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(21) International Application Number: PCT/US93/08056 (22) International Filing Date: 25 August 1993 (25.08.93) (30) Priority data: 07/939,266 2 September 1992 (02.09.92) US (71) Applicant: MALLINCKRODT MEDICAL, INC. [US/ US]; 675 McDonnell Boulevard, P.O. Box 5840, St. Louis, MO 63134 (US). (72) Inventors: KNELLER, Mills, T. ; 7314 Colgate Avenue, University City, MO 63130 (US). LIN, Youlin ; 333 Por- tico Court, Chesterfield, MO 63017 (US). WHEATLEY, James ; 5365A Knollwood Parkway Court, Hazelwood, MO 63042 (US).		(74) Agents: VACCA, Rita et al.; Mallinckrodt Medical, Inc., 675 McDonnell Boulevard, St. Louis, MO 63134 (US). (81) Designated States: AU, CA, JP, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i>
(54) Title: NONIONIC X-RAY CONTRAST AGENTS, COMPOSITIONS AND METHODS (57) Abstract Triiodinated isophthalamide derivatives, useful as X-ray contrast agents, having at least one amide group derived from the amino-alcohol, 3-(N-2-hydroxyethyl)-amino-1,2-propanediol, which provides high water solubility and low mammalian toxicity, and methods of preparing them. Methods of preparing 3-(N-2-hydroxy-ethyl)amino-1,2-propanediol are provided.		

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NONIONIC X-RAY CONTRAST AGENTS,
COMPOSITIONS AND METHODS

This is a continuation in part of application
5 Serial Number 07/801,980 filed December 3, 1991 which is a
continuation in part of application Serial Number 764,644
filed September 24, 1991, a division of application Serial
Number 450,693 filed December 13, 1989.

Field of the Invention

10 This invention relates to novel X-ray contrast
agents, methods of preparing them, radiological
compositions containing such agents, and methods for X-ray
visualization utilizing such compositions.

Background of the Invention

15 Nonionic contrast agents for intravascular and central
nervous system visualization are complex molecules. As is
known, the iodine in the molecule provides opacification to
the X-rays, while the remainder of the molecule provides
the framework for transport of the iodine atoms. However,
20 the structural arrangement of the molecule is important in
providing stability, solubility and biological safety in
various organs. A stable carbon-iodine bond is achieved in
most compounds by attaching it to an aromatic nucleus. An
enhanced degree of solubility as well as safety is
25 conferred on the molecule by the addition of suitable
solubilizing and detoxifying groups. Further, nonionic
contrast agents are particularly desirable compared to
contemporary ionic agents due to the minimization of those
pharmacological effects associated with colligative
30 properties, e.g., osmolality.

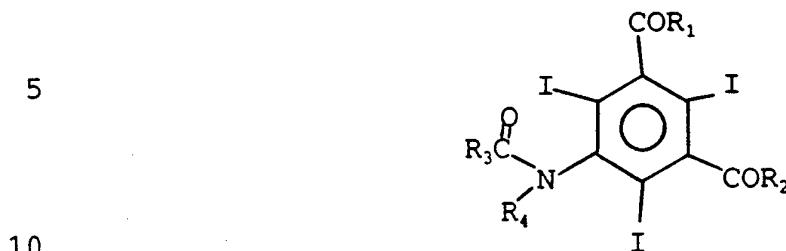
Several of the features that are desirable for intravascular and central nervous system nonionic contrast agents are often incompatible so that all such agents represent compromises. In searching for the best
5 compromise, the controlling factors are pharmacological inertness, i.e., in vivo safety, and high water solubility. Thus, the ideal intravascular or central nervous system nonionic agent represents a compromise in an attempt to obtain the following criteria: (1) maximum opacification
10 to X-rays; (2) pharmacological inertness; (3) high water solubility; (4) stability; (5) selective excretion; (6) low viscosity; and (7) minimal osmotic effects.

Illustrative nonionic contrast agents include N,N'-bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-
15 2,4,6-triiodoisophthalamide (Lin, U.S. Patent No. 4,396,598) and 5-N-(2,3-dihydroxypropyl)acetamido-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)isophthalamide (Nordal et al., U.S. Patent No. 4,250,113 and Rakli et al. U.S. Patent No. 4,396,597).

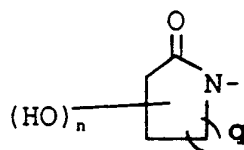
20 There is a continuing need for nonionic contrast agents which meet all or substantially all of the foregoing criteria. It is an object of the present invention to provide nonionic X-ray contrast agents which substantially meet these criteria. It is a further object of this
25 invention to provide nonionic X-ray contrast agents with improved pharmacological inertness, i.e., low toxicity, by means of the incorporation of highly hydrophilic side chains. It is a still further object of this invention to provide chemically stable nonionic X-ray contrast agents
30 having low osmolality. Other objects and features will be in part apparent and in part pointed out hereinafter.

Summary of the Invention

Briefly, the present invention is directed to compounds of the formula:

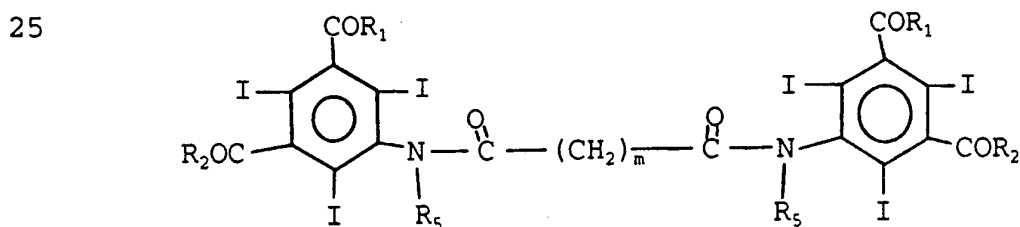


wherein R_1 is $N(CH_2CH_2OH)CH_2CHOHCH_2OH$; R_2 equals R_1 , $NHCH_3$, $NHCH_2CH_2OH$, $N(CH_3)CH_2CH_2OH$ or $NHCH_2CHOHCH_2OH$; R_3 equals CH_3 , CH_2CH_3 , CH_2OH , $CH(CH_3)OH$, $CH(CH_3)OCH_3$, $CHOHCH_2OH$, CH_2OCH_3 , or $CH_2OCH_2CH_3$; R_4 equals H , CH_3 , CH_2CH_2OH , $CH_2CH_2OCH_3$, $CH_2CHOHCH_2OH$, or $CH_2CHOHCH_2OCH_3$; or R_3 , R_4 , and the 5-N together form the group



20 wherein n equals 0, 1, 2 or 3, preferably 0 or 1 and q equals 0, 1, 2 or 3, but preferably 1, 2 or 3.

The present invention is also directed to dimers of the above compound connected at the 5-N position by means of a diamide, thus:



30 wherein R_1 and R_2 have the meanings given above; R_5 is H , CH_3 , CH_2CH_2OH , $CH_2CHOHCH_2OH$, and CH_2OCH_3 ; and m equals 0-4, preferably 0-2.

The present invention is further directed to methods for making such compounds by incorporation of an amino-alcohol, 3-(N-2-hydroxyethyl)amino-1,2-propanediol, and methods of making this amino-alcohol. The invention is also directed to radiological compositions containing such compounds and methods for utilizing such compounds in X-ray visualization.

Water solubility and safety of triiodinated aromatic compounds are obtained by attachment of suitable polar and hydrophilic side chains. 3-(N-2-Hydroxyethyl)amino-1,2-propanediol, as in the case of other amino-polyhydroxyl groups, such as 3-amino-1,2-propanediol used for N,N'-bis(2,3-dihydroxypropyl)-5-N-(2-hydroxyethyl)glycolamido-2,4,6-triiodoisophthalamide and 5-N-(2,3-dihydroxypropyl)acetamido-2,4,6-triiodo-N,N'-bis(2,3-dihydroxypropyl)isophthalamide and 2-amino-1,3-propanediol used for N,N'-bis(1,3-dihydroxypropyl)-L-5- α -hydroxypropionylamino-2,4,6-triiodoisophthalamide, provides good water solubility and in vivo safety for X-ray contrast media. However, an advantage of using 3-(N-2-hydroxyethyl)amino-1,2-propanediol is to provide even higher hydrophilicity for the contrast molecule due to the introduction of an additional hydroxyl group. This highly hydrophilic amino-triol can confer water-solubility and improve the safety of X-ray contrast media.

Detailed Description of the Invention

In accordance with the present invention, it has now been found that compounds of the formulas set out above are suitable for use as nonionic X-ray contrast agents. More specifically in the practice of the invention, the compounds may be used as nonionic X-ray contrast agents. These agents may be used in various radiographic procedures including those involving cardiology, coronary

arteriography, aortography, cerebral and peripheral angiography, arthrography, intravenous pyelography and urography.

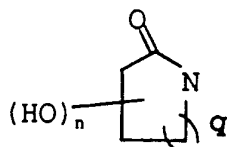
Each of the compounds of the present invention
5 has at least one amide group derived from the amino-alcohol, 3-(N-2-hydroxyethyl)amino-1,2-propanediol. This starting material may be prepared by reacting glycidol with ethanolamine under epoxide-opening conditions or by reacting 3-chloro-1,2-propanediol with ethanolamine under
10 secondary amine-forming conditions and neutralizing the hydrochloride salt thus formed.

Compounds having a 5-hydroxyacetylamino group (5-hydroxyacetamido or 5-glycolamido group) are unstable to basic conditions and will undergo a structural
15 reorganization (known in this case as the Smiles rearrangement) to a phenolic ether. The Smiles rearrangement products are generally insoluble in water and are not, therefore, useful as X-ray contrast agents. In accordance with the present invention, it has been found
20 that the Smiles rearrangement can be avoided when the 5-amino group is either a 5-methoxyacetylamino (methoxyacetamido) or a 5-ethoxyacetylamino moiety to give the compounds of the present invention wherein R₃ equals CH₂OCH₃ or CH₂OCH₂CH₃. The resulting compounds do not
25 undergo the Smiles rearrangement.

In a second, related stability enhancement effect of these methoxylated or ethoxylated agents, U.S. Patent No. 4,396,597 teaches that compounds with a 5-[N-(β-hydroxyalkyl)acetylamino] group are unstable and undergo a
30 base catalyzed cyclization and iodine elimination which renders this class of compounds less useful as X-ray contrast media. An example of such a compound is 5-N-(2,3-

dihydroxypropyl)acetamido-2,4,6,-triiodo-N,N'-bis(2,3-dihydroxypropyl)isophthalamide. The '597 patent further teaches that this problem may be overcome by utilizing a temperature dependent buffer. In accordance with the present invention, it has been found that the cyclization and deiodination problem may also be averted by replacing the 5-N-(β -hydroxyalkyl) group with 5-N-(β -methoxyalkyl) group. This replacement in compounds of the invention, that is wherein R_4 equals $\text{CH}_2\text{CH}_2\text{OCH}_3$, yields a compound that is stable to cyclization and iodine elimination at near neutral to basic pH.

Compounds of the present invention having a substituted lactam cyclic structure at the 5 position, that is, where R_3 , R_4 and the 5-amido are combined to form



have the added advantage of avoiding both types of instability, rearrangement and cyclization. The hydroxyl substitution of the lactam structure has the advantage of increasing the water solubility as needed for X-ray contrast compounds.

To further improve the osmotic effects of nonionic X-ray contrast media, the present invention also includes dimeric compounds. Hyperosmolality is known to cause vascular pain during the injection of an X-ray contrast agent. Furthermore, high osmolality has been shown to be an important factor in perturbation of the normal heart functions at the time of cardioangiography. The main advantage of the dimers of the present invention is the low osmolality with concomitant low toxicity. This is achieved by highly soluble dimeric compounds having six iodine atoms per molecule as provided by the present

invention. At a fixed iodine concentration, these compounds exhibit significantly lower osmotic effects than equivalent monomeric agents due to reduced number of solvated particles in the solution. The dimeric compounds of the present invention provide this advantage while maintaining acceptable solubility characteristics due to the high hydrophilicity of the amino-alcohol side chains.

In further accordance with the present invention, radiological compositions may be prepared containing one of the aforementioned compounds of the invention as an X-ray contrast agent together with a pharmaceutically acceptable radiological vehicle.

Pharmaceutically acceptable radiological vehicles include those that are suitable for injection such as aqueous buffer solutions; e.g., tris(hydroxymethyl)aminomethane (and its salts), phosphate, citrate, bicarbonate, etc., sterile water for injection, physiological saline, and balanced ionic solutions containing chloride and/or bicarbonate salts of normal blood plasma cations such as Ca, Na, K and Mg. Other buffer solutions are described in Remington's Practice of Pharmacy, Eleventh Edition, for example on page 170. The vehicles may contain a chelating amount, e.g., a small amount, of ethylenediamine tetraacetic acid, the calcium disodium salt, or other pharmaceutically acceptable chelating agent.

The concentration of the X-ray contrast agents of the invention in the pharmaceutically acceptable vehicle, for example an aqueous medium, varies with the particular field of use. A sufficient amount is present to provide satisfactory X-ray visualization. For example, when using aqueous solutions for angiography, the concentration of

iodine is generally 140-440 mg/ml and the dose is 25-300 ml.

The radiological compositions of the invention may be used in the usual way in X-ray procedures. For example, in the case of selective coronary arteriography, a sufficient amount of the radiological composition to provide adequate visualization is injected into the coronary system and then the system is scanned with a suitable device such as a fluoroscope.

Examples of the compounds of the present invention wherein R_1 and R_2 are the same are N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-acetamido-2,4,6-triiodoisophthalamide; N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-hydroxyacetamido-2,4,6-triiodoisophthalamide; N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-(2-hydroxy)propionamido-2,4,6-triiodoisophthalamide; N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-methoxyacetamido-2,4,6-triiodoisophthalamide; N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-[N-(2-hydroxyethyl)hydroxyacetamido]-2,4,6-triiodoisophthalamide; N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-[N-(2-hydroxyethyl)acetamido]-2,4,6-triiodoisophthalamide; N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-[N-(2-methoxyethyl)acetamido]-2,4,6-triiodoisophthalamide; N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-[(N-methyl)hydroxyacetamido]-2,4,6-triiodoisophthalamide; N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-[(N-methyl)acetamido]-2,4,6-triiodoisophthalamide; N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-N-(2-hydroxybutyrolactamido)-2,4,6-triiodoisophthalamide; N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-N-(S-2-hydroxybutyrolactamido)-2,4,6-triiodoisophthalamide; and 5-N-butyrolactamido-N,N'-

bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-2,4,6-triiodoisophthalamide.

These compounds may all be made starting from 5-amino-2,4,6-triiodoisophthaloyl chloride, which may be made from
5 5-amino-2,4,6-triiodoisophthalic acid, which is disclosed in U.S. Patent No. 4,396,598, incorporated herein by reference. Generally, the 5-amino group may first be substituted under amide-forming conditions to form the desired amide and the resulting compound reacted with 3-(N-
10 2-hydroxyethyl)amino-1,2-propanediol under amide-forming conditions to add the desired amide to the 1 and 3 carbonyl groups. Examples of the compounds that may be used to react with the 5-amine are acetyl chloride, acetoxycetyl chloride, 2-acetoxypionyl chloride, and methoxycetyl
15 chloride. The acetoxyc groups may later be hydrolyzed to produce a hydroxy group by various means, including acid hydrolysis or ion-exchange resins.

