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X-RAY CONTRAST AGENTS

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FIG. 1.

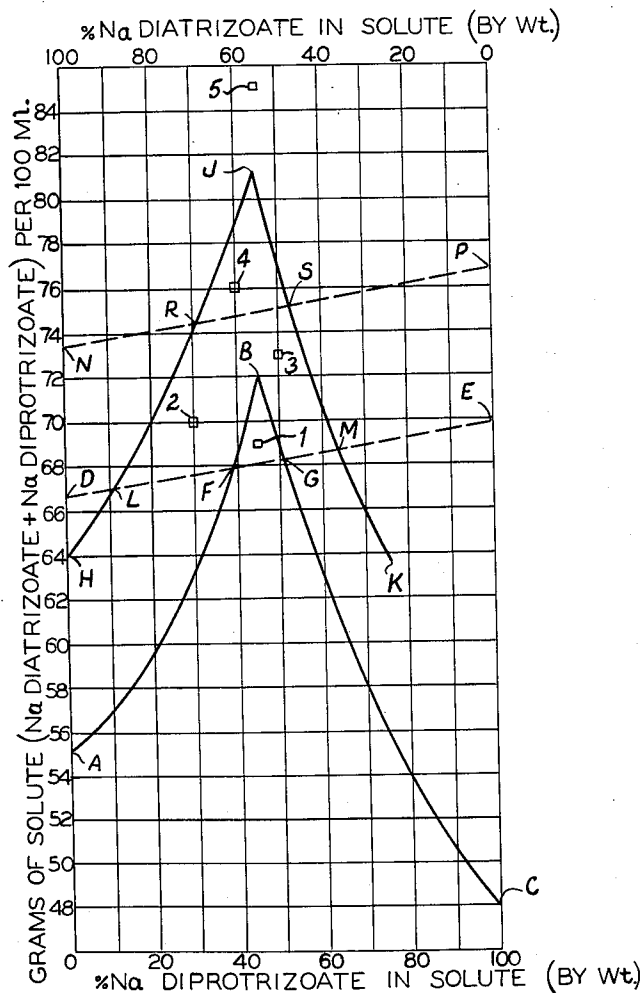
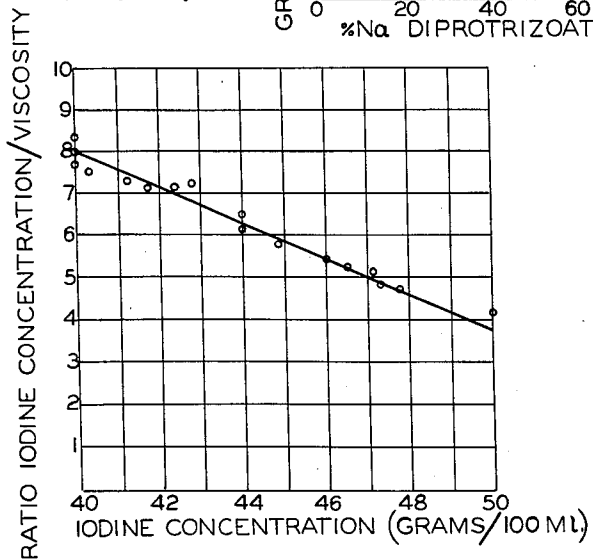


FIG. 2.



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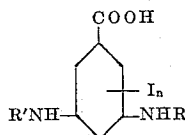
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This invention relates to X-ray contrast media and more particularly to aqueous solutions of relatively low viscosity containing high concentrations of organically bound iodine.

Briefly, the invention relates to X-ray contrast media suitable for intravascular administration comprising aqueous solutions of nontoxic salts of a plurality of 3-lower alkanamido-5-lower alkanamidopolyiodobenzoic acids, said solutions containing, in each 100 ml., not substantially less than 40 g. of iodine in stable organic combination, and being characterized by low viscosities, relative to their iodine concentration.

