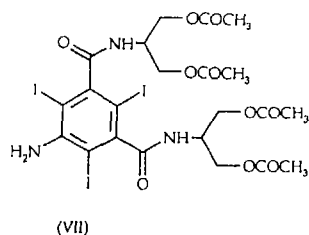


Scheme 3



wherein R_3 preferably represents a straight $\text{C}_1\div\text{C}_4$ alkyl group.

5-Amino-*N,N*-bis[2-acetoxy-1-(acetoxymethyl)ethyl]-2,4,6-triiodo-1,3-benzendicarboxamide of formula (VII) in which R_3 is methyl, is particularly preferred.



The reaction of step a) in Scheme 3 is usually carried out using at least four mol of the corresponding protecting agent per mol of compound (II), preferably in the presence of an aprotic dipolar solvent, of pyridine or of a mixture of inert solvents.

In case of compound (VII), the protection of the hydroxy groups of compound (II) is carried out by reaction with acetic anhydride in pyridine, preferably at a temperature of $10\div60^\circ\text{C}$, in anhydrous pyridine for 2 to 22 hours, depending on the conditions employed. The product is isolated from the mixture of the final reaction by precipitation, after dilution with water.

Step b) consists in the acylation reaction of the primary amino group of

the compound of formula (III), with at least 1 mol of (*S*)-2-(acetyloxy)propanoyl chloride to give the compounds of formula (IV).

The reaction is usually carried out in an inert dipolar aprotic solvent such as *N,N*-dimethylacetamide, *N,N*-dimethylformamide, *N*-methyl-2-pyrrolidone and in presence of an acid such as hydrohalic acid that can be introduced as the salts of the corresponding dipolar aprotic solvent or as acid as such, for example by bubbling the anhydrous hydrogen chloride gas.

Preferably, the hydrohalide acid is added as anhydrous gas and in an amount of from about 0.1 to about 0.4 mol per mol of product of formula (III), or in the form of a salt of the corresponding aprotic dipolar solvent such as *N,N*-dimethylacetamide hydrochloride.

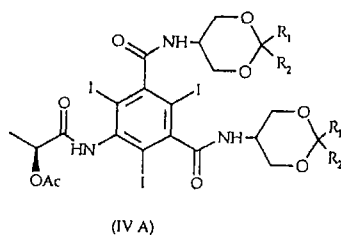
The temperature is generally comprised between about 5 and about 60 °C and the reaction time is comprised between 2 and about 20 hours, depending on the solvent employed and the reaction conditions adopted.

The reaction is preferably carried out in *N,N*-dimethylacetamide and at a temperature ranging from 25 and 50°C.

Step b) of Scheme 1 can also be carried out as disclosed in US 5,672,735.

In the following step c), in accordance with Schemes 1, 2 and 3, the deprotection reaction of the hydroxy groups depends on the type of compound of formula (IV).

In particular, compounds of formula (IV A),



are hydrolysed in two separate phases, initially operating at acid pH and then at basic pH.

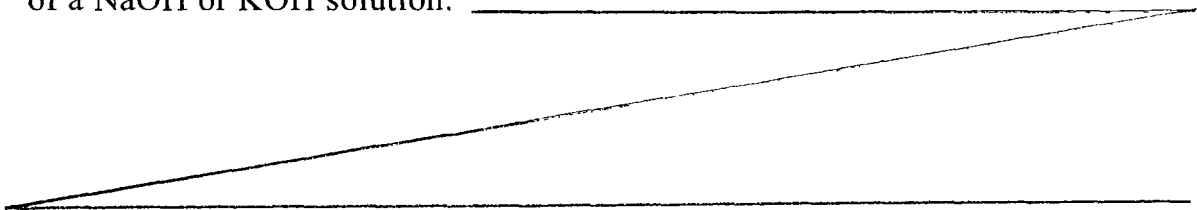
The starting deprotection and hydrolysis phase is generally carried out by addition of a strong cation exchange resin, preferably Duolite C20MB, Amberlite IR120 or Amberjet 1200 (Rohm & Haas) or of an aqueous solution of a strong acid, e.g. hydrochloric or sulfuric acid, in amounts of from 0.2 to 0.4 mol per mol of (IV A).

The deprotection reaction of compound (IV A) is generally carried out in aqueous or hydroalcoholic solution or in the presence of an aprotic dipolar solvent such as *N,N*-dimethylacetamide, *N,N*-dimethylformamide or *N*-methyl-2-pyrrolidone diluted with water.

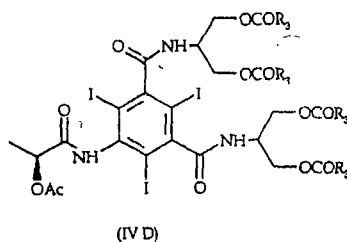
The temperature is generally comprised between 40 °C and 55 °C, and is typically complete in 2 to 5 hours depending on the reaction conditions employed.