Secondary substitution of the 5-amido group (i.e., where R₄ is other than hydrogen) is generally preferred to
20 follow addition of the amino-alcohol. Examples of compounds which may be used to react with the 5-amido group under basic, alkylating conditions are alkyl halides, for example, methyl halides, such as methyl iodide; 2-haloethylacetates, such as 2-bromoethylacetate; 2-
25 haloethanols, such as 2-chloroethanol; and 2-haloethyl methyl ethers, such as 2-bromoethyl methyl ether.

The substitution of the 5-amino group to form the cyclic butyrolactamide is also generally preferred to follow addition of the amino-alcohol. Substitution of the
30 amine may be accomplished by the addition, under amide-producing conditions, of various butyryl acid halides, such as 4-chlorobutyryl chloride, 2-acetoxy-4-(methylthio)butyryl chloride, or 2,4-dibromobutyryl

bromide. Use of the latter two will result in a hydroxy-substituted lactamide following hydrolysis. Cyclization of the butyramide chain is caused by exposure to cyclizing conditions appropriate to the starting material. For example, when 2-chlorobutyryl chloride is used, the cyclization may be accomplished by using alkaline alcohol mixtures, such as methanol and aqueous sodium hydroxide mixtures. When 2-acetoxy-4-(methylthio)butyryl chloride is used, the methyl iodide of the butyramide is preferably formed first, followed by treatment with alkaline alcohol.

Prior to addition of the butyryl group it is preferred to protect the hydroxyl groups of the amides, preferably by means of acetate groups. This may be simply done by any acetate addition method under suitable protecting conditions, such as by using acetic anhydride under ester-forming conditions, such as in the presence of a base, for example, pyridine. These protecting acetate groups and the one from 2-acetoxy-4-(methylthio)butyryl chloride, if used, can then be removed by hydrolysis utilizing various conditions such as using an aqueous sodium hydroxide and methanol mixture.

When R_2 does not equal R_1 , a different synthetic route is preferred. The R_2 substitution is preferably made first, followed by a substitution at the 5-amino group. For example, the intermediate compound 5-amino-2,4,6-triiodo-3-N-methylaminocarbonylbenzoic acid chloride may be used to produce compounds wherein R_2 equals NHCH_3 . 5-Amino-2,4,6-triiodo-3-[N-(2-hydroxyethyl)aminocarbonyl]benzoic acid or the acid chloride is used to produce compounds wherein R_2 equals $\text{NHCH}_2\text{CH}_2\text{OH}$. In the latter case, the hydroxyl group is preferably protected during later steps by means of an acetate group as described above.

The intermediate compounds may be prepared from 5-nitroisophthalic acid monomethyl ester via well-established synthetic routes. See, for example, U.S. Patent No. 3,290,366, incorporated herein by reference, and
5 European Application 0 308 364.

Examples of such compounds, wherein R_2 does not equal R_1 , are [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-DL-5- α -hydroxypropionylamino-2,4,6-triiodo-3-N-methylaminocarbonylbenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-5-hydroxyacetyl-amino-2,4,6-triiodo-3-N-methylaminocarbonylbenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-DL-5- α -hydroxypropionylamino-2,4,6-triiodo-3-N-(2-hydroxyethyl)aminocarbonylbenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-3-N-(2-hydroxyethylaminocarbonyl)-5-hydroxyacetyl-amino-2,4,6-triiodobenzamide, 5-(2,3-dihydroxypropanoylamino)-[N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-3-(N-2-hydroxyethylaminocarbonyl)-2,4,6-triiodobenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-DL-5-(N-methyl- α -hydroxypropionylamino)-2,4,6-triiodo-3-N-methylaminocarbonylbenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-5-(N-methyl-2-hydroxyacetyl-amino)-2,4,6-triiodo-3-N-methylamino-carbonylbenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-DL-5-(N-methyl- α -hydroxypropionylamino)-2,4,6-triiodo-3-N-(2-hydroxyethyl)aminocarbonylbenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-3-N-(2-hydroxyethylaminocarbonyl)-5-(N-methyl-2-hydroxyacetyl-amino)-2,4,6-triiodobenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-DL-5-(N-2-hydroxyethyl- α -hydroxypropionylamino)-2,4,6-triiodo-3-N-methylaminocarbonylbenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-5-(N-2-hydroxyethyl-2-hydroxyacetyl-amino)-2,4,6-triiodo-3-N-methylaminocarbonyl-

benzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-DL-5-(N-2-hydroxyethyl- α -hydroxypropionylamino)-2,4,6-triiodo-3-N-(2-hydroxyethyl)aminocarbonylbenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-3-N-(2-hydroxyethylaminocarbonyl)-5-(N-2-hydroxyethyl-2-hydroxyacetyl-amino)-2,4,6-triiodobenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-3-N-(2,3-dihydroxypropylaminocarbonyl)-5-hydroxyacetyl-amino-2,4,6-triiodobenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-DL-5-N-butyro-lactamido-2,4,6-triiodo-3-N-methylaminocarbonylbenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-5-N-butyrolactamido-2,4,6-triiodo-3-N-methylamino-carbonylbenzamide, [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-DL-5-N-butyrolactamido-2,4,6-triiodo-3-N-(2-hydroxyethyl)aminocarbonylbenzamide, and [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-3-N-(2-hydroxyethylaminocarbonyl)-5-N-butyrolactamido-2,4,6-triiodobenzamide.

Examples of the dimeric compounds of the present invention wherein R_2 equals R_1 are N,N'-bis[3,5-bis(N-2,3-dihydroxypropyl-N-2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]malondiamide; N,N'-bis[3,5-bis(N-2,3-dihydroxypropyl-N-2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]oxamide; and N,N'-bis[3,5-bis(N-2,3-dihydroxypropyl-N-2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]succinamide. These compounds may be prepared by first forming a dimer by reacting two moles of 5-amino-2,4,6-triiodoisophthaloyl chloride under amide-forming conditions with one mole of a diacid chloride such as oxalyl chloride, malonyl chloride, or succinyl chloride. 3-(N-2-Hydroxyethyl)amino-1,2-propanediol is then reacted with the intermediate dimer to form the compounds of the present invention.

Examples of dimeric compounds of the present invention wherein R_2 does not equal R_1 are N,N' -bis[3-(N -2-hydroxyethylaminocarbonyl)-5-(N -2,3-dihydroxypropyl- N -2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-malondiamide; N,N' -bis[3-(N -2-hydroxyethylaminocarbonyl)-5-(N -2,3-dihydroxypropyl- N -2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-oxamide; N,N' -bis[3-(N -2-hydroxyethylaminocarbonyl)-5-(N -2,3-dihydroxypropyl- N -2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-succinamide; N,N' -bis[3-(N -2,3-dihydroxypropylaminocarbonyl)-5-(N -2,3-dihydroxypropyl- N -2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-oxamide; N,N' -bis[3-(N -2,3-dihydroxypropylaminocarbonyl)-5-(N -2,3-dihydroxypropyl- N -2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-malondiamide; N,N' -bis[3-(N -2,3-dihydroxypropylaminocarbonyl)-5-(N -2,3-dihydroxypropyl- N -2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-succinamide; N,N' -dimethyl- N,N' -bis[3-(N -2-hydroxyethylaminocarbonyl)-5-(N -2,3-dihydroxypropyl- N -2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-malondiamide; N,N' -dimethyl- N,N' -bis[3-(N -2-hydroxyethylaminocarbonyl)-5-(N -2,3-dihydroxypropyl- N -2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-oxamide; N,N' -dimethyl- N,N' -bis[3-(N -2-hydroxyethylaminocarbonyl)-5-(N -2,3-dihydroxypropyl- N -2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-succinamide; N,N' -dimethyl- N,N' -bis[3-(N -2,3-dihydroxypropylaminocarbonyl)-5-(N -2,3-dihydroxypropyl- N -2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-oxamide; N,N' -dimethyl- N,N' -bis[3-(N -2,3-dihydroxypropylaminocarbonyl)-5-(N -2,3-dihydroxypropyl- N -2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-malondiamide; and N,N' -dimethyl- N,N' -bis[3-(N -2,3-dihydroxypropylaminocarbonyl)-5-(N -2,3-dihydroxypropyl- N -2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-succinamide.

These compounds are prepared by first making the desired R_2 substitution and then forming the dimer by reaction with the desired diacid chloride, such as oxalyl chloride, malonyl chloride, or succinyl chloride. The amino-alcohol is then added under amide-forming conditions. If secondary substitution of the diamide nitrogens is desired, i.e., when R_3 is other than hydrogen, this step is performed last. Examples of compounds which may be used to add the desired substituents under basic, alkylating conditions are alkyl halides, for example, methyl halides, such as methyl iodide; 2-haloethylacetates, such as 2-bromoethylacetate; 2-haloethanols, such as 2-chloroethanol; and 2-haloethyl methyl ethers, such as 2-bromoethyl methyl ether.

The reactions necessary to produce the compounds of the present invention may be carried out at any convenient temperature and pressure, such as at atmospheric pressure and ambient temperatures. It is preferred that amidation and alkylation reactions be performed at such ambient temperatures. It is preferred that hydrolysis steps be carried out at elevated temperatures to achieve a sufficient rate of hydrolysis, such as at temperatures between 90 and 100 °C.

Purification of the compounds of the present invention is desired for their use as X-ray contrast agents. Purification may be by standard isolation methods, such as crystallization, or by preparative HPLC, such as by reverse-phase HPLC, or combinations of these.

The following examples of the practice of the present invention are meant to be illustrative and are in no way limiting the scope of the invention.

EXAMPLE 1

Preparation of 5-Amino-2,4,6-triiodoisophthaloyl chloride.

5-Amino-2,4,6-triiodoisophthalic acid (234.5 g, 0.42 g-mole) is slurried in 200 ml of ethylacetate at 50°C. 5 Thionyl chloride (399.3 g, 243.8 ml, 3.36 g-mole) is added dropwise over a 1 hour period. The temperature is then increased to 68°C, and the contents are stirred for 7 hours, and then for an additional 16 hours at room temperature (20-25°C). EtOAc and excess thionyl chloride are partially 10 removed by vacuum distillation (vacuum, 35°C pot temperature) to leave a yellow paste. This paste is stirred with 200 ml 1,1,1-trichloroethane (TCE) at 0-5°C for 1 hour, and collected by suction filtration while cold. The fine yellow powder is washed twice with 100 ml cold 15 1,1,1-TCE, filtered and dried in a vacuum desiccator to give the desired product (12.5 g, 50% yield). The product develops as one spot by TLC(EtOAc/MeOH/HOAc; 10/5/1), and its ¹³C nmr spectrum is consistent with the structure.

EXAMPLE 2

20 Preparation of N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-acetamido-2,4,6-triiodoisophthalamide.

A. 5-Acetamido-2,4,6-triiodoisophthaloyl chloride. 5-Amino-2,4,6-triiodoisophthaloyl chloride (190 g, 0.32 g-mole) prepared as in Example 1 is dissolved in 475 ml of 25 N,N-dimethylacetamide (DMAc) (dried over molecular sieves), and the solution is stirred and cooled to 0-3°C. Acetyl chloride (75.1 g, 68 ml, 0.96 g-mole) is added dropwise over a period of 100 minutes, keeping the temperature between 0°C and 3°C. The ice bath is removed and the 30 solution is stirred overnight at room temperature (20-25°C). An additional charge of acetyl chloride (8.5 g, 0.11 g-mole) is added, and the mixture is stirred overnight (23

hours). The product (a creamy white solid) precipitates during this time. The mixture is cooled to 0-5°C and filtered while cold. After rinsing with three 100-ml portions of hexane on the funnel, the solution is stirred
5 with three 200-ml portions of cold hexane for 10 minutes each time, collected by suction filtration, and dried in a vacuum desiccator (183 g, 90% yield). The product shows one major spot by TLC analysis.

B. N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-acetamido-2,4,6-triiodoisophthalamide. A mixture of 5-
10 acetamido-2,4,6-triiodoisophthaloyl chloride (92.0 g, 0.14 g-mole) and anhydrous Na₂CO₃ (38 g, 0.36 g-mole) in a flask containing 200 ml of dry DMAc is immersed in an ice bath. At a temperature of 0-5°C, 3-(N-2-hydroxyethyl)amino-1,2-
15 propanediol (48 g, 0.36 g-mole) (96 ml of a 50% w/v DMAc solution) is added dropwise with stirring over a period of 1 hour, keeping the temperature below 5°C. The mixture is stirred for 1 additional hour at 0-5°C, then stirred for 48 hours at room temperature (20-25°C). The mixture is
20 filtered to remove the inorganic salts; the DMAc is removed by rotary evaporation (high vacuum, 80°C) to leave an orange-yellow gum (78.14 g). The gum is dissolved in water to make 250 ml of solution (pH 10.5) and passed through a bed of IRA-118H strong cation exchange resin (62 ml, 1.3
25 meq./ml). The resin is then washed with two 100 ml portions of water; the washes and the eluent are combined and evaporated to provide an off-white foam (49.8 g). The product is purified by reverse-phase preparative HPLC to
30 give 37.5 g of a white glassy solid (a 31% yield having a purity of 99.6% by HPLC). The ¹³C nmr spectrum is consistent with the structure. [Calculated % composition for C₂₀H₂₈I₃N₃O₉; C: 28.76; H: 3.38; N: 5.03; I: 45.58. Found: C: 28.31; H: 3.40; N: 5.04; I: 45.80.] The water

solubility (w/v) is 100%; the i.v. LD₅₀ in mice is 13.8 g I/kg; the osmolality is 590 mOsm/Kg, 32%I.

EXAMPLE 3

Preparation of N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-hydroxyacetamido-2,4,6-triiodoisophthalamide.

A. 5-Acetoxyacetamido-2,4,6-triiodoisophthaloyl chloride.
59.6 g (0.1 g-mole) of 5-amino-2,4,6-triiodoisophthaloyl chloride prepared as in Example 1, is dissolved in 100 ml of DMAc and 27.3 g (0.2 g-mole) of acetoxyacetyl chloride is added as the solution temperature is maintained at 25-35°C. After the addition, the solution is allowed to stir and heated at 35-40°C for 4 hours to complete the reaction. The solution is cooled to room temperature and poured slowly into 1 L of cold water (0-5°C) with stirring to precipitate the product.

The white solid is filtered, washed with cold water and dried, giving 69 g (99% yield) of the desired product. The product shows one spot by TLC analysis (EtOAc/CH₂Cl₂; 30/20). The ¹³C nmr data are consistent with the structure.