The invention is based on the discovery that improved X-ray contrast media containing high concentrations of organically bound iodine may be prepared by combining nontoxic salts of two or more different iodinated acids of the type mentioned above in a single solution. The particular compounds whose use in such media is contemplated by the invention are soluble nontoxic salts of the acids having the general formula



where R and R' are lower acyl radicals and n is 2 or 3.

Among the objects of this invention may be mentioned the provision of improved X-ray contrast media, particularly angiocardigraphic media; the provision of such media containing a plurality of 3-lower alkanamido-5-lower alkanamidopolyiodobenzoic acid compounds; the provision of media of the class described which combine high iodine concentration, low viscosity and low pharmacodynamic activity, and the provision of such media which are stable solutions at normal temperatures. Other objects and features will be in part apparent and in part pointed out hereinafter.

The invention accordingly comprises the products hereinafter described, the scope of the invention being indicated in the following claims.

In the accompanying drawings in which relationships of the invention are shown graphically,

FIG. 1 shows solubility related to composition of mixtures of sodium diatrizoate and sodium diprotrizoate, and

FIG. 2 shows the interrelation of certain physical properties of the solutions of FIG. 1.

The use of iodinated organic compounds as X-ray contrast media is well established and in wide variety of such compounds has been proposed for use in roentgenographic procedures. The choice of a medium is determined largely by the technique to be used. Certain techniques may be grouped under the heading of vasographic techniques. In these techniques the contrast medium is injected rapidly into a blood vessel and an X-ray film is exposed when blood containing a high concentration of the contrast medium arrives in the structure to be visualized, or, more frequently, a series of films is exposed in rapid succession during the passage of the contrast medium through the structure. Photographic apparatus especially adapted to the latter purpose is available.

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One of the most exacting of the vasographic techniques is angiocardigraphy, which is the X-ray visualization of the chambers of the heart and the large blood vessels of the chest, for example, the aorta, the pulmonary arteries, the venae cavae and the pulmonary veins, by means of an injected radiopaque medium. The injection is often made intravenously or by means of a catheter inserted through a vein into one of the chambers of the heart. Other techniques of injection are also used. In this procedure, the medium must be injected as rapidly as possible so that a considerable concentration of the radiopaque substance in the heart and/or vessel to be visualized is achieved. For example, it is normally considered desirable in the angiocardigraphic examination of an adult to inject 50 ml. or more of a highly concentrated contrast medium within an interval of one and one-half seconds. To be suitable for use in this technique, the medium must be satisfactorily opaque, even when diluted to a considerable extent by the blood. This requires a highly soluble compound containing a high proportion of the radiopaque element. Furthermore, the highly concentrated medium must be sufficiently fluid to be introduced into the vessel quickly through a needle or catheter small enough to enter the vessel without undue damage. Whereas smaller needles are ordinarily used for other techniques, a 12 gauge needle is normally considered advisable for use in angiocardigraphy.

Angiocardigraphy thus demands the following characteristics in the contrast media used.

(1) *High concentration of radiopaque element (iodine).*—This is necessary for proper visualization of the cardiac chambers and the large vessels of the chest in view of the fact that the medium is diluted by the large volume of blood present. Solutions containing a minimum of 40 g. of iodine per 100 ml. of medium have been generally accepted for routine work and a concentration 10% higher, or 44 g. per 100 ml. is considered desirable.

(2) *Minimal pharmacodynamic activity.*—This is necessary to minimize side effects such as pain at the site of injection, toxic manifestations and an anaphylactic shock-like reactions, with the exceptionally large doses of contrast agent that are administered.

(3) *Low viscosity.*—This is important because of the large volume of medium that must be injected within such a short time.

Although previously known angiocardigraphic media have fulfilled one or two of these criteria acceptably, no medium has fulfilled all three criteria adequately prior to the present invention.