In the following deprotection of the compounds of general formula (IV A) a basic hydrolysis, in the presence for example of NaOH or KOH, allows the hydrolysis of the acetoxy group, present in the compound of formula (IV A) to give compound (I), final product of the whole process.

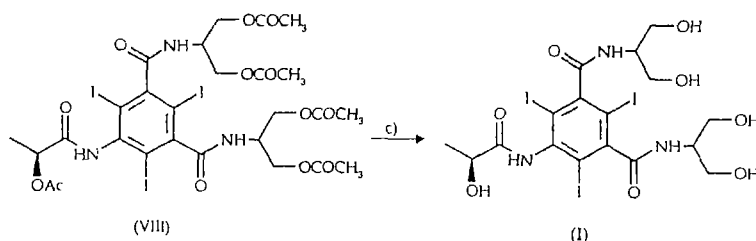
This second step of the hydrolysis reaction is generally carried out in aqueous or hydroalcoholic solution or in the presence of an aprotic dipolar solvent and at a temperature comprised between 15 and 60°C, at a pH comprised between 10 and 11, which is maintained by the following additions of a NaOH or KOH solution.



For compounds of formula (IV D)



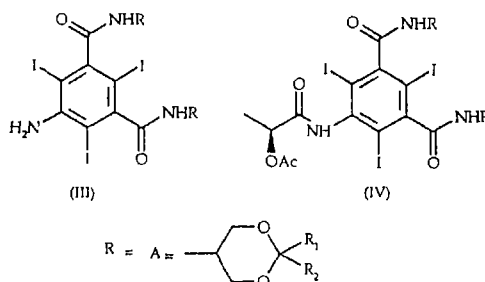
and in particular for the compound of formula (VIII) in which R₃ is methyl, the hydrolysis reaction is carried out in a single step and at basic pH.



In this case, the hydrolysis conditions are similar to those previously described relating to the hydrolysis at basic pH of compounds of general formula (IV A).

The isolation of the compound of formula (I) from the obtained solution usually takes place after purification of the same with ionic exchange resins and / or nanofiltration on membranes, as disclosed for example in US 5,811,581 and EP 888190 and with a final crystallisation of the product (I) as disclosed for example in US 5,571,941.

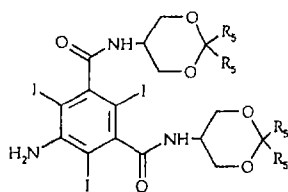
Compounds of general formulae (III) and (IV)



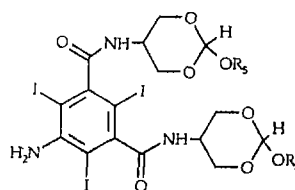
in which R corresponds to A and R₁ and R₂ have the meanings defined

above are a further object of the present invention.

Preferred compounds of formula (III A) are the compounds of general formula (III B) and (III C), wherein R_5 is a straight $C_1 \div C_4$ alkyl group.

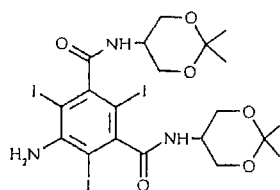


(III B)

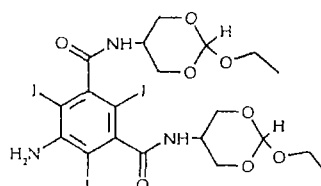


(III C)

The compound of formula (V) wherein R_5 is methyl and the compound of formula (VI) wherein R_5 is ethyl are particularly preferred.

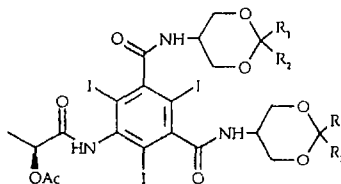


(V)



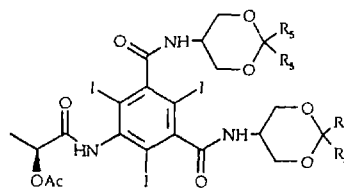
(VI)

Preferred compounds of formula (IV) are the compounds of formula (IV A), wherein R_1 and R_2 are as defined above.

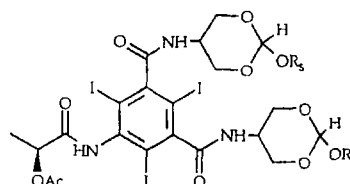


(IV A)

Particularly preferred compounds of formula (IV A) are compounds (IV B) and (IV C) wherein R_5 corresponds to a straight $C_1 \div C_4$ alkyl group.