B. 5-Acetoxyacetamido-N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-2,4,6-triiodoisophthalamide. 69 g (0.1 g-mole) of 5-acetoxyacetamido-2,4,6-triiodoisophthaloyl chloride is dissolved in DMAc (140 ml) and anhydrous Na₂CO₃ (31.8 g, 0.3 g-mole) is added. To the solution, a DMAc solution (87 ml) containing 26.2 g (0.3 g-mole) of 3-(N-2-hydroxyethyl)amino-1,2-propanediol is added. The mixture is heated and stirred at 35-40°C until the reaction is completed as determined by the TLC analysis (EtOAc/CH₂Cl₂; 30/20). After the reaction, the inorganic salts are filtered and the filtrate containing the desired product is

evaporated to dryness to give a gum. The gum is triturated with isopropyl alcohol to dissolve the excess amino-triol. The clear supernatant is decanted and the residual solid is dissolved in water (150 ml), treated with Amberlite® IR-120H resin and evaporated to dryness to give the desired product (77 g, 86% yield).

C. N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-hydroxyacetamido-2,4,6-triiodoisophthalamide. 5-Acetoxyacetamido-N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-2,4,6-triiodoisophthalamide (77 g, 0.086 g-mole) is dissolved in 270 ml of hot water containing 8.2 g (0.08 g-mole) sulfuric acid. The solution is stirred and heated at 95-100°C to hydrolyze the acetate. At the end of the reaction, the solution is cooled to room temperature and deionized using an anionic exchange resin, IRA-93 (Rohm and Haas Co.) to remove sulfuric acid. The solution is then concentrated and the crude product is purified by preparative liquid chromatography to provide the purified desired product (51 g; 0.06 g-mole, 70% yield). The ¹³C nmr spectra are consistent with the structure. The HPLC purity is 99.1% (C₁₈, H₂O/MeOH; 95/5). The water solubility (w/v) is 100%; the iv LD₅₀ in mice is 5 g I/kg (based on iodine content). Osmolality: 676 mOsm/kg (32% I); viscosity: 8.2 cps (37°), 10.0 cps (25°) (32% I).

25

EXAMPLE 4

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

This compound is prepared in the same manner as described in Example 3 starting from 5-amino-2,4,6-triiodoisophthaloyl chloride and (±)-2-acetoxypropionyl chloride.

EXAMPLE 5

Preparation of N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-(2-hydroxy)propionamido-2,4,6-triiodoisophthalamide, D- and L- optical isomers.

- 5 The D- and L- individual optical isomer of the title compound is prepared in the same manner as described in Example 4 from 5-amino-2,4,6-triiodoisophthaloyl chloride and the D- and L- optical isomer of 2-acetoxypropionyl chloride.

EXAMPLE 6

Preparation of N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-methoxyacetamido-2,4,6-triiodoisophthalamide.

A. 5-Methoxyacetamido-2,4,6-triiodoisophthaloyl chloride.

- 15 5-Amino-2,4,6-triiodoisophthaloyl chloride prepared in Example 1 (59.6 g, 0.1 g-mole) is dissolved in DMAc (100 ml). The solution is cooled to 5°C and methoxyacetyl chloride (21.7 g 0.2 g-mole) is added slowly keeping the temperature at 5-10°C. When the addition is complete, the
20 reaction mixture is allowed to warm to room temperature and stirred until the reaction is complete. The solution is cooled to room temperature and poured slowly into 1 L of cold water (0-5°C) with stirring to precipitate the product.

- The white solid is filtered, washed with cold water and
25 dried to provide the desired product.

B. N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-methoxyacetamido-2,4,6-triiodoisophthalamide. 5-

- Methoxyacetamido-2,4,6-triiodoisophthaloyl chloride (56.7 g, 0.085 g-mole) and anhydrous Na₂CO₃ (18 g, 0.17 g-mole)
30 are mixed in DMAc (70 ml). A solution of DMAc (57 ml)

containing 3-(N-2-hydroxyethyl)amino-1,2-propanediol (34.5 g, 0.255 g-mole) is added. The mixture is allowed to stir at 35-40°C until the reaction is complete. The mixture is then filtered to remove the inorganic salts and the
5 filtrate containing the desired product is evaporated to give a gum. The material is triturated with isopropyl alcohol to dissolve the excess amino-alcohol. The clear supernatant is decanted and the residual solid is evaporated to dryness to give the crude product. The crude
10 product is dissolved in water and purified by reverse-phase preparative HPLC to provide the purified product.

EXAMPLE 7

Preparation of N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-[N-(2-hydroxyethyl)hydroxyacetamido]-2,4,6-
15 triiodoisophthalamide.

A. 5[N-(2-Acetoxyethyl)acetoxyacetamido]-N,N'-bis(2,3-dihydroxypropyl)-2-hydroxyethyl]-2,4,6-triiodoisophthalamide. 5-Acetoxyacetamido-N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-2,4,6-triiodo-
20 isophthalamide, prepared as in Example 3, Step B, (89 g, 0.1 g-mole) is mixed with K₂CO₃ (27.6 g, 0.2-g mole) and 2-bromoethyl acetate (33.4 g, 0.2 g-mole) in DMAc (200 ml). The mixture is stirred at 35-40°C until the reaction is complete (approximately 8-12 hours). The solution is then
25 cooled to room temperature and the inorganic salts are filtered. The filtrate is then evaporated under vacuum at 70°C to yield a thick oil. The oil is triturated with isopropyl alcohol to dissolve the residual DMAc and bromoethyl acetate. The supernatant is decanted and the
30 residual solid is evaporated to dryness to provide the desired product.

B. N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-[2-hydroxyethyl)hydroxyacetamido]-2,4,6-triiodoisophthalamide. This compound is prepared from the hydrolysis of the product of Step A as described in Example 3, Step C.

EXAMPLE 8

Preparation of N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-[N-(2-hydroxyethyl)acetamido]-2,4,6-triiodoisophthalamide.

5-Acetamido-N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-2,4,6-triiodoisophthalamide, prepared as in Example 2, Step B, (83.5 g, 0.1 g-mole) is dissolved in 1 N NaOH (140 ml, 0.14 g-mole) and the solution is stirred at room temperature for 1 hour and 2-chloroethanol (13.7 g, 0.17 g-mole) is added. The solution is stirred at 50°C for 5 hours to complete the reaction. The solution is acidified with H₂SO₄ and evaporated to dryness under reduced pressure. The residue is triturated with MeOH and the precipitated solid is filtered. The mother liquor is concentrated under vacuum and the crude product is purified by reverse-phase (C₁₈) HPLC to give the purified final product. The yield of this reaction and purification is 80%.

EXAMPLE 9

Preparation of N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-[N-(2-methoxyethyl)acetamido]-2,4,6-triiodoisophthalamide.

This compound is prepared from 5-acetamido-N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-2,4,6-triiodoisophthalamide, prepared as in Example 2, Step B, with 2-bromoethyl methyl ether (BrCH₂CH₂OCH₃) in the same manner as described in Example 8.

EXAMPLE 10

Preparation of N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-(N-methyl)hydroxyacetamido-2,4,6-triiodoisophthalamide.

- 5 N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-hydroxyacetamido-2,4,6-triiodoisophthalamide, prepared as in Example 3, Step C, (85.1 g, 0.1 g-mole) is dissolved in 200 ml of water and 110 ml of 1N NaOH (0.11 g-mole) is added. The solution is stirred at room temperature for 1
10 hour and evaporated to dryness under vacuum. The residue is then dissolved in 100 ml of DMAc and the solution is warmed to 35°C. Methyl iodide (17 g, 0.12 g-mole) is added dropwise and the solution is stirred at 35°C for 12-16 hours until the reaction is complete as monitored by HPLC. The
15 solution is evaporated and the residue is dissolved in water. The solution is then treated with a cationic ion-exchange resin, e.g., Amberlite® IR-120H (Rohm & Haas Co.) to remove the salts. The solution is evaporated and the material is purified by reverse-phase HPLC to yield the
20 purified desired material.

EXAMPLE 11

Preparation of N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-N-methylacetamido-2,4,6-triiodoisophthalamide.

- 25 This compound is prepared from 5-acetamido-N,N'-bis[2,3-dihydroxypropyl)-2-hydroxyethyl]-2,4,6-triiodoisophthalamide in the same manner as described in Example 10.

EXAMPLE 12

Preparation of N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-N-(2-hydroxybutyrolactamido)-2,4,6-triiodoisophthalamide.

A. 5-Amino-N,N'-bis[(2-acetoxyethyl)(2,3-diacetoxypropyl)]-2,4,6-triiodoisophthalamide. 5-Amino-2,4,6-triiodoisophthaloyl chloride prepared as in Example 1 (59.6 g, 0.1 g-mole), and anhydrous Na₂CO₃ (31.8 g, 0.3 g-mole) are mixed in DMAc (200 ml). A solution of DMAc (100 ml) containing 3-(N-2-hydroxyethyl)amino-1,2-propanediol (40.5 g, 0.3 g-mole) is added slowly and the mixture is allowed to stir at 35-40°C overnight. The mixture is then filtered to remove the inorganic salts. The filtrate is evaporated under vacuum and the gummy residue is triturated with isopropyl alcohol to effect the precipitation of the product. The solid is collected and dried to provide 5-amino-N,N'-bis[(2,3-dihydroxy-propyl)-2-hydroxyethyl]-2,4,6-triiodoisophthalamide.

This compound (79 g, 0.1 g-mole) is slurried in pyridine, and acetic anhydride (71.4 g, 0.7 g-mole) is added dropwise with stirring and cooling so that the reaction temperature is maintained at <30°C. After the addition, the mixture is allowed to stir at room temperature overnight to complete the reaction.

The reaction solution is diluted with EtOAc (350 ml); ice water (350 ml) is added and the mixture is stirred for 30 minutes. A mixture of cold water (350 ml) and conc. HCl (70 ml) is added and the mixture is stirred for 30 minutes. The layers are separated and the organic layer is collected, washed with diluted HCl (two x 100 ml) and 10% NaCl solution (100 ml). The organic layer is then dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give the desired product. The product shows one spot by

the analysis (EtOAc/CH₂Cl₂, 30/20); HPLC purity: >97% yield: 99 g (95%).

B. 2,4-Dibromobutyryl bromide. This compound is prepared according to the general procedure in Org. Syn. Coll, Vol. V, p. 255, incorporated herein by reference. In a 2 L flask equipped with an addition funnel, a mechanical stirrer, a thermometer and a reflux condenser are placed 40 g of red phosphorous and 300 g of butyrolactone. The system is connected to a gas trap through the condenser.

10 The reaction mixture is cooled with an ice bath. Bromine (188.4 mL, 584 g) is added over 35 minutes. The reaction mixture reaches a maximum temperature of 54°C. The reaction mixture is warmed to 70°C with a steam bath. The remaining bromine (188.4 mL, 584 g) is added while the reaction is

15 cooled with an ice bath to keep its temperature between 70-80°C. The reaction mixture is heated with a steam bath to 80°C for 3 hours. The steam bath is turned off and nitrogen is bubbled through the reaction mixture for 3.5 hours to drive out hydrogen bromide and excess bromine. A slow

20 stream of nitrogen is bubbled through the reaction mixture over night. The reaction mixture is filtered through glass wool to remove the gummy residue. It is distilled at 155-170°C under vacuum (1.5 to 0.7 mm) to give 958.17 g (89% yield) of light yellow 2,4-dibromobutyryl bromide. Its NMR

25 spectrum is consistent with its structure.

C. N,N'-Bis[(2-acetoxyethyl)-2,3-diacetoxypropyl]-5-N-(2,4-dibromobutyramido)-2,4,6-triiodoisophthalamide. 2,4-Dibromobutyryl bromide (92 g, 0.3 g-mole) is placed into a flask equipped with a mechanical stirrer, a thermometer and

30 a drying tube. The compound prepared in Step A (78.5 g, 0.075 g-mole) in DMAc (200 ml) is added while the reaction mixture is cooled to room temperature with an ice bath. The mixture is stirred at room temperature until the

reaction is complete. The mixture is then poured slowly into 1 L of ice water and the mixture is stirred for 30 minutes as a solid form. The aqueous mixture is extracted 3 times with EtOAc (500 ml each). The combined EtOAc
5 extracts are washed with water (500 ml), saturated NaHCO₃ solution (two times 200 ml), water (400 ml) and saturated NaCl solution (200 ml). The organic layer was dried over anhydrous Na₂SO₄ and the solvent was evaporated under reduced pressure to provide the crude desired product to be
10 used in the next step.

D. 5-N-(2-Bromobutyrolactamido)-N,N'-bis[2,3-dihydroxypropyl]-2-hydroxyethyl]-2,4,6-triiodoisophthalamide. Crude product prepared in Step C (94 g, 0.074 g-mole) is dissolved in 450 ml of methanol in flask
15 equipped with a mechanical stirrer. Sodium hydroxide (50%) solution (76 ml) is diluted with 450 ml of water and added into the methanol solution with cooling (ice-bath). After the addition, the cooling is removed and the solution is stirred for 1.5 hours to complete the reactions (hydrolysis
20 of the acetate and the cyclization). The reaction mixture is then acidified to pH 3 with hydrochloric acid. The solution is concentrated to about 400 ml and ethanol (600 ml) is added to precipitate the inorganic salts. The salts are filtered off and the filtrate is evaporated to dryness
25 under reduced pressure to provide the crude product. The crude product is dissolved in water (45 g in 50 ml) and purified by prep HPLC to give 28 g of purified desired product (40% yield).

E. N,N'-Bis[2,3-dihydroxypropyl]-2-hydroxyethyl]-5-N-(2-hydroxybutyrolactamido)-2,4,6-triiodoisophthalamide. The
30 compound prepared in Step D (28 g, 0.03 g-mole), distilled ethanol (500 ml) and potassium acetate (11.8 g, 0.12 g-mole) are mixed in a 2 L flask equipped with a mechanical

stirrer, a reflux condenser and a thermometer. The mixture is refluxed until the reaction is complete. The solvent is removed under vacuum and a solid is obtained. The solid is dissolved in water (200 ml) and the solution is treated
5 with 150 g of pre-washed mixed-bed ion-exchange resins. After stirring for 15 minutes, the resins are filtered off and the solution is evaporated under vacuum to give a foamy solid of crude product. The material is dissolved in water (40 ml) and purified by preparative HPLC to give 8 g of the
10 purified product as an overall 32% yield.

EXAMPLE 13

Preparation of N,N'-Bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-5-N-(S-2-hydroxybutyrolactamido)-2,4,6-triiodoisophthalamide.

15 A. DL-2-Acetoxy-4-(methylthio)butyric acid. Calcium 2-hydroxy-4-(methylthio)butyrate (33.8 g, 0.1 g-mole) and acetyl chloride (110 g) are refluxed in a 250 ml round-bottom flask for 2.5 hours. The mixture is evaporated to a syrup and treated with 150 ml acetone. The brown mixture
20 is stirred for 30 minutes, filtered, and the filtrate evaporated to dryness to give 37 g, 96.4% of brown viscous oil which is identified by TLC and nmr.