It is evident that both the viscosity and the iodine concentration are factors which govern the rate at which the iodine may be injected. Therefore, the relationship between these two properties must be taken into account in evaluating an angiocardigraphic medium, the combination of high iodine concentration and low viscosity being particularly desirable.

Among the compounds which have been used commercially for angiocardigraphy may be mentioned salts of certain 3-lower alkanamido-5-lower alkanamido-2,4,6-triiodobenzoic acids. Such compounds are disclosed in the co-pending application of Wallingford and Turner, S.N. 445,902, filed July 26, 1954, and in the publication by Larsen et al., JACS 78, 3210-3216 (1956). These acids are also sometimes referred to as 3-lower alkanoylamino-5-lower alkanoylamino-2,4,6-triiodobenzoic acids and sometimes as 3-lower acylamino-5-lower acylamino-2,4,6-triiodobenzoic acids.

Table 1 shows pertinent physical characteristics of some of the most recently proposed media for angiocardigraphy.

TABLE 1
Angiocardiographic Media

Common Name	Parent compound	Salt	Salt concentration (g./100 ml.)	Iodine concentration (g./100 ml.)	Absolute viscosity ¹ (centipoises)	
					25° C.	37.5° C.
Sodium acetrizoate.....	3-acetamido-2, 4, 6-triiodobenzoic acid	Sodium.....	70	46.1	4.6	3.0
Methylglucamine diatrizoate.....	3, 5-diacetamido-2, 4, 6-triiodobenzoic acid.	N-methylglucamine.	85	40	23	13.4
Combination of sodium diatrizoate and methylglucamine diatrizoate	3, 5-dipropionamido-2, 4, 6-triiodobenzoic acid.	(Sodium.....	30)	46.2	39	21
Combination of sodium diprotrizoate and methylglucamine diprotrizoate.		(N-methylglucamine.	60)			
		(Sodium.....	30)	44.5	44	24
		(N-methylglucamine.	60)			

¹ Viscosity data are obtained by the following method: The kinematic viscosity is determined by means of an Ostwald viscometer. The absolute viscosity is then obtained by the following calculation: [Kinematic viscosity (in centistokes) x Sp. Gr. = absolute viscosity (in centipoises)].

It will be noted that the diatrizoate and diprotrizoate media have been customarily compounded using N-methylglucamine salts or mixtures of the sodium and N-methylglucamine salts. Since the sodium salts are not sufficiently soluble to permit the preparation of solutions of sufficiently high iodine concentration for angiocardiography, the use of the N-methylglucamine salt either alone or in combination with the sodium salt was introduced to overcome this solubility problem. However, as the table indicates, the highly concentrated solutions thus produced are relatively viscous. Thus a solution containing in each 100 ml., 30 g. of the sodium salt and 60 g. of the N-methylglucamine salt of diatrizoic acid (3,5-diacetamido-2,4,6-triiodobenzoic acid) contains 46.2 g. of organically bound iodine, but its viscosity is 21 centipoises at 37.5° C.

In addition to its high viscosity such a solution is supersaturated at ordinary temperatures and a voluminous precipitate forms when the solution is stored for any substantial period. This makes it necessary for the radiologist to redissolve the precipitate by warming and swirling the solution immediately before he is ready to use it. Although this deficiency is of secondary importance, solutions that are stable at room temperature (25° C.) are to be preferred for routine use.

From the data in the table it will be seen that the sodium acetrizoate medium has the necessary high iodine content and low viscosity but the salts of acetrizoic acid are pharmacodynamically more active than those of diatrizoic acid and diprotrizoic acid.

Various means have been suggested to permit the injection of the relatively viscous concentrated diatrizoate solutions at the rates deemed desirable in angiocardiography. Among the means suggested are:

(1) The use of a larger needle, for example 10 gauge (0.105 in. diameter) instead of the usual 12 gauge (0.085 in.);

(2) The use of a mechanical injector, such as a lever operated device or a device actuated by compressed gas, to apply increased pressure to the plunger of the syringe;

(3) Heating the solution to decrease its viscosity before injecting it. Injection at temperatures as high as 55° C. (130° F.) has been proposed.