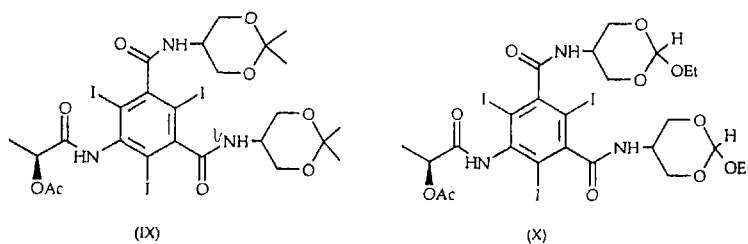


(IV B)



(IV C)

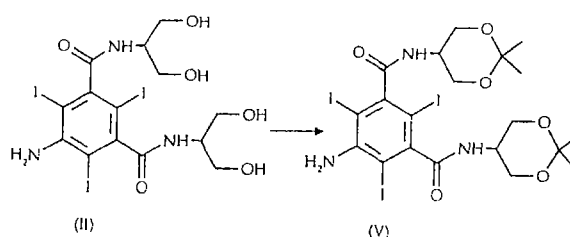
More preferred compounds are those of formula (IX) and, among the compounds of formula (IV C), compound (X).



The following examples illustrate the invention in further detail.

Example 1

Preparation of 5-amino-*N,N'*-bis(2,2-dimethyl-1,3-dioxan-5-yl)-2,4,6-triiodo-1,3-benzenedicarboxamide (V)



2,2-Dimethoxypropane (9.5 mL, 77.8 mmol) and sulfuric acid (0.25 g, 2.6 mmol) are dropped into a 0.5 L flask containing a solution of the compound of formula (II) (18.3 g, 25.9 mmol) (prepared as described in GB1472050) in dimethylacetamide (90 mL) under stirring. After 20 hours under stirring at 25°C the solution is neutralised with NaHCO₃ and concentrated under vacuum. Acetone (250 mL) and 3 % aq. NaHCO₃ (50 mL) are then added to the obtained oily residue and the solid is recovered by filtration and crystallized from 70% ethanol to give the compound of formula (V) (13 g, 16.5 mmol after drying).

Yield: 64 %

The ¹H-NMR, ¹³C-NMR, IR and MS are consistent with the indicated structure.

Example 2

Alternative preparation of the compound of formula (V)

25 g of compound (II) (35.5 mmol) (prepared as disclosed in GB

1472050) are added to dimethylacetamide (100 mL) in a 1 L flask equipped with a thermometer and stirring, dropping and refrigerating means under reflux.

Acetone (500 mL) and sulphoric acid (0.4 g, 4 mmol) are added to the solution obtained by heating to 45°C, and triethyl orthoformate (14.3 g, 96.5 mmol) are dropped in 30 minutes at 23°C.

After 16 hours under reaction, the solution is neutralised with NaHCO₃. The solvent is concentrated under vacuum and the obtained oily residue is loaded on a reactor suitable for crystallisation and containing 4% aq. NaHCO₃ (350 mL).

The precipitated solid is filtrated and crystallised with 70% ethanol (200 mL).

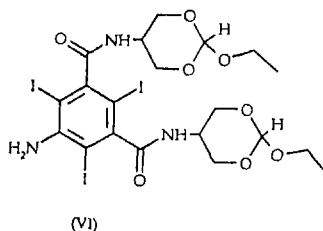
19.3 g of the solid product (24.6 mmol) are obtained with the described procedure.

Yield: 69 %

The ¹H-NMR, ¹³C-NMR, IR and MS are consistent with the indicated structure.

Example 3

Preparation of 5-amino-*N,N'*-bis(2-ethoxy-1,3-dioxan-5-yl)-2,4,6-triiodo-1,3-benzenedicarboxamide (VI)



Methanesulfonic acid (0.27 g, 2.8 mmol) and triethyl orthoformate (9.25 g, 62.4 mmol) are dropped in 1 hour into a 0.5 L 3-necked flask equipped with

a thermometer and stirring means containing a solution of the compound of formula (II) (20 g, 28.4 mmol) (prepared as described in GB1472050) in dimethylacetamide (150 mL) stirred at 25 °C. After 1 hour the solution is neutralised with NaHCO₃. The solvent is evaporated under vacuum and the oily residue obtained is taken up in a reactor suitable for the crystallisation and containing aq. 5 % NaHCO₃ (300 mL).

The solid thus obtained is filtered and crystallized twice from 70% ethanol.

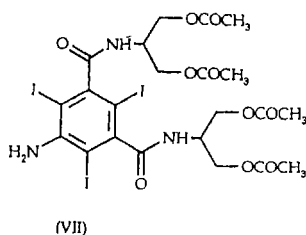
14.7 g of the solid product (18.7 mmol) are isolated with the described procedure after filtration and drying.

Yield: 66 %

The ¹H-NMR, ¹³C-NMR, IR and MS are consistent with the indicated structure.

Example 4

Preparation of 5-amino-*N,N'*-bis[2-acetoxy-1-(acetoxymethyl)ethyl]-2,4,6-triiodo-1,3-benzenedicarboxamide (VII)



Acetic anhydride (9 mL, 95 mmol) is dropped into a suspension of the compound of formula (II) (7 g, 10 mmol) (prepared as described in GB1472050) in pyridine (40 mL) stirred at 25 °C. The solution is dropped and then stirred for 3 hours at the same temperature. The obtained solution obtained is added dropwise to deionized water (0.3 L) in a 1 L flask and the precipitate is recovered by filtration, washed with 5 % acetic acid aqueous solution, then

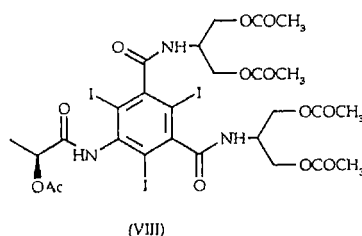
with deionized water, and finally dried under vacuum at the temperature of 40 °C for 12 hour to obtain 7.86 g (9 mmol).