B. Resolution of DL-2-Acetoxy-4-(methylthio)butyric acid. Resolution is accomplished with brucine. Thus, a solution
25 of the mixed isomers 486 g (2.53 mol) in 500 ml ethanol, is filtered in a 12 L resin pot and treated with a hot filtered solution of brucine, 1 kg, (2.53 mol, Sigma Chemical) in 3 L of ethanol. The precipitate formed is left overnight at room temperature, filtered, washed with
30 2 L of ethanol and 1 L of ether to yield 900 g material. This is crystallized from 6 L of ethanol to give 640 g solid, m.p. 184-186°C, and then recrystallized once more

from ethanol, 6L, to give 570 g solid, 38.3%, m.p. 185-187°C, $[\alpha]$ -31° (1% H₂O).

The free acid is released from the brucine salt by dissolving 570 g of the solid obtained above in 5.5 L water in a 12 L resin pot. This is treated with concentrated HCl to pH 0.7 (200 ml), and the pale brown solution is extracted twice with 2.5 L ethyl acetate. The extract is washed with water, three times 300 ml, dried over anhydrous sodium sulfate, evaporated to dryness to give brown thick oil, 182.2 g, 97.8% $[\alpha]$ -33.78° (0.1258 g in 10 ml CHCl₃).

C. Verification of Optical Purity. This preparation is made in order to verify optical purity of the above compound as generally disclosed at Angew. Chem. Int. Ed. 18, 797 (1979); and J. Am. Chem. Soc. 78, 2429 (1956), incorporated herein by reference.

L-2-Hydroxy-4-(methylthio)butyric acid and acetylation.

In a 1 L, 3-necked flask is dissolved L-2-amino-4-(methylthio)butyric acid (14.9 g, 0.1 g-mole) in aqueous H₂SO₄ solution (80 ml) and cooled to -5°C. This is treated with a solution of NaNO₂ in 30 ml water. The mixture is stirred overnight at room temperature and extracted with three times 100 ml ether, dried over anhydrous Na₂SO₄ and evaporated to dryness to give an oil, 1.4 g 9.3%. TLC shows one major spot and IR is in agreement with the structure. Acetylation of the compound (1.5 g, 0.01 mol) is carried out with acetyl chloride (0.07 mol, 6.5 ml); the mixture was refluxed for 1 hour, evaporated to dryness and the residue dissolved in CHCl₃. This is extracted three times with 30 ml NaHCO₃ solution (5%), washed twice with 30 ml CHCl₃, filtered and acidified with concentrated HCl (pH 1). The precipitated oil is extracted with chloroform,

washed with 30 ml water, dried over anhydrous Na_2SO_4 and evaporated to dryness to give brown oil, 1.76 g (91.6%).

The brucine salt is prepared by dissolving 1.1 g (0.0057 ml) of the above material L-2-acetoxy-4-(methylthio)-butyric acid, in 10 ml EtOH and treatment with a hot filtered solution of brucine (0.0057 mol, 2.26 g in ethanol, 20 ml). The salt obtained is filtered and recrystallized from ethanol (40 ml) three times to obtain pure salt, m.p. 184-186°C [α] -31° (1% H_2O), identical in m.p., mixed m.p. (undepressed), and optical rotation to compound prepared in Steps A and B.

D. L-2-Acetoxy-4-(methylthio)butyryl chloride. In a 1 L, 3-necked flask is dissolved 173 g of compound prepared in (Step B) in 500 ml CH_2Cl_2 , cooled in ice-methanol bath and treated with SOCl_2 (120 g) followed by 3 ml DMF. The mixture is stirred overnight at room temperature. The solvent is distilled and the residue purified by distillation at 84-86°C (0.1-0.05 mm Hg) to give pale yellow oil 157 g, 83%. IR and nmr data are consistent with the structure for the desired acid chloride.

E. N,N'-Bis[2-Acetoxyethyl-2,3-diacetoxypropyl]-5-N-[(S-2-acetoxy-4-methylthiobutyramido)]-2,4,6-triiodoisophthalamide. 5-Amino-N,N'-bis[(2-acetoxyethyl)(2,3-diacetoxypropyl)]-2,4,6-triiodoisophthalamide, prepared as in Example 12, Step A, (200 g, 0.2 g-mole) is dissolved in DMAc (175 ml) and cooled in ice-methanol bath and treated with the acid chloride prepared in Step D (84.2 g, 0.4 g-mole) in 84 ml DMAc. The solution is stirred at room temperature overnight and then poured over a solution of sodium bicarbonate (50.4 g, 0.6 g-mole) in 750 ml water and filtered. The solid is washed with 100 ml water twice and

dried to give a glassy material of the desired compound (241 g, 99% yield).

- F. N,N'-Bis[2-Acetoxyethyl-2,3-diacetoxypropyl]-5-N-(S-2-acetoxy-4-methylthiobutyramido)]-2,4,6-triiodoisophthalamide, methyl iodide. A solution of the compound prepared in Step E (232 g, 0.19 g-mole) in DMF (475 ml) is stirred with methyl iodide (165 g, 11.6 g-mole) at room temperature overnight. The mixture is evaporated to dryness and the residue triturated with three times 1 L ether. The residue is dissolved in acetone (170 ml) and the product is precipitated with the treatment of cold ether. The crystals are filtered, washed with ether to obtain a nearly quantitative yield of the desired compound (255 g).
- G. N,N'-Bis[(2,3-Dihydroxypropyl)-2-hydroxyethyl]-5-N-(S-2-hydroxybutyrolactamido)-2,4,6-triiodoisophthalamide. A solution of the compound prepared in Step F (136 g, 0.1 g-mole) in 500 ml of MeOH and NaOH solution (80 g in 640 ml water) are mixed while cooling with ice-water. The mixture is stirred at room temperature overnight and then treated with 65 ml of AcOH. Methanol is removed under reduced pressure and the solution is treated with mixed-bed ion-exchange resins. The solution is filtered and concentrated to provide the crude product. The crude product is dissolved in water and purified by preparative HPLC (C₁₈, water as the mobile phase) to provide the purified material.

EXAMPLE 14

- Preparation of 5-N-Butyrolactamido-N,N'-bis[(2,3-dihydroxypropyl)-2-hydroxyethyl]-2,4,6-triiodoisophthalamide.

A. N,N'-Bis[(2-acetoxyethyl)-2,3-diacetoxypropyl]-5-(4-chlorobutyramido)-2,4,6-triiodoisophthalamide. In a flask equipped with a mechanical stirrer, dropping funnel, thermometer and drying tube, 5-amino-N,N'-bis[(2-acetoxyethyl)(2,3-diacetoxypropyl)]-2,4,6-triiodoisophthalamide, prepared as in Example 12, Step A, (48 g, 0.046 g-mole) is dissolved in DMAc (120 ml). The solution is cooled to 15°C and 4-chlorobutyryl chloride (13 g, 0.092 g-mole) is added slowly with stirring. The reaction solution is then stirred at room temperature until the reaction is completed as determined by tlc.

The solution is poured into 1 L of ice-water with stirring. A gummy material precipitates. After stirring for 10 minutes, EtOAc (350 ml plus 150 ml twice) is added to dissolve the gum and extract the solution. The combined EtOAc solution is washed with water (200 ml), 5% NaHCO₃ (two times 200 ml), saturated NaCl solution (two times 150 ml), dried over anhydrous Na₂SO₄ (100 g) and evaporated to give a crude solid product. Without further purification, the crude product is utilized in the following step.

B. 5-N-Butyrolactamido-N,N'-bis[(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide. The crude compound prepared in Step A (18.4 g, 0.016 g-mole) is suspended in MeOH (100 ml) in a flask equipped with a mechanical stirrer, an addition funnel and a thermometer. The suspension is cooled to 10°C and NaOH solution (98 ml of 1 N solution) is added slowly so the temperature is maintained at 10-20°C. When 25 ml of NaOH solution is added, the suspension became a clear solution. After the addition, the cooling (ice-bath) is removed and the solution is stirred at room temperature overnight.

The solution is stirred with Amberlite IR-120H resin (120 ml) for 2 hours and filtered. The filtrate is evaporated to dryness to give the crude desired product at a quantitative yield. The purification of the product is carried out by preparative HPLC using C₁₈ column and H₂O/MeOH as the mobile phase. The elutions containing the desired product are combined and evaporated to dryness to provide the purified product (8.2 g, 60% yield).

EXAMPLE 15

10 Preparation of [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-DL-5- α -hydroxypropionylamino-2,4,6-triiodo-3-N-methylaminocarbonylbenzamide.

A. DL-5- α -Acetoxypionylamino-2,4,6-triiodo-3-N-methylaminocarbonylbenzoyl chloride. 5-Amino-2,4,6-triiodo-3-N-methylaminocarbonylbenzoyl chloride (59 g, 0.1 g-mole) is slurried in DMAc (110 ml) at 35-40°C. DL-2-Acetoxypionyl chloride (30.2 g, 0.2 g-mole) is added dropwise keeping the temperature at 40-48°C. The slurry is stirred at 40°C for 30 minutes, turning into a clear brown solution. After stirring overnight at 40°C, HPLC analysis indicates complete reaction. The solution is slowly poured into 1.1 L of cold water (0-5°C) with stirring. A creamy, white solid precipitates. It is collected, washed three times with 50 ml water, and dried to give the desired product (62.4 g, 88.6% yield) as confirmed by TLC and nmr.

B. DL-5- α -Acetoxypionylamino-[N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-2,4,6-triiodo-3-N-methylaminocarbonylbenzamide. The compound prepared in Step A (60 g, 0.085 g-mole) is added to a mixture of 3-(N-2-hydroxyethyl)amino-1,2-propanediol dissolved in DMAc (23 g, 0.17 g-mole, in 56.4 ml solution, 40.87% w/v), additional DMAc (70 ml) and sodium carbonate (18 g, 0.17 g-

mole) at 40°C. The mixture is stirred at room temperature for 20 hours, then warmed to 40°C for 5 hours, and again stirred overnight at room temperature. The mixture is filtered and the solid collected and washed twice with 50 ml DMAc. The filtrate and washes are combined and evaporated to give a thick oil (105.8 g). The oil is triturated with 200 ml isopropyl alcohol, yielding some solid and again with 700 ml acetone, yielding more solid. The supernatant is decanted and the solid washed with 200 ml acetone. The acetone is decanted and the solid evaporated to dryness, yielding 32 g of crude, desired product. The combined decantations, isopropyl alcohol and acetone, are evaporated to yield a thick oil, which when triturated with 100 ml acetone yields a gummy solid. The solid is dried, yielding 44 g crude product, for a combined yield of 76 g.

C. [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-DL-5- α -hydroxypropionylamino-2,4,6-triiodo-3-N-methylamino-carbonylbenzamide. The crude product prepared in Step B (theoretically 0.085 g-mole) is dissolved in 300 ml water (pH 9.2). Conc. H₂SO₄ (5 ml) is added to adjust the pH to 1. The solution is refluxed for 7 hours and then evaporated to dryness. The gummy solid remaining is dissolved in 300 ml water and the solution is stirred at 100°C overnight. HPLC analysis showed approx. 80% purity. The solution is then treated with ion exchange resins IRA-68, IRA-458, and IR-120 H, 100 ml each, and the resins are washed four times each with 100 ml water. The washings and solution are combined and evaporated to dryness giving a yellow glassy solid (48 g, 80.5% pure). The crude product is then purified by reverse-phase preparative HPLC to yield 34 g. The structure was verified by nmr. The product is 100% water soluble. The i.v. LD₅₀ in mice is 13.1 g I/kg.

Osmolality: 506 mOsm/kg (32% I); viscosity: 4.9 cps (37°),
8.1 cps (25°) (32% I).

EXAMPLE 16

Preparation of [N-(2,3-dihydroxypropyl)-N-(2-
5 hydroxyethyl)]-5-hydroxyacetyl-amino-2,4,6-triiodo-3-N-
methylaminocarbonylbenzamide.

A. 5-Acetoxyacetyl-amino-2,4,6-triiodo-3-N-
methylaminocarbonylbenzoyl chloride. 5-Amino-2,4,6-
triiodo-3-N-methylaminocarbonylbenzoyl chloride (61 g,
10 0.1033 g-mole) is added to DMAc (100 ml) with stirring and
heated to 30°C. Acetoxyacetyl chloride is added slowly with
stirring. After stirring at 40°C for 4 hours and overnight
at room temperature, the product completely solidifies from
the solution. Tetrahydrofuran (200 ml) is added and the
15 slurry stirred for 1 hour at room temperature. The white
solid is filtered, washed three times with THF (30-40 ml)
and dried under vacuum at 50°C to produce the crude, desired
product.

B. 5-Acetoxyacetyl-amino-[N-(2,3-dihydroxypropyl)-N-(2-
20 hydroxyethyl)]-2,4,6-triiodo-3-N-methylaminocarbonyl-
benzamide. The crude product of Step A (theoretically
0.1033 g-mole) is added to a mixture of 3-(N-2-
hydroxyethyl)amino-1,2-propanediol (28 g dissolved in 110
ml DMAc) and sodium bicarbonate (17.7 g, 0.21 g-mole) with
25 stirring and heating to 55°C. Carbon dioxide evolution
occurs. After stirring at 55-60°C for five hours, the
solution is allowed to stir overnight at room temperature
and filtered. The solid is washed three times with 50 ml
methanol, and the washings are combined with the filtrate.
30 The combined solution is evaporated under vacuum at 70°C
yielding a thick oil. The oil is triturated with 500 ml
isopropyl alcohol at 65°C for 30 minutes and then allowed to

cool. The supernatant is decanted. The residue is again trituated with 350 ml isopropyl alcohol and then allowed to cool. The supernatant is decanted and the residue evaporated to dryness under vacuum at 75°C yielding the
5 desired product (57 g, 70% yield), confirmed by nmr.

C. [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-5-hydroxyacetyl-amino-2,4,6-triiodo-3-N-methylaminocarbonylbenzamide. The product of Step B is hydrolyzed and purified as in Example 15, Step C, yielding 10.8 g, 99.8%
10 pure. However, the solubility in water (w/v) was found to be less than 25%.

EXAMPLE 17

Preparation of [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-5-[(hydroxyacetyl)(2-hydroxyethyl)amino]-2,4,6-triiodo-3-N-methylaminocarbonylbenzamide.
15

The title compound is prepared by hydrolysis of [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-5-[(acetoxyacetyl)(2-acetoxyethyl)amino]-2,4,6-triiodo-3-N-methylaminocarbonylbenzamide by a procedure similar to the
20 hydrolysis of Example 15, Step C. The diacetate is prepared by reacting 5-acetoxyacetyl-amino-[N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-2,4,6-triiodo-3-N-methylaminocarbonylbenzamide (prepared as in Example 16, Steps A and B) with 2-bromoethylacetate in DMSO in the
25 presence of a base such as potassium carbonate.

EXAMPLE 18

Preparation of [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-5-(2-hydroxyacetyl)amino-2,4,6-triiodo-3-N-(2-hydroxyethyl)aminocarbonylbenzamide.