It is thus seen that these previously known media are deficient in important characteristics and that workers in the art have been searching for means to overcome these deficiencies.

The present invention is directed to improved X-ray contrast media suitable for intravascular administration, and particularly for angiocardiography. Such media comprise aqueous solutions of nontoxic salts of a plurality of 3-lower alkanamido-5-lower alkanamidopolyiodobenzoic acids, said solutions containing, in each 100 ml., not substantially less than 40 grams of organically bound iodine, and being characterized by low viscosities, relative to their iodine concentration. While suitable solutions may be prepared from salts of two 3-lower alkanamido-5-lower alkanamidopolyiodobenzoic acids, salts of

three or more such acids may be used if desired. These media are characterized by the following properties relative to those possessed by the most desirable angiocardiographic media previously known:

(1) In the lower concentrations, iodine content in the same range, increasing in higher concentrations to iodine contents well above those previously attained;

(2) Substantially lower viscosities, relative to iodine content;

(3) Pharmacodynamic activity in the same range; and

(4) In the lower concentrations, stable solutions at normal room temperatures.

For example, there may be prepared concentrated solutions containing combinations of sodium diatrizoate and sodium diprotrizoate which meet the iodine concentration and viscosity criteria mentioned above and have minimal pharmacodynamic activity and improved solubility characteristics.

While sodium salts are generally preferred because of the excellent physical and physiological properties of the sodium ion, special circumstances may indicate the use of other soluble nontoxic salts.

In accordance with established practice the novel combinations of the invention may contain optional additives, such as preservatives, buffers and stabilizers.

To illustrate the present invention, the properties of concentrated aqueous solutions containing various proportions of sodium diatrizoate and sodium diprotrizoate have been determined, and the various relationships discovered are presented graphically in FIG. 1.

In FIG. 1 the curve ABC represents the solubility at 25° C. of solutes consisting of sodium diatrizoate and sodium diprotrizoate in proportions varying from 100% sodium diatrizoate and no sodium diprotrizoate (left side) to 100% sodium diprotrizoate and no sodium diatrizoate (right side).

Any system whose composition is defined by a point lying beneath the curve ABC forms a complete, stable solution at 25° C. In other words, the solute is completely dissolved and the solution is not saturated at 25° C. Conversely, a system whose composition is defined by a point lying above curve ABC does not form a complete, stable solution at 25° C.

Curve HJK is the corresponding solubility curve at 37.5° C., which is approximately normal body temperature, the preferred temperature for injection.

The line DE defines the sodium diatrizoate-sodium diprotrizoate-water systems which contain 40 grams of combined iodine in a volume of 100 ml. The line NP defines such systems containing 44 grams of iodine per 100 ml.

Points B and J, which are the peaks of the two solubility curves, and points F, G, L, M, R and S, which are the points of intersection of the two solubility curves with the 40% and 44% iodine lines, are of particular interest in setting forth the present invention. The important physical characteristics of solutions whose compositions correspond to these points are set forth in Table 2.

TABLE 2

Point on Fig. 1	Solute concentration (g./100 ml.)	Percent Na diatrizoate in solute (by weight)	Percent Na diprotrizoate in solute (by weight)	Ratio Na diatrizoate/Na diprotrizoate	Iodine concentration (g./100 ml.)	Absolute viscosity at 37.5° C. (cps.)	Ratio iodine conc./viscosity
B.....	72	55	45	1.22	42.3	6.0	7.1
F.....	68.	61.5	38.5	1.60	40	5.0	8.0
G.....	68.3	48.5	51.5	0.94	40	5.2	7.7
J.....	81.2	55	45	1.22	47.7	9.9	4.8
L.....	67	89	11	8.1	40	4.5	8.9
M.....	68.7	35.5	64.5	0.55	40	5.4	7.4
R.....	74.4	69	31	2.22	44	6.8	6.5
S.....	75.2	47	53	0.89	44	7.1	6.2