Yield: 90 %

The ^1H -NMR, ^{13}C -NMR, IR and MS are consistent with the indicated structure.

Example 5

Preparation of (*S*)-*N,N'*-bis[2-acetoxy-1-(acetoxymethyl)ethyl]-5-[(2-acetoxy-1-(oxopropyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (VIII)



In a 0.5 L flask, the compound (VII) prepared as in Example 4 (11 g, 12,6 mmol) is dissolved in *N,N*-dimethylacetamide (200 mL) containing gaseous HCl (0.055 g, 1.5 mmol) and the solution is maintained at a temperature comprised between 15 and 17°C. (*S*)-2-(Acetyloxy)propanoyl chloride (4.75 g, 31.5 mmol) is dropped therein and the obtained solution is stirred at 23 °C for 20 hours. The solvent is then evaporated under vacuum and the oily residue is taken up with 4 % aq. NaHCO_3 (250 mL). The crystallised solid is recovered by filtration, washed and dried to 9.9 g (10 mmol).

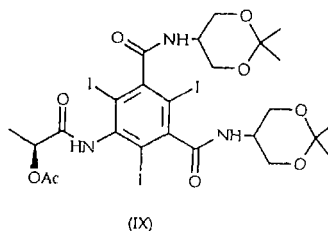
Yield: 80%

The ^1H -NMR, ^{13}C -NMR, IR and MS are consistent with the indicated structure.

Example 6

Preparation of (*S*)-5-[(2-acetyloxy-1-oxopropyl)amino]-*N,N'*-bis(2,2-

dimethyl-1,3-dioxan-5-yl)-2,4,6-triiodo-1,3-benzenedicarboxamide (IX)



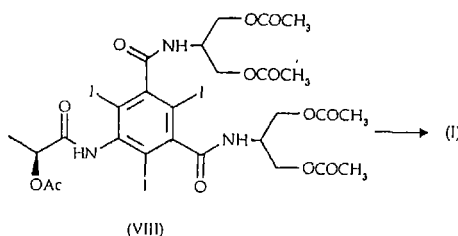
In a 0.5 L flask, the compound (V) prepared as in Example 1 (15 g, 19 mmol) is dissolved in dimethylacetamide (80 mL) containing HCl gas (0.073 g, 2 mmol). (*S*)-2-(Acetyloxy)propanoyl chloride (8 g, 53 mmol) is dropped over 30 min into the obtained solution cooled to 15 °C. After two hours at the same temperature, the reaction mixture is allowed to warm up to room temperature and stirred for additional 12 hours. The solvent is then evaporated under vacuum and the residue is taken up with 4 % NaHCO₃ (130 mL). The solid obtained is filtered, washed and dried to give the compound (IX) (14 g, 15,6 mmol).

Yield: 82 %

The ¹H-NMR, ¹³C-NMR, IR and MS are consistent with the indicated structure.

Example 7

Preparation of (*S*)-*N,N'*-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2-hydroxy-1-oxopropyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (I)



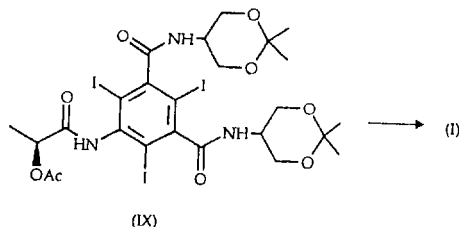
In a 0.1 L flask, a solution of compound (VIII) (4.9 g, 5 mmol) prepared as in Example 5 is admixed with deionized water (30 mL) and methanol (30 mL). The suspension is warmed to 50 °C, then 2M NaOH (12.8 mL) is dropped

therein over a period of 4 hours, keeping the pH of the mixture in the range of from 10 to 11. The obtained solution is passed through two ion exchange resin columns (cationic and anionic, respectively) and the neutral eluate is concentrated under vacuum by means of a rotavapor until a glassy residue is obtained. The following crystallisation from ethanol gives 2.8 g (3.6 mmol) of the solid product with a 72% yield.

The ^1H -NMR, ^{13}C -NMR, IR and MS are consistent with the indicated structure.

Example 8

Alternative preparation of (I)



0.2 M HCl (15 mL) is added to a solution of compound (IX) (9 g, 10 mmol) prepared as described in the Example 6, in methanol (60 mL), and the obtained mixture is stirred at 50 °C for 2 hours, and then cooled to 40 °C. 1M NaOH (14 mL in total) is then dropped therein to keep the pH between 10.5 and 11.