A. 3-[N-(2-Acetoxyethyl)aminocarbonyl]-5-amino-2,4,6-triiodobenzoic acid. To a stirred solution of 5-amino-2,4,6-triiodo-3-N-(2-hydroxyethyl)aminocarbonylbenzoic acid (107.24 g, 0.178 g-mole) in anhydrous DMAc (100 ml) containing a catalytic amount of 4-dimethylaminopyridine (600 mg, 5 mmole) is added acetic anhydride (29.10 g, 0.285 g-mole, 1.6 equiv.) dropwise over 20 minutes at room temperature. Stirring is continued at room temperature for 16 hours and then 200 ml water is added with vigorous stirring. The resulting suspension is filtered, and the collected solids washed with 100 ml water and dried in a vacuum oven (70°C, 140 mm Hg) for 24 hours to yield 98.23 g (86% yield) desired product. The product exhibits one spot by tlc employing a solvent system of ethyl acetate/methanol (95:5, v/v). ¹H and ¹³C nmr spectra are consistent with the assigned structure.

B. 3-[N-(2-Acetoxyethyl)aminocarbonyl]-5-amino-2,4,6-triiodobenzoyl chloride. To the product of Step A (75.0 g, 0.117 g-mole) is added thionyl chloride (207.9 g, 1.75 g-mole, 15 equiv.) with stirring at room temperature. The resulting solution is heated to reflux with stirring for 3 hours. Excess thionyl chloride is removed by distillation under reduced pressure, partly as an azeotrope with THF (200 ml). The residue is taken up in methylene chloride (1 L) and washed with water (250 ml), saturated aqueous sodium bicarbonate solution (250 ml), and saturated aqueous sodium chloride solution (100 ml). The organic solution is separated, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to yield the desired product (74.25 g, 96% yield). The product exhibited one spot by tlc employing a solvent system of ethyl acetate/hexane (70:30 v/v). ¹H and ¹³C nmr spectra are consistent with the structure.

C. 5-Acetoxyacetyl-amino-3-N-(2-acetoxyethyl)amino-carbonyl-2,4,6-triiodobenzoyl chloride. To a solution of the product of Step B (60 g, 0.091 g-mole) in DMAc (60 ml) is added acetoxyacetyl chloride (24.73 g, 0.18 g-mole, 2 equiv.) with stirring over 20 minutes at room temperature. Stirring is continued at room temperature for 16 hours and the reaction mixture then added to vigorously stirred ice cold water. The resulting solid product is collected by vacuum filtration and dried in a vacuum oven to yield 66.95 g (96% yield) of the desired product, confirmed by tlc and nmr.

D. [N-(2,3-Dihydroxypropyl)-N-(2-hydroxyethyl)]-5-(acetoxyacetyl-amino)-2,4,6-triiodo-3-N-(acetoxyethyl)-aminocarbonylbenzamide. To a solution of the product of Step C (66.65 g, 0.087 g-mole) in DMAc (60 ml) containing anhydrous sodium carbonate (9.22 g, 0.087 g-mole, 1 equiv.) is added 3-(N-2-hydroxyethyl)amino-1,2-propanediol (43.5 ml of a 41% w/v solution in DMAc, 1.5 equiv.) with stirring at room temperature under an atmosphere of dry nitrogen. After stirring at room temperature for 16 hours, the mixture is filtered through celite to remove inorganic salts and then distilled under high vacuum. This yields 102.8 g of crude product.

E. [N-(2,3-Dihydroxypropyl)-N-(2-hydroxyethyl)]-5-(2-hydroxyacetyl)amino-2,4,6-triiodo-3-N-(2-hydroxyethyl)aminocarbonylbenzamide. The crude diacetate product of Step D is dissolved in methanol (90 ml) and water (90 ml) is added. The pH is adjusted to 1 with sulfuric acid, and the mixture is stirred and heated to reflux for 2 hours. The mixture is then concentrated by distillation and purified by passing it through ion-exchange resins and by preparative HPLC, yielding 25.77 g of 98% pure product as confirmed by HPLC, tlc, and nmr.

The product is 100% w/v water-soluble. Osmolality: 597 mOsm/kg (32% I); viscosity: 5.3 cps (37°), 7.4 cps (25°) (32% I); the i.v. LD50 in mice is 20.6 gI/kg.

EXAMPLE 19

- 5 Preparation of [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-3-N-(2-hydroxyethyl)aminocarbonyl-DL-5- α -hydroxypropionylamino-2,4,6-triiodobenzamide.

As in Example 18, the title compound is prepared stepwise by reacting the product of Example 18, Step B with (+)-2-acetoxypropionyl chloride, as in Step C and completing the
10 synthesis.

EXAMPLE 20

- Preparation of [N-(2,3-Dihydroxypropyl)-N-(2-hydroxyethyl)]-3-N-(2,3-dihydroxypropylaminocarbonyl)-5-
15 (hydroxyacetylamino)-2,4,6-triiodobenzamide

A. 3-N-(2,3-Dihydroxypropylaminocarbonyl)-5-acetoxyacetylamino-2,4,6-triiodobenzoyl chloride. To 5-acetoxyacetylamino-2,4,6-triiodoisophthaloyl chloride (100g, 0.1437 moles) was added anhydrous DMAc (360mL). The
20 reaction mixture was cooled to 20°C and then 3-amino-1,2-propanediol (27.49g, 0.3018 moles) as a solution in DMAc (108mL) was added at such a rate that the temperature remained below 25°C. The reaction mixture was stirred at room temperature for 2.5 hours and the reaction progress
25 checked by TLC employing a mobile phase of EtOAc/CH₂Cl₂/HOAc (30:20:1, volume ratio) which indicated a trace of starting material remaining. At this time the DMAc solvent was removed under high vacuum until a thick oil was obtained. To this oil was added dioxane (1 L) and the cloudy mixture
30 was heated to 80°C. A yellow oily impurity separated out of solution. The solution was decanted away from the oily

impurity into CH_2Cl_2 (3 L) with rapid stirring. The CH_2Cl_2 slurry was cooled to 10-15°C while stirring. The product was collected by vacuum filtration on Whatman #4 filter paper, the collected solids were dried in a forced-air oven
5 at 45°C for 3 hours to give the desired product as a tan powder (61 g, 57% yield). TLC employing a solvent system of EtOAc/ CH_2Cl_2 /HOAc (30:20:1 v/v) of both the mother liquor and the dried solid product revealed only a single spot with no trace of starting material.

10 B. [N-(2,3-Dihydroxypropyl)-N-(2-hydroxyethyl)]-3-N-(2,3-dihydroxypropylaminocarbonyl)-5-(acetoxycetyl-amino)-2,4,6-triiodobenzamide. To 3-N-(2,3-dihydroxypropylaminocarbonyl)-5-acetoxycetyl-amino-2,4,6-triiodobenzoyl chloride (60 g, 0.0817 moles) was added DMAc (150mL) and
15 the mixture stirred until dissolution was complete. 3-(N-2-hydroxyethyl)amino-1,2-propanediol (8.14mL of a 41% w/v solution in DMAc, 33.37 g (HE)APD, 0.245 moles) was then added rapidly in one portion. Starting temperature was 23°C, final temperature was 24°C. The addition funnel was
20 rinsed with 30mL DMAc and this was added into the reaction mixture. The cooling bath was removed and the mixture was stirred at room temperature for 16 hours. The mixture was then concentrated on a rotavapor under high vacuum with warming of the reaction flask in a 70°C water bath to
25 remove DMAc which afforded the crude product as an oil (115g). This product was not purified but was used directly in the next reaction.

C. N-(2,3-Dihydroxypropyl)-N-(2-hydroxyethyl)-3-N-(2,3-dihydroxypropylaminocarbonyl)-5-(hydroxycetyl-amino)-2,4,6-triiodobenzamide. To N-(2,3-Dihydroxypropyl)-N-(2-hydroxyethyl)-3-N-(2,3-dihydroxypropylaminocarbonyl)-5-(acetoxycetyl-amino)-2,4,6-triiodobenzamide was added
30 deionized water (200mL) and the mixture was stirred until

all the oil dissolved. The pH was adjusted to $\text{pH} \approx 1$ by the addition of concentrated H_2SO_4 (9.8g, 0.1005 moles) (initial pH 8.54; final pH 0.945). The reaction mixture was steam distilled and the distillate collected while maintaining the original volume of the reaction mixture by periodic addition of additional deionized water. The progress of the reaction was monitored by HPLC [employing a C18 reverse phase 10 μm silica gel column employing a mobile phase of water-acetonitrile (70:30 v/v) at a flow rate of 2 mL/min, and detection at 254 nm]. After 6 hours of steam distillation, HPLC analysis indicated an 84.5 area % for the desired product. At this time an additional aliquot of concentrated sulfuric acid (3.7g, 0.0377 moles) was added, and steam distillation was continued for another 2 hours. The steam distillation was stopped, the solution was allowed to cool to room temperature, and the reaction mixture checked by HPLC, which indicated an 85.2 area % yield of the desired product. This crude material was purified as described in step D.

D. Product Purification:

D-1. Deionization and decolorization. Into a 5 cm i.d. fritted glass chromatography column was added IR-120H (172mL wet volume) and IRA-68 (208mL wet volume) ion exchange resins (Rohm and Haas Company). The column bed was topped with washed sand. The acidic solution of the crude product was eluted through the column at a flow rate of not less than 29 mL/min. The column was rinsed with deionized water until the eluant no longer contained product. The pH of the eluant was adjusted to $\text{pH} \approx 4$ by stirring with additional IRA-68 resin and filtration. Darco G-60 (4 grams) was added to the filtrate and the suspension was stirred briefly and then filtered (filtrate $\text{pH} = 4.5$). The light yellow filtrate was evaporated under

high vacuum on a rotavapor with warming of the rotary flask in a 70°C water bath to afford the crude deionized product (75g).

D-2. Preparative Chromatography. To the crude deionized product (75 g) was added deionized water (91mL) to give ~65% w/v solution.. An M-70 stainless steel column (Whatman, Inc.) packed with C-18 bonded phase silica gel was washed with 10 L of methanol and then equilibrated with 20 L of deionized water. The above solution of the crude deionized product was injected onto the column and the column eluted with water at 250 mL/min. Fifteen fractions of 4L each were collected. Fractions 4 through 11 were determined to contain the desired product by analytical HPLC analysis with detection at 254 nm. These fractions were combined and concentrated under reduced pressure to a final volume of ~1 L. This solution was passed through a 0.22 µm Millipore filter and then completely concentrated under reduced pressure to give the purified product as a white solid (41 g, 55% yield). NMR spectral analysis of the product was consistent with the desired product contaminated with traces of DMAc. The product was further purified by repeating the above preparative chromatography procedure. Thus, the above purified sample (41 g) was dissolved in deionized water (50 mL) and injected onto the above M-70 reverse phase HPLC column which had been preequilibrated with deionized water. The column was eluted with deionized water at a flow of 150 mL/min. Fractions containing the purified product were combined and concentrated under reduced pressure to a volume of ~250mL. This solution was stirred for 1 hour with 1.2g of activated charcoal and then filtered through a Millipore 0.22 µm membrane filter. The filtered solution was completely concentrated under reduced pressure to afford 29.45 g (39.5% yield) of N-(2,3-Dihydroxypropyl)-N-(2-

hydroxyethyl)-3-N-(2,3-dihydroxypropylaminocarbonyl)-5-(hydroxyacetyl-amino)-2,4,6-triiodobenzamide. Mp. 235°C (dec.), Anal. calcd for $C_{18}H_{24}I_3N_3O_9$: C, 26.79; H, 3.00; N, 5.21; I, 47.17. Found: C, 26.45; H, 3.09; N, 5.16; I, 47.07. The ^{13}C NMR spectrum was consistent with the assigned structure. LD₅₀ (i.v.) in mice employing a 35% I (w/v) solution was determined to be 16-17.5 gI/kg.

EXAMPLE 21

Preparation of [N-(2,3-Dihydroxypropyl)-N-(2-hydroxyethyl)]-5-hydroxyacetyl-amino-3-(N-2-hydroxyethyl-N-methylaminocarbonyl)-2,4,6-triiodobenzamide

A. 5-Amino-3-(N-2-acetoxyethyl-N-methylaminocarbonyl)-2,4,6-triiodobenzoic Acid. To a stirred solution of 5-amino-3-(N-2-acetoxyethyl-N-methylaminocarbonyl)-2,4,6-triiodobenzoic acid (203g, 0.33 g-mole) in DMAc (385 ml) containing 4-dimethylaminopyridine (8.1g, 0.066 g-mole) is added acetic anhydride (135g, 1.32 g-mole) at 25-35°C. Stirring is continued at room temperature for 16 hours to complete the reaction.

The solution is then evaporated under vacuum to distill off 350 ml of the solvent to provide a thin oil. The oil is dissolved in 150 ml of DMAc and the solution is added slowly into 2L of water with stirring to precipitate yellow solid. The resulting slurry is acidified with 150 ml of 6N HCl to pH 1. The solid is collected, reslurried in 500 ml of water, treated with NaHSO₃ (20g), collected, washed three times each with 50 ml of water and dried to obtain 180g of the desired product (83% yield).

B. 5-Amino-3-(N-2-acetoxyethyl-N-methylaminocarbonyl)-2,4,6-triiodobenzoyl Chloride. The product of Step A (49g, 0.075 g-mole) and thionyl chloride (89g, 0.75 g-mole) are

mixed and refluxed for 4 hours. The excess thionyl chloride is evaporated to give a thick oil. A mixture of THF (150 ml) and EtOAc (50 ml) is added to dissolve the oil and the resulting solution is washed twice with 10% NaCl (200 and 100 ml). After drying over anhydrous MgSO_4 , the solution is evaporated to dryness to yield 46.2g of the desired product (91.7% yield). The product exhibited one major spot by TLC employing EtOAc as the elution solvent. The structure is confirmed by ^{13}C NMR.

- 10 C. 5-Acetoxyacetyl-amino-3-(N-2-acetoxyethyl-N-methylaminocarbonyl-2,4,6-triiodobenzoyl Chloride. To a solution of the product (46g, 0.068 g-mole) obtained from Step B in 100 ml of THF is added acetoxyacetyl chloride (28.1g, 0.206 g-mole) and the solution is heated and stirred at 55°C for 20 hours. The solvent is evaporated and DMAc (50 ml) is added. Stirring and heating (60°C) continue for another 16 hours to complete the reaction.

DMAc is evaporated and THF (50 ml) is added to give a thin slurry. The slurry is added into a mixture of methanol (1L) and water (0.4L) with vigorous stirring at 10°C to precipitate the desired product (15g, 28% yield). The structure is confirmed by ^{13}C NMR. The methanol-water solution still contains the remaining product. However, no attempt is made to isolate the product.

- 25 D. 5-Acetoxyacetyl-amino-3-(N-2-acetoxyethyl-N-methylaminocarbonyl)-N-2,3-dihydroxypropyl-N-2-hydroxyethyl-2,4,6-triiodobenzamide. The product of Step C (14.9g, 0.02 g-mole) is dissolved in dioxane (40 ml) and a solution of DMAc (14.5 ml) containing 6g (0.044 g-mole) of 3-(N-2-hydroxyethyl)amino-1,2-propanediol is added. The solution is stirred at room temperature overnight to complete the reaction. The solvent is then evaporated to

provide the crude desired product. The material is used directly in the following reaction without further purification.