Referring again to FIG. 1, all points lying within the triangular figure FBG represent systems containing more than 40 g. of iodine per 100 ml. which form stable solutions at 25° C. Lines FB and BG are slightly curved. If their curvature be neglected, or in other words, if they be considered straight lines, the following equations for these lines may be readily derived:

For FB,

(1) $Y=0.615X+44.3$

and for line BG

(2) $Y=97.6-0.569X$

where Y represents the solute concentration in grams per 100 ml., and X represents the percentage of sodium diprotrizoate in the solute.

Similarly, the triangular figure RJS encloses all points representing combinations containing more than 44 grams of iodine per 100 ml. which forms stable solutions at 37.5° C. Neglecting the slight curvature of RJ and JS, their equations are found to be:

For line RJ

(3) $Y=0.486X+59.4$

and for line JS

(4) $Y=115-0.75X$

where X and Y have the meanings given above.

As has been pointed out above, the relationship between the iodine concentration and the viscosity of an angiocardigraphic medium is important because both of these factors affect the rate of injection of iodine. As would be expected, the viscosity of media comprising sodium diatrizoate and sodium diprotrizoate increases, in general, with increasing iodine concentration. However, the relationship is not a linear one.

It has been found informative to plot the ratio, iodine concentration/viscosity, against iodine concentration. Such a plot is found in FIG. 2. Although there is some scattering, it is seen that the data may be fitted reasonably well to a straight line. Departures of individual points from the line are largely accounted for by variations in the relative proportions of sodium diatrizoate and sodium diprotrizoate in the solute.

From the relationship disclosed in FIG. 2 the following relationship between iodine concentration and viscosity may be derived:

(5) $V=\frac{C}{24.8-0.42C}$

where V represents the absolute viscosity at 37.5° C. and C represents the iodine concentration in grams per 100 ml.

In general, viscosities calculated by means of Equation 5 will be within ±1 centipoise of the experimentally determined value at iodine concentrations above 40 g./100 ml.

It will be obvious that the relationships set forth in the foregoing figures, tables, and equations are approximations, being subject to various minor experimental and other errors. Nevertheless the relationships thus set forth are believed to be important to an understanding of the invention.

The invention is further illustrated by the following ex-

amples. (All percentages are by weight, unless otherwise specified.)

EXAMPLE 1

A solution is prepared containing, in each 100 ml., 69 grams of a solute consisting of 45% sodium diprotrizoate and 55% sodium diatrizoate. The composition of the solution corresponds to point 1 on FIG. 1. The solution is stable at 25° C. and contains more than 40 g. of combined iodine per 100 ml. Its viscosity at 37.5° C. is less than 6 centipoises.

EXAMPLE 2

A solution is prepared containing, in each 100 ml., 70 grams of a solute consisting of 30% sodium diprotrizoate and 70% sodium diatrizoate. The composition of the solution corresponds to point 2 on FIG. 1. The solution is supersaturated at 25° C. but is stable at 37.5° C. and contains more than 40 g. of combined iodine per 100 ml. Its viscosity at 37.5° C. is less than 7 centipoises.

EXAMPLE 3

A solution is prepared containing, in each 100 ml., 73 grams of a solute consisting of 50% sodium diprotrizoate and 50% sodium diatrizoate. The composition of the solution corresponds to point 3 on FIG. 1. The solution is supersaturated at 25° C. but is stable at 37.5° C. and contains more than 40 g. of combined iodine per 100 ml. Its viscosity at 37.5° C. is less than 8 centipoises.