After two hours, the reaction mixture is cooled to room temperature and purified on two cationic and anionic exchange resins. The neutral eluate is concentrated and the oily residue is crystallized from ethanol (80 mL). The crystalline precipitate is filtered and dried to give the compound (I) (7 g, 9 mmol).

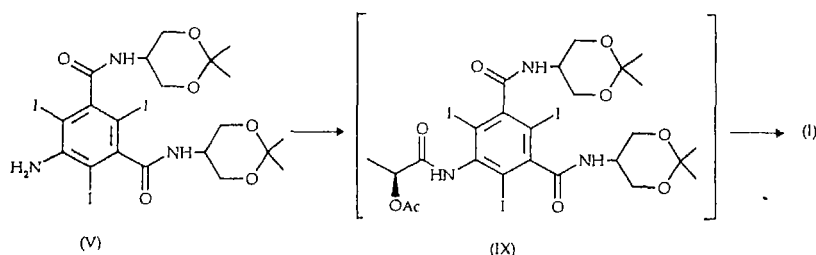
Yield: 90 %

The ^1H -NMR, ^{13}C -NMR, IR and MS are consistent with the indicated

structure.

Example 9

Alternative preparation (I)

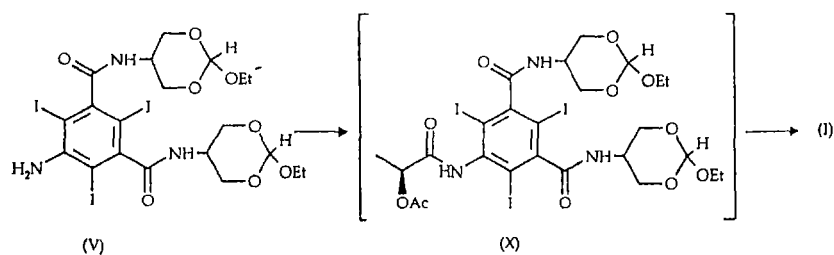


Compound (V), prepared as described in Example 1, is reacted as described in Example 6. Compound (IX) obtained from the reaction is not isolated, but directly deprotected according to the method described in Example 8 above to give the compound (I) with a global yield of 65 %.

The ^1H -NMR, ^{13}C -NMR, IR and MS are consistent with the indicated structure.

Example 10

Alternative preparation of (I)