E. N-2,3-Dihydroxypropyl-N-2-hydroxyethyl-5-hydroxyacetyl amino-3-(N-2-hydroxyethyl-N-methylaminocarbonyl)-2,4,6-triiodobenzamide. The crude product from Step D is dissolved in MeOH (100 ml) and the solution is diluted with water (100 ml). The pH of the solution is adjusted to approximately 1 with 1 ml of concentrated sulfuric acid. The resulting solution is stirred and heated at 90°C overnight to complete the hydrolysis of the acetate groups.

The solution is passed through ion-exchange resins (50 ml of IRA-68, 40 ml of IRA-458 and 50 ml of IR-120 H) and the resins washed four times with 50 ml of a 1:1 mixture of methanol-water. The solutions are combined and evaporated to provide a yellow glassy solid (13.7g, 80% pure by HPLC). The crude product is then purified by reverse-phase preparative HPLC to provide the purified desired product.

20

EXAMPLE 22

Preparation of [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-5-N-(2-hydroxybutyrolactamido)-2,4,6-triiodo-3-N-methylaminocarbonylbenzamide.

As in Example 12, the title compound is prepared stepwise by first reacting 5-amino-2,4,6-triiodo-3-N-methylaminocarbonylbenzoyl chloride with 3-(N-2-hydroxyethyl)amino-1,2-propanediol dissolved in DMAc in the presence of sodium carbonate. The product, 5-amino-[N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-2,4,6-triiodo-3-N-methylaminocarbonylbenzamide, is reacted with acetic anhydride in the presence of pyridine to produce the

triacetate, [N-(2-acetoxyethyl)-N-(2,3-diacetoxypropyl)]-5-amino-,4,6-triiodo-3-N-methylaminocarbonylbenzamide. This compound is then reacted with 2,4-dibromobutyryl bromide, prepared as in Example 12, Step B, and the product is then
5 cyclized, hydrolyzed, and purified as in Example 12, Steps D and E to produce the final product.

EXAMPLE 23

Preparation of [N-(2,3-dihydroxypropyl)-N-(2-hydroxyethyl)]-5-N-(2-hydroxybutyrolactamido)-2,4,6-
10 triiodo-3-[N-(2-hydroxyethyl)aminocarbonyl]benzamide.

The title compound is prepared as in Examples 12 and 18 starting from 3-N-(2-acetoxyethyl)aminocarbonyl-5-amino-2,4,6-triiodobenzoyl chloride.

EXAMPLE 24

15 Preparation of N,N'-bis[3,5-bis(N-2,3-dihydroxypropyl-N-2-hydroxyethyl)aminocarbonyl]-2,4,6-triiodophenyl]-malondiamide.

A. N,N'-bis[3,5-bis(chlorocarbonyl)-2,4,6-triiodophenyl]-malondiamide. 5-Amino-2,4,6-triiodoisophthaloyl chloride
20 (59.58 g, 0.1 g-mole) is dissolved in 130 ml dioxane (dried over molecular sieves). The solution is heated to 90°C and stirred while malonyl chloride (8.5 g, 0.06 g-mole) is added dropwise. The mixture was stirred at 90°C for 3 hours. A pasty precipitate forms. The solid is filtered,
25 washed three times with 25 ml dioxane on the filter, suction-dried and then vacuum dried at 60°C to yield the desired product (51.4 g, 81% yield). The structure of the dimer was confirmed by nmr.

B. N,N'-Bis[3,5-bis(N-2,3-dihydroxypropyl-N-2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-
30

malondiamide. The product of Step A (50 g, 0.04 g-mole) is added slowly to a mixture of 3-(N-2-hydroxyethyl)amino-1,2-propanediol (32.4 g, 0.24 g-mole) dissolved in DMAc (115 ml) and sodium carbonate (17 g, 0.16 g-mole), with
5 stirring. After 7 hours stirring at room temperature, the reaction is complete as determined by HPLC. The reaction mixture is diluted with 200 ml DMAc and filtered to remove the salts. The clear filtrate is evaporated to dryness yielding a clear yellow gummy solid (86.5 g). The solid is
10 triturated with 50 ml isopropanol at 60°C for 10 minutes. After standing overnight the supernatant is decanted and the solid evaporated to dryness. The solid is dissolved in 150 ml water at 60-65°C yielding a clear solution, pH 10. The solution is stirred with Amberlite IR-120 plus H resin
15 for 30 minutes (pH 1-2) and filtered. The filtrate is evaporated to dryness to give the crude desired product (61.4 g, 95% purity by HPLC). The crude product is purified by preparative reverse-phase HPLC, yielding 37 g (56% yield) having 98% purity. The compound is 100% (w/v)
20 water soluble. Osmolality: 213 mOsm/kg (32% I), 191 mOsm/kg (28% I); viscosity: 18.8 cps (37°, 32% I), 11.4 cps (37°, 28% I); the i.v. LD₅₀ in mice: 17.5 gI/kg.

EXAMPLE 25

Preparation of N,N'-bis[3,5-bis(N-2,3-dihydroxypropyl-N-2-
25 hydroxyethyl)aminocarbonyl]-2,4,6-triiodophenyl]-oxamide.

This compound is prepared as in Example 24 using oxalyl chloride in place of malonyl chloride.

EXAMPLE 26

Preparation of N,N'-Bis[3,5-bis(N-2,3-dihydroxypropyl-N-2-
30 hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-succinamide.

This compound is prepared as in Example 24 using succinyl chloride in place of malonyl chloride.

Example 27

Preparation of N,N'-Bis[3-(N-2-hydroxyethyl-aminocarbonyl)-
5 5-(N-2,3-dihydroxypropyl-N-2-hydroxyethylaminocarbonyl)-
2,4,6-triiodophenyl]-oxamide.

The title compound is prepared by reacting 3-N-(2-acetoxyethyl)aminocarbonyl-5-amino-2,4,6-triiodobenzoyl chloride, prepared as in Example 18, Step B, with oxalyl
10 chloride in dioxane; reacting the product with 3-(N-2-hydroxyethyl)amino-1,2-propanediol in DMAc; and hydrolyzing the acetate groups with aqueous sulfuric acid (as in Example 18, Step E).

Example 28

15 Preparation of N,N'-Bis[3-(N-2-hydroxyethyl-aminocarbonyl)-
5-(N-2,3-dihydroxypropyl-N-2-hydroxyethylaminocarbonyl)-
2,4,6-triiodophenyl]-malondiamide.

The title compound is prepared as in Example 27 using malonyl chloride instead of oxalyl chloride.

20

Example 29

Preparation of N,N'-Bis[3-(N-2-hydroxyethyl-aminocarbonyl)-
5-(N-2,3-dihydroxypropyl-N-2-hydroxyethylaminocarbonyl)-
2,4,6-triiodophenyl]-succinamide.

The title compound is prepared as in Example 27 using
25 succinyl chloride instead of oxalyl chloride.

Example 30

Preparation of N,N'-Bis[3-(N-2,3-dihydroxypropionamino-carbonyl)-5-(N-2,3-dihydroxypropyl-N-2-hydroxyethyl-aminocarbonyl)-2,4,6-triiodophenyl]-malondiamide.

5 This compound is prepared by reacting two equivalents of 5-amino-3-(N-2,3-diacetoxypropionaminocarbonyl)-2,4,6-triiodobenzoyl chloride with malonyl chloride, then reacting the dimer with two equivalents of 3-(N-2-hydroxyethyl)amino-1,2-propanediol, and finally removing the acetate groups by hydrolysis.

10

Example 31

Preparation of N,N'-Bis[3-(N-2,3-dihydroxypropionamino-carbonyl)-5-(N-2,3-dihydroxypropyl-N-2-hydroxyethyl-aminocarbonyl)-2,4,6-triiodophenyl]-oxamide.

15 The title compound is prepared as in Example 30 using oxalyl chloride instead of malonyl chloride.

Example 32

Preparation of N,N'-Bis[3-(N-2,3-dihydroxypropionamino-carbonyl)-5-(N-2,3-dihydroxypropyl-N-2-hydroxyethyl-aminocarbonyl)-2,4,6-triiodophenyl]-succinamide.

20 The title compound is prepared as in Example 30 using succinyl chloride instead of malonyl chloride.

EXAMPLE 33

25 Preparation of N,N'-dimethyl-N,N'-bis[3,5-bis(N-2,3-dihydroxypropyl-N-2-hydroxyethyl)aminocarbonyl]-2,4,6-triiodophenyl]-malondiamide.

The title compound is prepared by reacting the product of Example 24 with methyl iodide under basic, alkylating conditions.

EXAMPLE 34

Preparation of N,N'-dimethyl-N,N'-bis[3,5-bis(N-2,3-dihydroxypropyl-N-2-hydroxyethyl)aminocarbonyl]-2,4,6-triiodophenyl]-oxamide.

- 5 The title compound is prepared by reacting the product of Example 25 with methyl iodide under basic, alkylating conditions.

EXAMPLE 35

- 10 Preparation of N,N'-dimethyl-N,N'-bis[3,5-bis(N-2,3-dihydroxypropyl-N-2-hydroxyethyl)aminocarbonyl]-2,4,6-triiodophenyl]-succinamide.

The title compound is prepared by reacting the product of Example 26 with methyl iodide under basic, alkylating conditions.

15

Example 36

Preparation of N,N'-dimethyl-N,N'-Bis[3-(N-2-hydroxyethylaminocarbonyl)-5-(N-2,3-dihydroxypropyl-N-2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-oxamide.

- 20 The title compound is prepared by reacting the product of Example 27 with methyl iodide under basic, alkylating conditions.

Example 37

- 25 Preparation of N,N'-dimethyl-N,N'-Bis[3-(N-2-hydroxyethylaminocarbonyl)-5-(N-2,3-dihydroxypropyl-N-2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-malondiamide.

The title compound is prepared by reacting the product of Example 28 with methyl iodide under basic, alkylating conditions.

Example 38

- 5 Preparation of N,N'-dimethyl-N,N'-Bis[3-(N-2-hydroxyethyl-aminocarbonyl)-5-(N-2,3-dihydroxypropyl-N-2-hydroxyethylaminocarbonyl)-2,4,6-triiodophenyl]-succinamide.

- 10 The title compound is prepared by reacting the product of Example 29 with methyl iodide under basic, alkylating conditions.

Example 39

- 15 Preparation of N,N'-dimethyl-N,N'-bis[3-(N-2,3-dihydroxypropionamino-carbonyl)-5-(N-2,3-dihydroxypropyl-N-2-hydroxyethyl-aminocarbonyl)-2,4,6-triiodophenyl]-malondiamide.

The title compound is prepared by reacting the product of Example 30 with methyl iodide under basic, alkylating conditions.

20

Example 40

- Preparation of N,N'-dimethyl-N,N'-bis[3-(N-2,3-dihydroxypropionamino-carbonyl)-5-(N-2,3-dihydroxypropyl-N-2-hydroxyethyl-aminocarbonyl)-2,4,6-triiodophenyl]-oxamide.

- 25 The title compound is prepared by reacting the product of Example 31 with methyl iodide under basic, alkylating conditions.

Example 41

Preparation of N,N'-dimethyl-N,N'-bis[3-(N-2,3-dihydroxypropionamino-carbonyl)-5-(N-2,3-dihydroxypropyl-N-2-hydroxyethyl-aminocarbonyl)-2,4,6-triiodophenyl]-succinamide.

- 5 The title compound is prepared by reacting the product of Example 32 with methyl iodide under basic, alkylating conditions.

Example 42

10 Preparation of 3-(N-2-hydroxyethyl)amino-1,2-propanediol (Two methods).

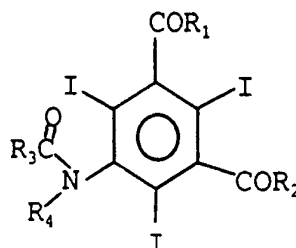
A. Glycidol (128 g, 115 ml, 1.73 g-mole) is added dropwise over a 1 hour period to ethanolamine (854 g, 843 ml, 14.0 g-mole) with stirring, keeping the temperature below 10 °C. After the addition is complete, the temperature is allowed to rise to room temperature and the solution is stirred for 15 20 hours. TLC analysis of the yellow solution indicates the reaction is complete. The product is separated from the excess ethanolamine by Kugelrohr distillation (b.p. 170 - 182 °C at 1-1.2 mm Hg) to give a colorless thick oil which solidifies on standing (196 g, 84% yield). ¹³C nmr spectrum and elemental analysis data are consistent with the structure.

B. 3-Chloro-1,2-propanediol (110.5 g, 1 g-mole) is added dropwise over a 3 hour period to ethanolamine (305.4 g, 5.0 g-mole) with stirring. The temperature of the reaction is kept at 10 - 15 °C. After the addition is complete, the solution is allowed to warm to room temperature, then stirred overnight. The excess ethanolamine is removed by Kugelrohr distillation to yield 145 g of a thick oil, the hydrochloride salt of the desired product. The oil is 30 dissolved in 160 ml water. To this solution is added 50%

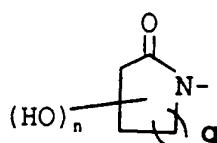
w/w NaOH solution (44.21 ml, 33.8 g, 0.85 g-mole), with stirring, keeping the temperature below 20 °C. After the addition is complete, the solution is stirred overnight at room temperature. Water is removed by rotary evaporation
5 (80 °C, under vacuum) to yield an orange oil. The oil is dissolved in 125 ml of methanol to precipitate sodium chloride. The salt is filtered off and the filtrate is evaporated to yield 98.3 g of an orange oil. The desired product is isolated from this oil by Kugelrohr distillation
10 (148 - 168 °C, 0.8-0.9 mm Hg) to give a colorless oil which solidifies on standing (71 g, 53% yield). ¹³C nmr data are consistent with the structure.

What is claimed is:

1. A compound of the formula:

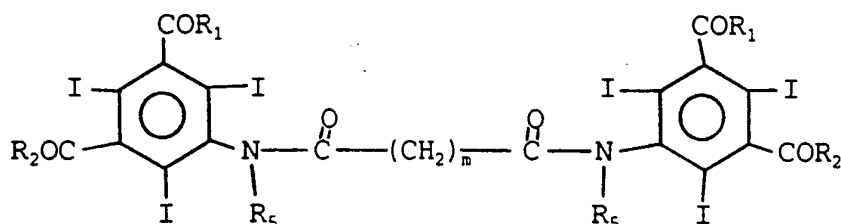


wherein R_1 is $N(CH_2CH_2OH)CH_2CHOHCH_2OH$; R_2 equals R_1 , $NHCH_3$, $NHCH_2CH_2OH$ or $NHCH_2CHOHCH_2OH$; R_3 equals CH_3 , CH_2OH , $CH(CH_3)OH$, $CHOHCH_2OH$, CH_2OCH_3 , or $CH_2OCH_2CH_3$; R_4 equals H , CH_3 , CH_2CH_2OH , $CH_2CH_2OCH_3$, $CH_2CHOHCH_2OH$, or $CH_2CHOHCH_2OCH_3$; or R_3 and R_4 together form the group



wherein n equals 0, 1, 2 or 3 and q equals 0, 1, 2 or 3.