EXAMPLE 4

A solution is prepared containing, in each 100 ml., 76 grams of a solute consisting of 40% sodium diprotrizoate and 60% sodium diatrizoate. The composition of the solution corresponds to point 4 on FIG. 1. The solution is stable at 37.5° C. and contains more than 44 g. of combined iodine per 100 ml. Its viscosity at 37.5° C. is less than 9 centipoises.

EXAMPLE 5

A solution is prepared containing, in each 100 ml., 85.1 grams of a solute consisting of 45.1% sodium diprotrizoate and 54.9% sodium diatrizoate. The composition of the solution corresponds to point 5 on FIG. 1. Heating above 37.5° C. is necessary to complete the initial dissolution of the solute. The resulting solution contains approximately 50 g. of combined iodine per 100 ml. Upon cooling to 37.5° C. the solution becomes supersaturated. The viscosity of the solution at 37.5° C. is approximately 12-13 centipoises. Upon standing at 37.5° C. the solution slowly deposits crystals, which redissolve on warming.

EXAMPLE 6

An angiocardigraphic medium is prepared according to the following formula:

Contrast agent (47% sodium diprotrizoate) (53% sodium diatrizoate).....	grams..	68.1
70 Stabilizer (calcium disodium ethylenediaminetetraacetate)	mg..	18
Buffer (sodium biphosphate)	mg..	20
Water for injection to make.....	ml..	100

The solution is sterilized by autoclaving. It contains approximately 40 grams of bound iodine per 100 ml. and

is stable toward crystallization at 25° C. Its viscosity at 37.5° C. is approximately 5 centipoises.

Although compositions containing sodium diatrizoate and sodium diprotrizoate are preferred, the invention also contemplates the use of other highly soluble nontoxic salts of diatrizoic and diprotrizoic acids and salts of other 3-lower alkanamido-5-lower alkanamido-polyiodobenzoic acids as components of the improved concentrated contrast media of the invention. Examples of other 3-lower alkanamido-5-lower alkanamido-polyiodobenzoic acids include 3-acetamido-5-formamidotriiodobenzoic acid, 3-acetamido-5-propionamidotriiodobenzoic acid, 3,5-diacetamidodiiiodobenzoic acid and 5-acetamido-3-propionamidodiiiodobenzoic acid. Additional examples of still other compounds useful in accordance with the present invention are disclosed in the aforementioned co-pending application of Wallingford and Turner and publication of Larsen et al.

In view of the above, it will be seen that the several objects of the invention are achieved and other advantageous results attained.

As various changes could be made in the above products without departing from the scope of the invention, it is intended that all matter contained in the above description or shown in the accompanying drawings shall be interpreted as illustrative and not in a limiting sense.

I claim:

1. An X-ray contrast medium comprising an aqueous solution of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid and the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid, said solution containing, in each 100 ml., not more than 85.1 grams of solute and not substantially less than 40 grams of iodine in organic combination, the ratio, by weight, of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid to the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid being not substantially less than 0.55 and not substantially greater than 8.1, the viscosity of said solution at 37.5° C. being not substantially greater than that defined by the expression

$$V = \frac{C}{24.8 - 0.42C}$$

where V represents the absolute viscosity at 37.5° C. (in centipoises) and C represents the iodine concentration (in grams per 100 ml. of solution).

2. An X-ray contrast medium comprising an aqueous solution of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid and the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid, said solution containing in each 100 ml., not more than 85.1 grams of solute and not substantially less than 40 grams of iodine in organic combination, the ratio, by weight, of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid to the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid being not substantially less than 0.89 and not substantially greater than 2.22, the viscosity of said solution at 37.5° C. being not substantially greater than that defined by the expression

$$V = \frac{C}{24.8 - 0.42C}$$

where V represents the absolute viscosity at 37.5° C. (in centipoises) and C represents the iodine concentration (in grams per 100 ml. of solution).