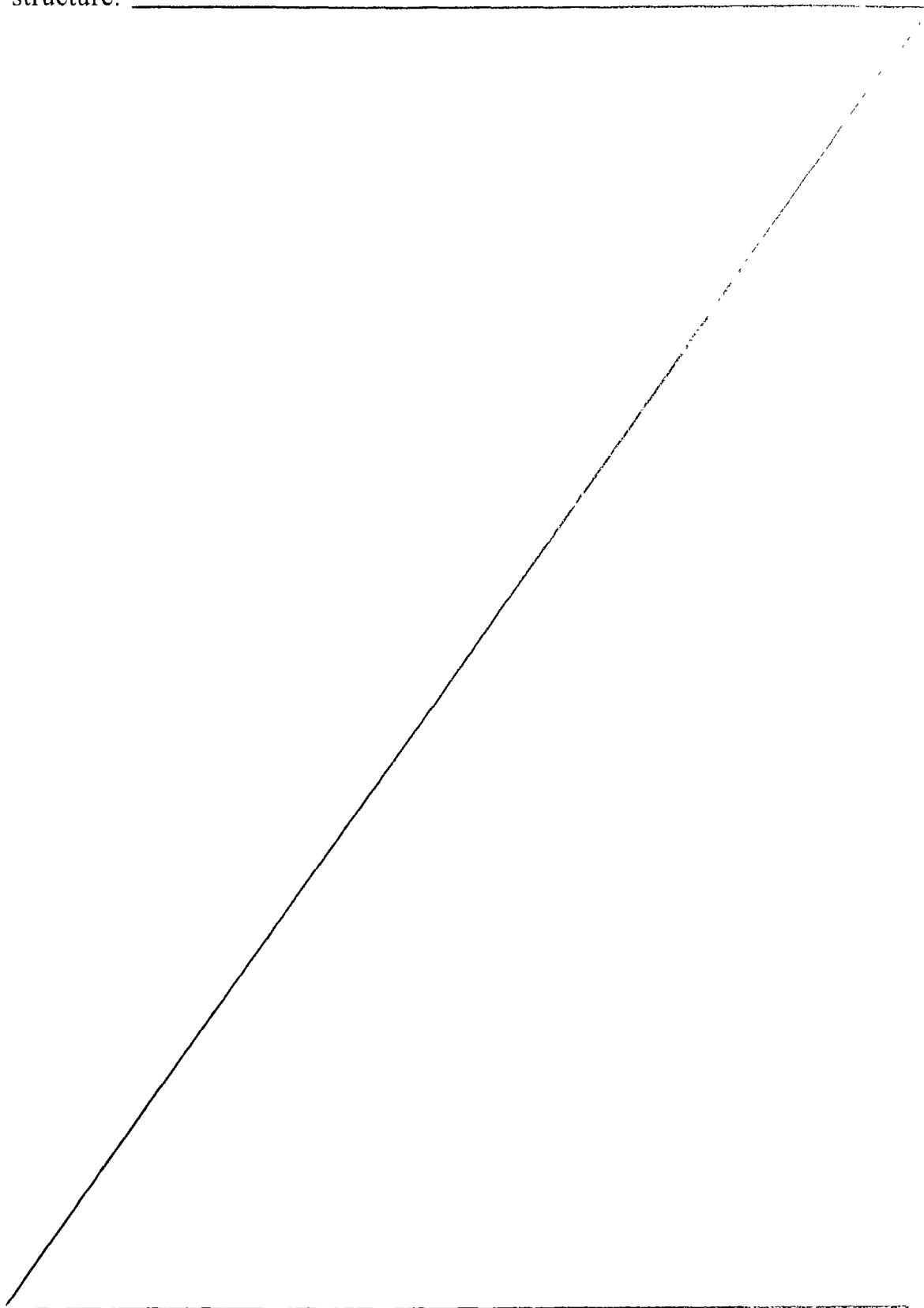


In a 250 mL flask, compound (V) (10 g, 12.2 mmol), prepared as described in example 3, is loaded with dimethylacetamide (50 mL) containing HCl gas (0.055 g, 1.5 mmol). (*S*)-2-(acetyloxy)propanoyl chloride (4 g, 26.6 mmol) is added to the solution, cooled to 15°C. After 15 hours at room temperature the solvent is evaporated under vacuum. The intermediate compound of formula (X) thus obtained is not isolated, but directly deprotected

following the procedure of Example 8 above.

Yield: 685 %

The ^1H -NMR, ^{13}C -NMR, IR and MS are consistent with the indicated structure.

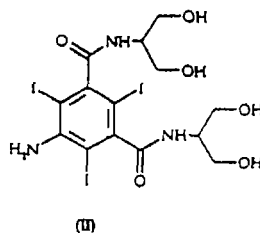


CLAIMS

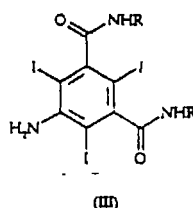
1. Process for the preparation of (*S*)-*N,N'*-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-5-[(2-hydroxy-1-oxopropyl)amino]-2,4,6-triiodo-1,3-benzenedicarboxamide (I)

which process comprises:

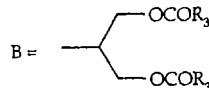
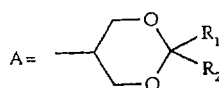
a) protection of the hydroxy groups of compound (II)



with a suitable protecting agent, to give the compounds of formula (III),



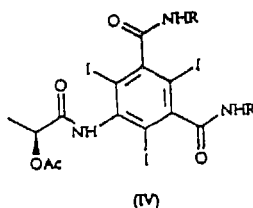
wherein R is a group of formula A or B



wherein R_1 and R_2 , which are the same or different, are hydrogen, a $C_1 \div C_4$ alkyl or OR_4 group, wherein R_4 is a straight or branched $C_1 \div C_4$ alkyl group;

R_3 is a straight or branched $C_1 \div C_4$ alkyl group;

b) acylating the amino group in position 5 of the compound of formula (III), by reaction with at least one mol of (*S*)-2-(acetyloxy)propanoyl chloride to give the compounds of formula (IV)

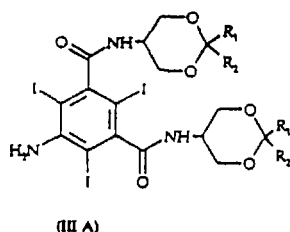


wherein R is as defined above;

c) hydrolysis of the protecting groups present on the hydroxy groups of the compound of formula (IV).

2. The process of claim 1 which comprises:

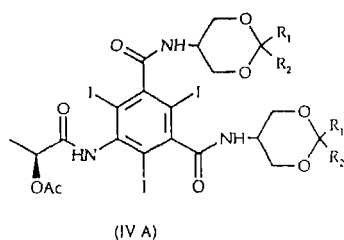
a) formation of the intermediate compounds of formula (III A)



wherein R is the group A,

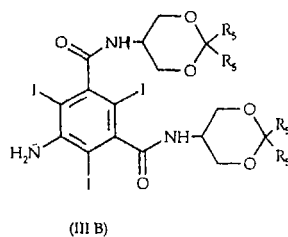
by reaction of the compounds of formula (II) with an amount of 2 to 3 mol of the corresponding protecting agent per mol of compound (II), in the presence of acid catalyst selected from sulfuric, methanesulfonic, *p*-toluenesulfonic, hydrochloride, formic, acetic and propionic acid, in amounts ranging from 0.1 to 2 mol per mol of compound (II).

b) acylation with at least one mol of (*S*)-2-(acetyloxy)propanoyl chloride to give the compounds of formula (IV A)



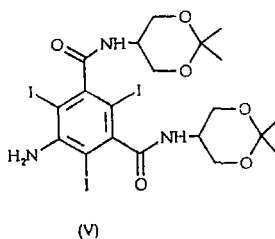
c) hydrolysis of the compounds of general formula (IV A) initially at acidic pH and then at basic pH.