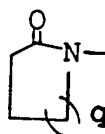
2. A compound of the formula



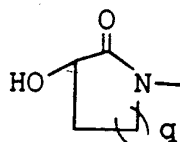
wherein R_1 is $N(CH_2CH_2OH)CH_2CHOHCH_2OH$; R_2 equals R_1 , $NHCH_3$, $NHCH_2CH_2OH$, or $NHCH_2CHOHCH_2OH$; R_5 is H , CH_3 , CH_2CH_2OH , $CH_2CHOHCH_2OH$, or CH_2OCH_3 ; and m equals 0-4.

3. The compound of Claim 1, wherein R_2 equals R_1 .
4. The compound of Claim 1, wherein R_2 is selected from the group consisting of $NHCH_3$, $NHCH_2CH_2OH$, and $NHCH_2CHOHCH_2OH$.

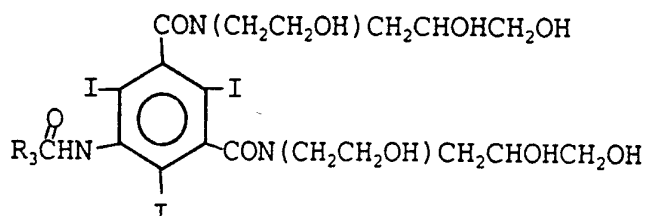
5. The compound of Claim 1, wherein R_4 is hydrogen.
6. The compound of Claim 1, wherein R_4 is selected from the group consisting of CH_3 , $\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CH}_2\text{OCH}_3$, $\text{CH}_2\text{CHOHCH}_2\text{OH}$, and $\text{CH}_2\text{CHOHCH}_2\text{OCH}_3$.
7. The compound of Claim 1, wherein R_3 and R_4 together form the group



8. The compound of Claim 1, wherein R_3 and R_4 together form the group



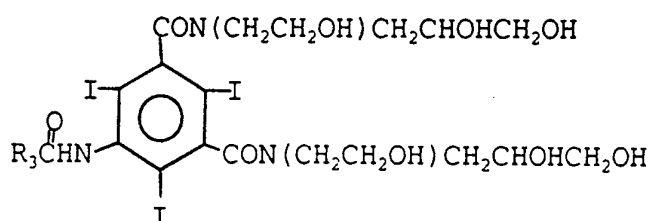
9. The compound of Claim 2, wherein R_2 equals R_1 and m equals 0.
10. The compound of Claim 2, wherein R_2 equals R_1 and m equals 1.
11. The compound of Claim 2, wherein R_2 equals R_1 and m equals 2.
12. The compound of Claim 2, wherein R_2 is selected from the group consisting of NHCH_3 , $\text{NHCH}_2\text{CH}_2\text{OH}$, and $\text{NHCH}_2\text{CHOHCH}_2\text{OH}$.
13. A method for preparing a compound of the general formula



wherein R_3 is selected from the group consisting of CH_3 , CH_2OCH_3 , and $\text{CH}_2\text{OCH}_2\text{CH}_3$, comprising the steps of

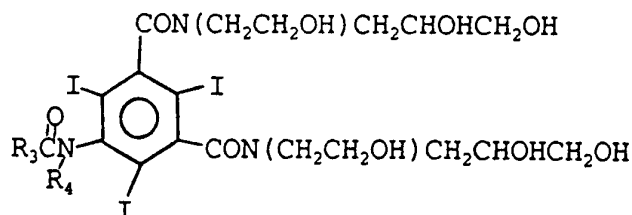
- a. reacting 5-amino-2,4,6-triiodoisophthaloyl chloride with a compound selected from the group

- consisting of acetyl chloride, methoxyacetyl chloride, and acetoxyacetyl chloride, under amide-producing conditions; and
- b. reacting the product of step a with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-producing conditions.
14. A method for preparing a compound of the general formula



wherein R_3 is selected from the group consisting of CH_2OH , $\text{CH}(\text{CH}_3)\text{OH}$, and CHOHCH_2OH , comprising the steps of

- a. reacting 5-amino-2,4,6-triiodoisophthaloyl chloride with a compound selected from the group consisting of acetoxyacetyl chloride, 2-acetoxypropionyl chloride, 2,3-diacetoxypropionyl chloride, under amide-producing conditions;
- b. reacting the product of step a with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-producing conditions; and
- c. hydrolyzing the product of step b under hydrolyzing conditions to remove the acetate groups.
15. A method for preparing a compound of the general formula

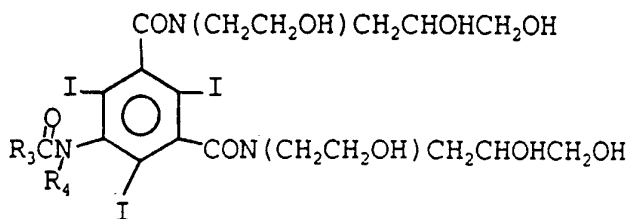


wherein R_3 is selected from the group consisting of CH_3 , CH_2OCH_3 , and $\text{CH}_2\text{OCH}_2\text{CH}_3$, and R_4 is selected from a

group consisting of CH_3 and $\text{CH}_2\text{CH}_2\text{OCH}_3$, comprising the steps of

- a. reacting 5-amino-2,4,6-triiodoisophthaloyl chloride with a compound selected from the group consisting of acetyl chloride, methoxyacetyl chloride, and ethoxyacetyl chloride, under amide-producing conditions;
- b. reacting the product of step a with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-producing conditions; and
- c. reacting the product of step b with a compound selected from the group consisting of methyl halides, and 2-haloethyl methyl ethers under alkylating conditions.

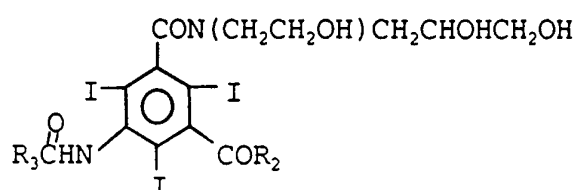
16. A method for preparing a compound of the general formula



wherein R_3 is selected from the group consisting of CH_2OH , $\text{CH}(\text{CH}_3)\text{OH}$, and CHOHCH_2OH , and R_4 is selected from a group consisting of $\text{CH}_2\text{CH}_2\text{OH}$ and $\text{CH}_2\text{CHOHCH}_2\text{OH}$, comprising the steps of

- a. reacting 5-amino-2,4,6-triiodoisophthaloyl chloride with a compound selected from the group consisting of acetoxyacetyl chloride, 2-acetoxypropionyl chloride, 2,3-diacetoxypropionyl chloride, under amide-producing conditions;
- b. reacting the product of step a with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-producing conditions; and
- c. reacting the product of step b with a compound selected from the group consisting of 2-haloethyl

- acetates, halo-2,3-propanediol, and 2,3-diacetoxyhalopropane under secondary amide-substituting conditions; and
- d. hydrolyzing the product of step c under hydrolyzing conditions to remove the acetate groups.
17. A method for preparing a compound of the general formula

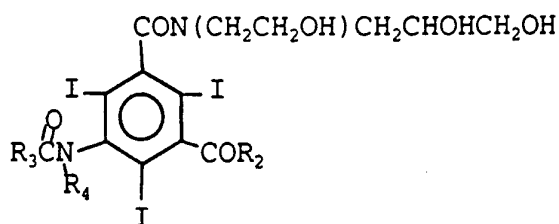


wherein R_2 is selected from the group consisting of NHCH_3 , $\text{NHCH}_2\text{CH}_2\text{OH}$, and $\text{NCH}_2\text{CHOHCH}_2\text{OH}$, and R_3 is selected from the group consisting of CH_3 , CH_2OH , $\text{CH}(\text{CH}_3)\text{OH}$, CHOHCH_2OH , CH_2OCH_3 , and $\text{CH}_2\text{OCH}_2\text{CH}_3$, comprising the steps of

- a. reacting a compound selected from the group consisting of 5-amino-2,4,6-triiodo-3-(N-methylaminocarbonyl)benzoyl chloride, 3-[N-(2-acetoxyethyl)aminocarbonyl]-5-amino-2,4,6-triiodobenzoyl chloride, and 5-amino-3-[N-(2,3-diacetoxypropyl)aminocarbonyl]-2,4,6-triiodobenzoyl chloride; with a compound selected from the group consisting of acetyl chloride, methoxyacetyl chloride, ethoxyacetyl chloride, acetoxyacetyl chloride, 2-acetoxypropionyl chloride, and 2,3-diacetoxypropionyl chloride; under amide-forming conditions;
- b. reacting the product of step a with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-producing conditions; and
- c. if acetate protecting groups are present, thereafter hydrolyzing the product of step b

under hydrolyzing conditions to remove said acetate groups.

18. A method for preparing a compound of the general formula



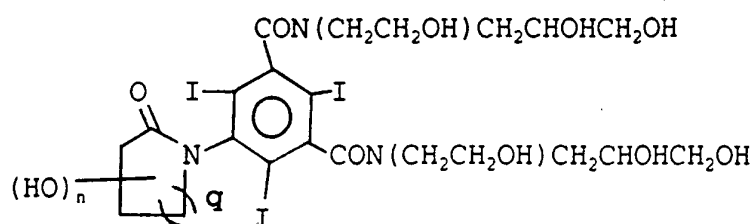
wherein R_2 is selected from the group consisting of NHCH_3 , $\text{NHCH}_2\text{CH}_2\text{OH}$, and $\text{NCH}_2\text{CHOHCH}_2\text{OH}$, R_3 is selected from the group consisting of CH_3 , CH_2OH , $\text{CH}(\text{CH}_3)\text{OH}$, CHOHCH_2OH , CH_2OCH_3 , and $\text{CH}_2\text{OCH}_2\text{CH}_3$, and R_4 is selected from a group consisting of CH_3 , $\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CH}_2\text{OCH}_3$, $\text{CH}_2\text{CHOHCH}_2\text{OH}$, and $\text{CH}_2\text{CHOHCH}_2\text{OCH}_3$, comprising the steps of

- a. reacting a compound selected from the group consisting of 5-amino-2,4,6-triiodo-3-(N-methylaminocarbonyl)benzoyl chloride, 3-[N-(2-acetoxyethyl)aminocarbonyl]-5-amino-2,4,6-triiodobenzoyl chloride, and 5-amino-3-[N-(2,3-diacetoxypropyl)aminocarbonyl]-2,4,6-triiodobenzoyl chloride; with a compound selected from the group consisting of acetyl chloride, methoxyacetyl chloride, ethoxyacetyl chloride, acetoxyacetyl chloride, 2-acetoxypropionyl chloride, and 2,3-diacetoxypropionyl chloride; under amide-forming conditions;
- b. reacting the product of step a with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-producing conditions;
- c. reacting the product of step b with a compound selected from the group consisting of methyl halides, 2-haloethyl methyl ethers, haloethyl acetates, halo-2,3-propanediol, and 2,3-

diacetoxyhalopropane under alkylating conditions;
and

- d. if acetate protecting groups are present, thereafter hydrolyzing the product of step c under hydrolyzing conditions to remove said acetate groups.

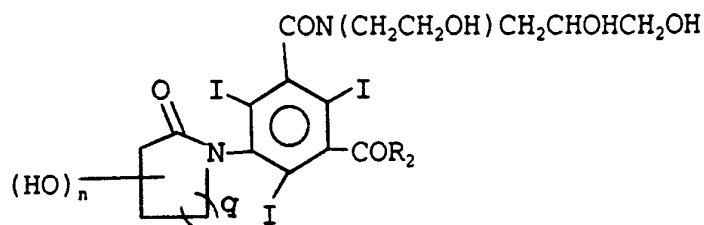
19. A method for preparing a compound of the general formula



wherein n equals 0, 1, 2 or 3 and q equals 0, 1, 2 or 3 comprising the steps of

- a. reacting 5-amino-2,4,6-triiodoisophthaloyl chloride with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-forming conditions;
- b. adding acetate protecting groups to the hydroxyl groups of the product of step a;
- c. reacting the product of step b with a compound selected from the group consisting of 2,4-dibromobutyryl bromide, 2-acetoxy-4-(methylthio)butyryl chloride, and 4-chlorobutyryl chloride under amide-producing conditions;
- d. exposing the product of step c to cyclizing conditions such that butyrolactamide is formed;
and
- e. hydrolyzing the product of step d to under hydrolyzing conditions remove the acetate groups.

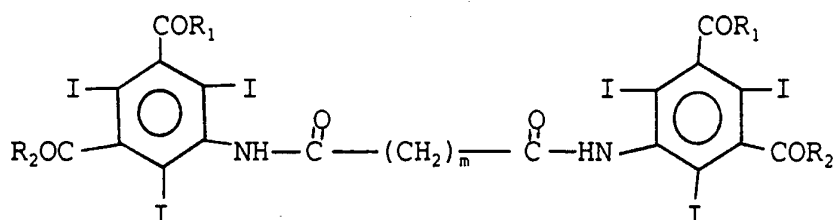
20. A method for preparing a compound of the general formula



wherein R_2 is selected from the group consisting of NHCH_3 , $\text{NHCH}_2\text{CH}_2\text{OH}$, and $\text{NCH}_2\text{CHOHCH}_2\text{OH}$, n equals 0, 1, 2 or 3 and q equals 0, 1, 2 or 3, comprising the steps of

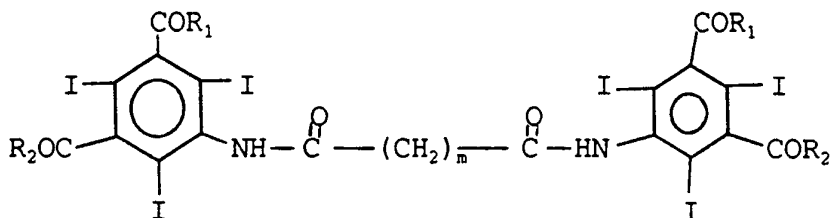
- a. reacting a compound selected from the group consisting of 5-amino-2,4,6-triiodo-3-(N-methylaminocarbonyl)benzoyl chloride, 3-[N-(2-acetoxyethyl)aminocarbonyl]-5-amino-2,4,6-triiodobenzoyl chloride, and 5-amino-3-[N-(2,3-diacetoxypropyl)aminocarbonyl]-2,4,6-triiodobenzoyl chloride; with a compound selected from the group consisting of acetyl chloride, methoxyacetyl chloride, ethoxyacetyl chloride, acetoxyacetyl chloride, 2-acetoxy-propionyl chloride, and 2,3-diacetoxypropionyl chloride; under amide-forming conditions;
- b. reacting the product of step a with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-producing conditions;
- c. adding acetate protecting groups to the hydroxyl groups of the product of step a;
- d. reacting the product of step b with a compound selected from the group consisting of 2,4-dibromobutyryl bromide, 2-acetoxy-4-(methylthio)butyryl chloride, and 4-chlorobutyryl chloride under amide-producing conditions;

- e. exposing the product of step c to cyclizing conditions such that butyrolactamide is formed; and
 - f. hydrolyzing the product of step d under hydrolyzing conditions to remove the acetate groups.
21. A method for preparing a compound of the general formula



wherein R_1 and R_2 are $N(CH_2CH_2OH)CH_2CHOHCH_2OH$ and m equals 0-2, comprising the steps of