3. An X-ray contrast medium comprising an aqueous solution of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid and the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid, said solution containing in each 100 ml., not more than 85.1 grams of solute and not substantially less than 44 grams of iodine in organic combination, the ratio, by weight, of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid to the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid being not substantially less than 0.89 and not substantially greater than 2.22, the viscosity of said solution at 37.5°

C. being not substantially greater than that defined by the expression

$$V = \frac{C}{24.8 - 0.42C}$$

where V represents the absolute viscosity at 37.5° C. (in centipoises) and C represents the iodine concentration (in grams per 100 ml. of solution).

4. An X-ray contrast medium comprising an aqueous solution of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid and the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid, said solution containing in each 100 ml., not more than 85.1 grams of solute and not substantially less than 40 grams of iodine in organic combination, the ratio, by weight, of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid to the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid being not substantially less than 0.94 and not substantially greater than 1.6, the viscosity of said solution being not substantially greater than that defined by the expression

$$V = \frac{C}{24.8 - 0.42C}$$

where V represents the absolute viscosity at 37.5° C. (in centipoises) and C represents the iodine concentration (in grams per 100 ml. of solution).

5. An X-ray contrast medium comprising an aqueous solution of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid and the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid, said solution containing in each 100 ml., not more than 85.1 grams of solute and not substantially less than 40 grams of iodine in organic combination, the ratio, by weight, of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid to the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid being approximately 1.2, the viscosity of said solution being not substantially greater than that defined by the expression

$$V = \frac{C}{24.8 - 0.42C}$$

where V represents the absolute viscosity at 37.5° C. (in centipoises) and C represents the iodine concentration (in grams per 100 ml. of solution).

6. An X-ray contrast medium comprising an aqueous solution of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid and the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid, said solution containing in each 100 ml., not more than 85.1 grams of solute and not substantially less than 40 and not substantially more than 42.3 grams of iodine in organic combination, the ratio, by weight, of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid to the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid being not substantially less than 0.94 and not substantially greater than 1.6, the viscosity of said solution being not substantially greater than that defined by the expression

$$V = \frac{C}{24.8 - 0.42C}$$

where V represents the absolute viscosity at 37.5° C. (in centipoises) and C represents the iodine concentration (in grams per 100 ml. of solution).

7. An X-ray contrast medium comprising an aqueous solution of a solute consisting essentially of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid and the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid, the proportion of the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid in the solute being not substantially less than that defined by the relationship.

$$Y = 0.615X + 44.3$$

and not substantially greater than that defined by the relationship

$$Y = 97.6 - 0.569X$$

where Y represents the concentration of solute expressed as grams of solute contained in each 100 ml. of solution, and X represents the percentage of the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid by weight in the solute, said solution containing in each 100 ml., not more than 85.1 grams of solute and not substantially less than 40 grams of iodine in organic combination, and the viscosity of said solution being not substantially greater than that defined by the expression

$$V = \frac{C}{24.8 - 0.42C}$$

where V represents the absolute viscosity at 37.5° C. (in centipoises) and C represents the iodine concentration (in grams per 100 ml. of solution).

8. An X-ray contrast medium comprising an aqueous solution of a solute consisting essentially of the sodium salt of 3,5-bisacetamido-2,4,6-triiodobenzoic acid and the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid, the proportion of the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid in the solute being not substantially less than that defined by the relationship

$$Y = 0.486X + 59.4$$

and not substantially greater than that defined by the relationship

$$Y = 115 - 0.75X$$

where Y represents the concentration of solute expressed

as grams of solute contained in each 100 ml. of solution, and X represents the percentage of the sodium salt of 3,5-bispropionamido-2,4,6-triiodobenzoic acid by weight in the solute, said solution containing in each 100 ml., not more than 85.1 grams of solute and not substantially less than 44 grams of iodine in organic combination, and the viscosity of said solution being not substantially greater than that defined by the expression

$$V = \frac{C}{24.8 - 0.42C}$$

where V represents the absolute viscosity at 37.5° C. (in centipoises) and C represents the iodine concentration (in grams per 100 ml. of solution).

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