3. The process of claim 2, wherein, in the intermediate compounds of formula (III B) is obtained



wherein R_1 and R_2 are R_5 , and wherein R_5 is a straight $C_1 \div C_4$ alkyl, by reaction of the compounds of formula (II) with dialkylketons of formula $(R_5)_2C=O$, ketales of formula $(R_5)_2C(OR_6)_2$, or with dialkylketons $(R_5)_2C=O$ in the presence of alkyl orthoformate of formula $HC(OR_4)_3$, wherein R_4 , R_5 and R_6 , which are the same or different, are a straight $C_1 \div C_4$ alkyl group, and in amounts of at least two mol per mole of compound (II), under anhydrous conditions.

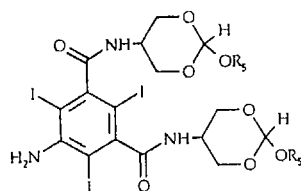
4. The process of claim 3 in which the compound of formula (V) 5-amino-*N,N'*-bis(2,2-dimethyl-1,3-dioxan-5-yl)-2,4,6-triiodo-1,3-benzenedicarboxamide is formed



wherein R_5 is methyl;

by reaction of the compound of formula (II) with 3 mol of 2,2-dimethoxypropane or acetone together with alkyl orthoformate and in the presence of 0.1 mol of sulphuric acid per mol of compound (II).

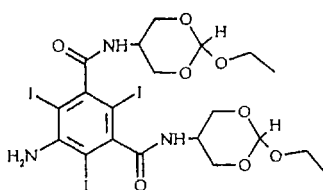
5. The process of claim 2, wherein the intermediate compound of formula (III C) is formed _____



(III C)

wherein R_1 is OH and R_2 is OR_5 , and wherein R_5 is a straight C_1-C_4 alkyl, by reaction of the compounds of formula (II) with alkyl orthoformate $HC(OR_5)_3$, in amounts of at least two mol per mol of compound (II), under anhydrous reaction conditions.

6. The process of claim 5, wherein the compound (VI) 5-amino-*N,N'*-bis(2-ethoxy-1,3-dioxan-5-yl)-2,4,6-triiodo-1,3-benzenedicarboxamide is formed



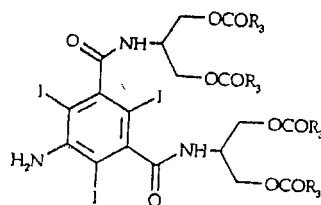
(VI)

wherein R_5 is ethyl,

by reaction of the compound of formula (II) with 2.2 mmol of triethyl orthoformate and in the presence of 0.1 mol of metansulphonic acid per mol of (II).

7. The process of claim 1 which comprises:

a) formation of the intermediate compounds of formula (III D),

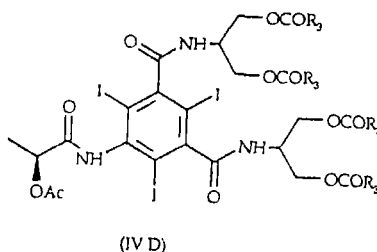


(III D)

wherein R is group B and R_3 is a straight or branched C_1-C_4 alkyl, by reaction

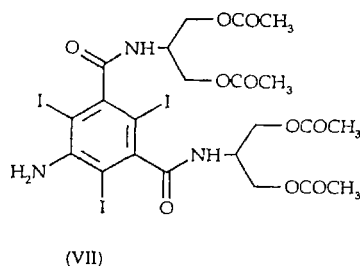
of the compounds of formula (II) with $(R_3CO)_2$, anhydride of the corresponding acid;

b) acylation with at least one mol of (*S*)-2-(acetyloxy)propanoyl chloride to give the compounds of formula (IV D)



c) basic hydrolysis of the compounds of formula (IV D).

8. The process of claim 7, wherein the compound of formula (VII) 5-amino-*N,N'*-bis(2-acetoxy-1(acetoxymethyl)ethyl]-2,4,6-triiodo-1,3-benzenedicarboxamide is formed,



wherein R_3 is methyl,

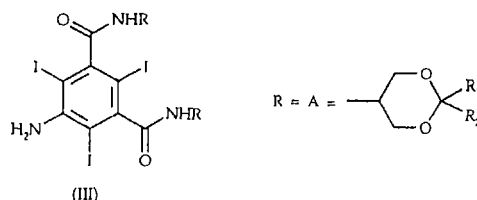
by acetylation reaction of the compound of formula (II) with acetic anhydride in piridine.