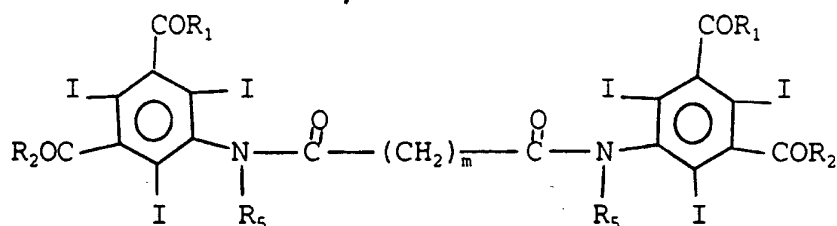
- a. reacting 5-amino-2,4,6-triiodoisophthaloyl chloride with a compound selected from the group consisting of malonyl chloride, oxalyl chloride, and succinyl chloride under amide-forming conditions; and
 - b. reacting the product of step a with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-forming conditions.
22. A method for preparing a compound of the general formula



wherein R_1 is $N(CH_2CH_2OH)CH_2CHOHCH_2OH$, R_2 is selected from the group consisting of $NHCH_3$, $NHCH_2CH_2OH$, and

$\text{NCH}_2\text{CHOHCH}_2\text{OH}$, and m equals 0-2, comprising the steps of

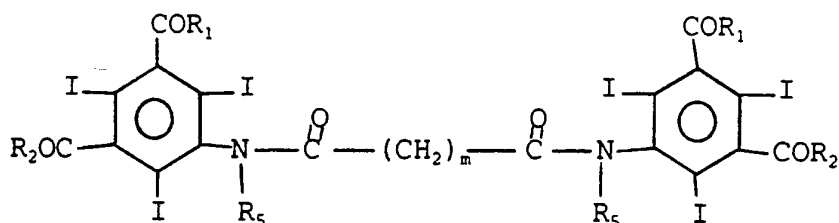
- a. reacting a compound selected from the group consisting of 3-N-(2-acetoxyethyl)-amino-carbonyl-5-amino-2,4,6-triiodobenzoyl chloride, 5-amino-3-(N-2,3-diacetoxypropionamino-carbonyl)-2,4,6-triiodobenzoyl chloride, and 5-amino-3-methylaminocarbonyl-2,4,6-triiodo-benzoyl chloride, with a compound selected from the group consisting of malonyl chloride, oxalyl chloride, and succinyl chloride under amide-forming conditions;
 - b. reacting the product of step a with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-forming conditions; and
 - c. if acetate protecting groups are present, thereafter hydrolyzing the product of step c to remove said acetate groups.
23. A method for preparing a compound of the general formula



wherein R_1 and R_2 are $\text{N}(\text{CH}_2\text{CH}_2\text{OH})\text{CH}_2\text{CHOHCH}_2\text{OH}$, R_5 is selected from the group consisting of CH_3 , $\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CHOHCH}_2\text{OH}$, and CH_2OCH_3 , and m equals 0-2, comprising the steps of

- a. reacting 5-amino-2,4,6-triiodoisophthaloyl chloride with a compound selected from the group consisting of malonyl chloride, oxalyl chloride, and succinyl chloride under amide-forming conditions;

- b. reacting the product of step a with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-forming conditions;
 - c. reacting the product of step b with a compound selected from the group consisting of methyl halides, 2-haloethyl methyl ethers, 2-haloethyl acetates, halo-2,3-propanediol, and 2,3-diacetoxyhalopropane; and
 - d. if acetate protecting groups are present, thereafter hydrolyzing the product of step c under hydrolyzing conditions to remove said acetate groups.
24. A method for preparing a compound of the general formula

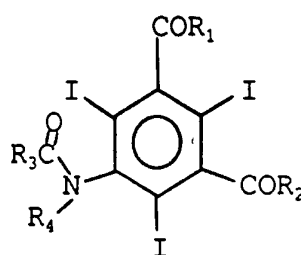


wherein R_1 is $N(CH_2CH_2OH)CH_2CHOHCH_2OH$, R_2 is selected from the group consisting of $NHCH_3$, $NHCH_2CH_2OH$, and $NCH_2CHOHCH_2OH$, R_5 is selected from the group consisting of CH_3 , CH_2CH_2OH , $CH_2CHOHCH_2OH$, and CH_2OCH_3 , and m equals 0-2, comprising the steps of

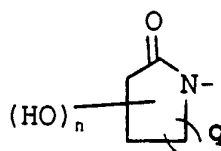
- a. reacting a compound selected from the group consisting of 3-N-(2-acetoxyethyl)-aminocarbonyl-5-amino-2,4,6-triiodobenzoyl chloride, 5-amino-3-(N-2,3-diacetoxypropion-aminocarbonyl)-2,4,6-triiodobenzoyl chloride, and 5-amino-3-methylaminocarbonyl-2,4,6-triiodobenzoyl chloride, with a compound selected from the group consisting of malonyl chloride, oxalyl chloride, and succinyl chloride under amide-forming conditions;

- b. reacting the product of step a with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-forming conditions;
 - c. reacting the product of step b with a compound selected from the group consisting of methyl halides, 2-haloethyl methyl ethers, 2-haloethyl acetates, halo-2,3-propanediol, and 2,3-diacetoxyhalopropane; and
 - d. if acetate protecting groups are present, thereafter hydrolyzing the product of step c under hydrolyzing conditions to remove said acetate groups.
25. A method for preparing 3-(N-2-hydroxyethyl)amino-1,2-propanediol comprising reacting glycidol with ethanolamine under epoxide-adding conditions.
26. A method for preparing 3-(N-2-hydroxyethyl)amino-1,2-propanediol, comprising the steps of reacting 3-chloro-1,2-propanediol with ethanolamine under secondary amine-forming conditions, and thereafter neutralizing the hydrochloride salt formed thereby.
27. A radiological composition containing a compound of Claim 1 in a sufficient amount to provide satisfactory X-ray visualization together with a pharmaceutically acceptable radiological vehicle.
28. A radiological composition containing a compound of Claim 2 in a sufficient amount to provide satisfactory X-ray visualization together with a pharmaceutically acceptable radiological vehicle.
29. A method for X-ray visualization comprising injecting a radiological composition comprising a compound of Claim 1 in a pharmaceutically acceptable radiological vehicle in a sufficient amount to provide adequate visualization and thereafter carrying out X-ray visualization.

30. A method for X-ray visualization comprising injecting a radiological composition comprising a compound of Claim 2 in a pharmaceutically acceptable radiological vehicle in a sufficient amount to provide adequate visualization and thereafter carrying out X-ray visualization.
31. A compound of the formula:



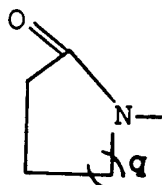
wherein R_1 is $N(CH_2CH_2OH)CH_2CHOHCH_2OH$; R_2 equals R_1 , $NHCH_3$, $NHCH_2CH_2OH$, $N(CH_3)CH_2CH_2OH$ or $NHCH_2CHOHCH_2OH$; R_3 equals CH_3 , CH_2OH , $CH(CH_3)OH$, $CHOHCH_2OH$, CH_2OCH_3 , or $CH_2OCH_2CH_3$; R_4 equals H , CH_3 , CH_2CH_2OH , $CH_2CH_2OCH_3$, $CH_2CHOHCH_2OH$, or $CH_2CHOHCH_2OCH_3$; or R_3 and R_4 together form the group



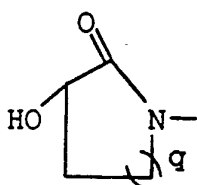
wherein n equals 0, 1, 2 or 3 and q equals 0, 1, 2 or 3.

32. The compound of Claim 31, wherein R_2 equals R_1 .
33. The compound of Claim 31, wherein R_2 is selected from the group consisting of $NHCH_3$, $NHCH_2CH_2OH$, $N(CH_3)CH_2CH_2OH$ and $NHCH_2CHOHCH_2OH$.
34. The compound of Claim 31, wherein R_4 is hydrogen.
35. The compound of Claim 31, wherein R_4 is selected from the group consisting of CH_3 , CH_2CH_2OH , $CH_2CH_2OCH_3$, $CH_2CHOHCH_2OH$, and $CH_2CHOHCH_2OCH_3$.

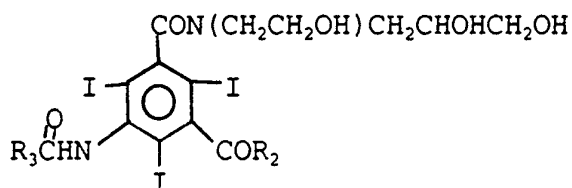
36. The compound of Claim 31, wherein R_3 and R_4 together form the group



37. The compound of Claim 31, wherein R_3 and R_4 together form the group



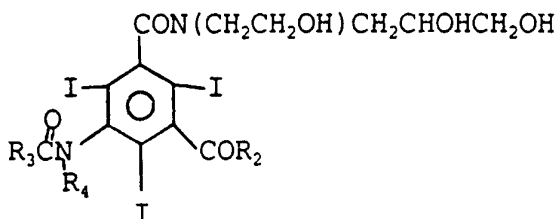
38. A method for preparing a compound of the general formula



wherein R_2 is selected from the group consisting of NHCH_3 , $\text{NHCH}_2\text{CH}_2\text{OH}$, $\text{N}(\text{CH}_3)_3$, $\text{CH}_2\text{CH}_2\text{OH}$, and $\text{NCH}_2\text{CHOHCH}_2\text{OH}$, and R_3 is selected from the group consisting of CH_3 , CH_2OH , $\text{CH}(\text{CH}_3)\text{OH}$, CHOHCH_2OH , CH_2OCH_3 , and $\text{CH}_2\text{OCH}_2\text{CH}_3$, comprising the steps of

- a. reacting a compound selected from the group consisting of 5-amino-2,4,6-triiodo-3-(N-methylaminocarbonyl)benzoyl chloride, 3-[N-(2-acetoxyethyl)aminocarbonyl]-5-amino-2,4,6-triiodobenzoyl chloride, and 5-amino-3-[N-(2,3-diacetoxypropyl)aminocarbonyl]-2,4,6-triiodobenzoyl chloride; with a compound selected from the group consisting of acetyl chloride, methoxyacetyl chloride, ethoxyacetyl chloride, acetoxyacetyl chloride, 2-acetoxypropionyl

- chloride, and 2,3-diacetoxypionyl chloride; under amide-forming conditions;
- b. reacting the product of step a with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-producing conditions; and
- c. if acetate protecting groups are present, thereafter hydrolyzing the product of step b under hydrolyzing conditions to remove said acetate groups.
39. A method for preparing a compound of the general formula



wherein R_2 is selected from the group consisting of NHCH_3 , $\text{NHCH}_2\text{CH}_2\text{OH}$, $\text{N(CH}_3)_3\text{CH}_2\text{CH}_2\text{OH}$, and $\text{NCH}_2\text{CHOHCH}_2\text{OH}$, R_3 is selected from the group consisting of CH_3 , CH_2OH , $\text{CH(CH}_3)_2\text{OH}$, CHOHCH_2OH , CH_2OCH_3 , and $\text{CH}_2\text{OCH}_2\text{CH}_3$, and R_4 is selected from a group consisting of CH_3 , $\text{CH}_2\text{CH}_2\text{OH}$, $\text{CH}_2\text{CH}_2\text{OCH}_3$, $\text{CH}_2\text{CHOHCH}_2\text{OH}$, and $\text{CH}_2\text{CHOHCH}_2\text{OCH}_3$, comprising the steps of

- a. reacting a compound selected from the group consisting of 5-amino-2,4,6-triiodo-3-(N-methylaminocarbonyl)benzoyl chloride, 3-[N-(2-acetoxyethyl)aminocarbonyl]-5-amino-2,4,6-triiodobenzoyl chloride, and 5-amino-3-[N-(2,3-diacetoxypionyl)aminocarbonyl]-2,4,6-triiodobenzoyl chloride; with a compound selected from the group consisting of acetyl chloride, methoxyacetyl chloride, ethoxyacetyl chloride, acetoxyacetyl chloride, 2-acetoxypionyl chloride, and 2,3-diacetoxypionyl chloride; under amide-forming conditions;

- b. reacting the product of step a with 3-(N-2-hydroxyethyl)amino-1,2-propanediol under amide-producing conditions;
- c. reacting the product of step b with a compound selected from the group consisting of methyl halides, 2-haloethyl methyl ethers, haloethyl acetates, halo-2,3-propanediol, and 2,3-diacetoxyhalopropane under alkylating conditions; and
- d. if acetate protecting groups are present, thereafter hydrolyzing the product of step c under hydrolyzing conditions to remove said acetate groups.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/08056

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/153, 155, 16, 158, 133, 142, 143, 478; 548/543, 546, 556; 540/200, 362; 546/200; 424/4, 5

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE STRUCTURAL SEARCH (attached herewith)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4,250,113 (Nordal et al) 10 February 1981.	1-39
A	US, A, 4,396,598 (Lin) 02 Augut 1983.	1-39
A	US, A, 4,426,371 (Pfeiffer et al) 17 January 1984.	1-39

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be part of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

03 December 1993

Date of mailing of the international search report

16 DEC. 1993.

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. NOT APPLICABLE

Authorized officer

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US93/08056

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

(Telephone Practice)

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐

The additional search fees were accompanied by the applicant's protest.

☐

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/08056

A. CLASSIFICATION OF SUBJECT MATTER:

IPC (5):

A61K 49/04; C07C 233/16, 233/17, 233/18, 233/24; C07D 207/12, 211/40, 205/08

A. CLASSIFICATION OF SUBJECT MATTER:

US CL :

564/153, 155, 16, 158, 133, 142, 143, 478; 548/543, 546, 556; 540/200, 362; 546/200; 424/4, 5

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING

This ISA found multiple inventions as follows:

- I. Claims 1, 3-8, 13-16, 29 and 30, drawn to compounds, process of making and method of use, Class 564/153, 155, 156, 158; 548/543, 546, 556; 540/362, 200; 546/220; 424/4, 5.
- II. Claims 2 and 9-12, drawn to compounds, Class 564/153.
- III. Claims 17 and 18, drawn to process of making, Class 564/153.
- IV. Claims 19 and 20, drawn to process of making, Class 564/133, 142, 143.
- V. Claims 21-24, drawn to process of making, Class 564/133, 142, 143.
- VI. Claims 25 and 26, drawn to process of making, Class 564/478.
- VII. Claims 27 and 28, drawn to radiological compositions, 424/4, 5.
- VIII. Claims 31-37, drawn to process of making, Class 564/153, 155, 156, 158; 548/543, 546, 556; 540/200, 362; 546/220; 424/4, 5.
- IX. Claims 38 and 39, drawn to process of making, Class 564/153, 142, 143, 133.

Groups I-IX do not relate to a group of inventions so linked as to form a single general inventive concept. Further, applicants claim more categories of invention than permitted in PCT Rule 13.2 (i) to (iii).