9. The process of claims 1-7, wherein step b) is carried out in a solvent selected from the group consisting of *N,N'*-dimethylacetamide, *N,N'*-dimethylformamide, *N'*-methyl-2-pyrrolidone and in the presence of an halohydric acid as such or in the form of the salt of the correspondent employed solvent, in amounts of $0.1 \div 0.4$ mol per mol of the product of formula (III).

10. The process as claimed in claims 2-6 and 9, wherein the first phase of step c) is carried out with a strong cationic exchange resin or with an aqueous solution of an acid selected from sulphoric acid and hydrochloric acid, in amounts of 0.2÷0.4 mol per mol of (IV A) and the second phase is carried out in aqueous solution, at a pH comprised between 10 and 11, by addition of an aqueous solution of a base selected from KOH and NaOH.

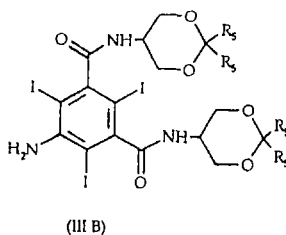
11. The process of claims 7, 8 and 9 in which the hydrolysis reaction of the compounds of formula (IV D) is carried out in a single step at basic pH.

12. Compounds of formula (III)



wherein R corresponds to the group A, R₁ and R₂, which are the same or different, are hydrogen, a straight or branched C₁÷C₄ alkyl or a OR₄.

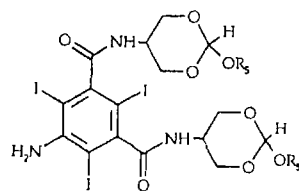
13. Compounds as claimed in claim 12, of formula (III B)



wherein R₁ and R₂ correspond to R₅, and wherein R₅ is a straight C₁÷C₄ alkyl group.

14. Compound as claimed in claim 13, corresponding to 5-amino-*N,N'*-bis(2,2-dimethyl-1,3-dioxane-5-yl)-2,4,6-triiodo-1,3-benzendicarboxamide.

15. Compounds as claimed in claim 12, of formula (III C),

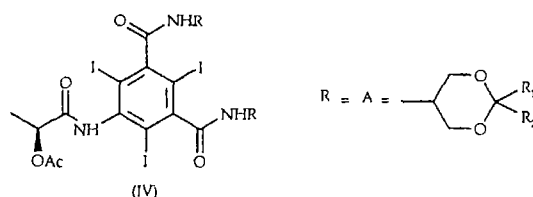


(III C)

wherein R_1 is H, R_2 is OR_5 and wherein R_5 is a straight $C_1 \div C_4$ alkyl group.

16. Compound as claimed in claim 15, corresponding to 5-amino-*N,N'*-bis(2-ethoxy-1,3-dioxane-5-yl)-2,4,6-triiodo-1,3-benzendicarboxamide.

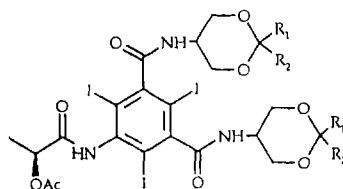
17. Compounds of formula (IV)



(IV)

wherein R corresponds to the group A, R_1 and R_2 , which are the same or different, are hydrogen, a straight or branched $C_1 \div C_4$ alkyl group or a OR_4 group wherein R_4 is a straight or branched $C_1 \div C_4$ alkyl.

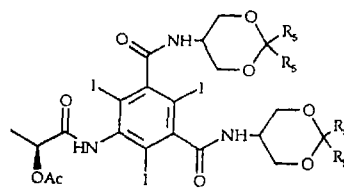
18. Compounds as claimed in claim 17, of formula (IV A),



(IV A)

wherein R_1 and R_2 are as defined above.

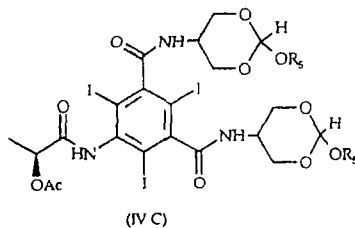
19. Compounds as claimed in claim 18, of formula (IV B),



(IV B)

wherein R_1 and R_2 correspond to R_5 and R_5 is a straight $C_1 \div C_4$ alkyl group.

20. Compounds as claimed in claim 18, of formula (IV C)



wherein R_1 is H, R_2 is OR_5 and R_5 is a straight $C_1 \div C_4$ alkyl group.

21. Compounds as claimed in claims 19 and 20, selected from the group consisting of:

(S)-5-[(2-acetyloxy-1-oxopropyl)amino]-N,N'-bis(2,2-dimethyl-1,3-dioxan-5-yl)-2,4,6-triiodo-1,3-benzendicarboxamide and

(S)-5-[(2-acetyloxy-1-oxopropyl)amino]-N,N'-bis(2-ethoxy-1,3-dioxan-5-yl)-2,4,6-triiodo-1,3-benzendicarboxamide.

22. Use of the compounds of formula (III) and (IV) of claims 12-21 as intermediates in the process according to claims 1-11.

Milan, December 1, 2000

The Agent
(Minoja Fabrizio)
of Bianchetti Bracco Minoja S.r.l.
(Signature)