ABSTRACT OF THE DISCLOSURE

This invention relates to novel triiodobenzoic acid derivatives of use as X-ray contrast agents, particularly in the visualisation of the cardiovascular system and the cavities containing the cerebrospinal fluid.

In the X-ray visualisation of relatively extensive regions of the human body, for example the cardiovascular system or the cavities containing the cerebrospinal fluid, very large quantities of X-ray contrast agents have to be injected in order to provide sufficient opacity in the region concerned. Consequently, the toxicity of the contrast agent at high concentrations is of great importance. In the visualisation of the cardiovascular system a large number of compounds have been proposed as contrast agents and while many have been used successfully, their toxicity, although often very slight, does give rise to some undesirable side effects. In the visualisation of the cavities containing the cerebrospinal fluid, the compounds used in vascular visualisation are frequently far too toxic as is explained below.

The space which contains the cerebrospinal fluid consists of several different cavities associated with the central nervous system and comprises the ventricles of the brain, the cisterns and the subarachnoidal space around the brain in addition to the spinal column. The radiological examination of these cavities may be divided into three main groups; ventriculography, cisternography and myelography. Myelography, is the radiological examination of the spinal subarachnoidal space, which may be divided into two zones; the radiological examination of the lowest part of the spine is termed myelography and examination of the remaining part is termed lumbar myelography.

The tolerance of these areas towards, for example, water soluble X-ray contrast agents, differs considerably and an approximate order of decreasing tolerance is radiography, ventriculography, lumbar myelography and cisternography. These different fields cannot, however, be regarded as separate areas because there exists a communication throughout the entire system making leakage from one area into adjacent areas possible. Lumbar myelography, for example, is especially demanding with regard to tolerance of the contrast medium but the higher cavities are even more demanding in this respect. One reason for this is the risk of leakage to the cisterns, an area which is far more sensitive than, for example, the ventricles.

Agents for use in this field should ideally be safely usable in all areas but an ideal medium has not yet been found. Iodinated oils used as such or as aqueous emulsions, the water soluble sodium iodomethanesulphonate and gas (oxygen) are examples of media which are commonly used. The oils have the disadvantage among others that they remain in the system without being resorbed and excreted whereas radiologists today will generally not accept contrast agents which remain in the organism for an extremely long time. Furthermore, use of these oils in myelography may give rise to aseptic meningitis which is regarded as a very serious complication. Gases such as oxygen which in many ways represent good contrast agents, give a so-called negative contrast and this is in many cases not sufficient.

When a positive contrast is required and the contrast agent cannot be allowed to remain in the system (even though mechanical removal of most of the oil is possible), the water soluble sodium iodomethanesulphonate is the principal conventional medium. This substance, however, is far from ideal; it is commonly used for radiculography but simultaneous application of an anaesthetic is necessary and its use for lumbar myelography is contraindicated.

We have now found that triiodobenzoic acids carrying in the molecule at least one grouping 

\[-N-R^-\]

where \(R^-\) represents a hydroxyalkyl group, are generally more suitable than the corresponding compounds carrying no hydroxy-alkyl grouping for use in the visualisation of the cardiovascular system and of the cavities containing the cerebrospinal fluid, from the point of view of tolerance by the tissues concerned, and also from the point of view of water-solubility and viscosity, properties which are important in allowing very concentrated aqueous solutions to be used. The compounds

3-N-([\(\beta\)-hydroxyethyl])acetamido-5-acetamido-2,4,6-triiodobenzoic acid,
3,5-bis-N-([\(\beta\)-hydroxyethyl])acetamido-2,4,6-triiodobenzoic acid,
3-N-([\(\beta\)-hydroxyethyl])acetamido-3,4,6-triiodobenzoic acid,
3-([\(\beta\)-hydroxyethylacetamido]-5-[\(\beta\)-hydroxyethylacetamido]-methyl)-2,4,6-triiodobenzoic acid

have previously been proposed as cardiovascular X-ray contrast agents but no other hydroxyalkyl triiodobenzoic acids have been described.

According to the present invention we provide 2,4,6-triiodobenzoic acids, carrying at least one group of the formula

\[-N-R^-\]

where \(R^-\) is a hydroxyalkyl group, there being no N-([\(\beta\)-hydroxyethyl])acetamido group in the 3-position when there is a hydrogen atom or an amino, acetamido or N-([\(\beta\)-hydroxyethylacetamido]-acetamido group in the 5-position; and suffix thereof.

The new compounds may largely be summarised by the following formula:

[Diagram]

where

A1 is an acyl group,
R1 is a hydrogen atom or an alkyl group which may be
3,702,866

3-(N-β-hydroxyethyl-acetamido)-5-N'-methylacetamido-2,4,6-triiodobenzoic acid;
4-(N-β-hydroxypropyl-acetamido)-5-N'-methylacetamido-2,4,6-triiodobenzoic acid;
5-(N'-β-hydroxyacetamido)-2,4,6-triiodo-N'-methylisophthalamic acid;
4-(N-β-hydroxypropionyl-acetamido)-5-N'-methylacetamido-2,4,6-triiodobenzoic acid;
3-(N-β-hydroxyethyl-acetamido)-5-N'-methylpropionylacetamido-2,4,6-triiodobenzoic acid,
and their salts.

The following table gives LD₉₀ values, determined by both intracerebral and intravenous injection into mice and expressed in mg. I/kg., for a number of related contrast agents.

### ACUTE TOXICITIES IN MICE

<table>
<thead>
<tr>
<th>Compound</th>
<th>LD₉₀ Intracerebral, mg. I/kg.</th>
<th>LD₉₀ Intravenous, mg. I/kg.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-(N-β-hydroxyethyl-acetamido)-5-N'-methylacetamido-2,4,6-triiodobenzoic acid</td>
<td>425</td>
<td>9,800</td>
</tr>
<tr>
<td>3-(N-β-hydroxypropyl-acetamido)-5-N'-methylacetamido-2,4,6-triiodobenzoic acid</td>
<td>423</td>
<td>8,300</td>
</tr>
<tr>
<td>3-(N-β-hydroxypropionyl-acetamido)-5-N'-methylacetamido-2,4,6-triiodobenzoic acid</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>3-(N-β-hydroxyethyl-acetamido)-5-N'-methylpropionylacetamido-2,4,6-triiodobenzoic acid</td>
<td>345</td>
<td>9,800</td>
</tr>
<tr>
<td>3-(N-β-hydroxypropyl-acetamido)-5-N'-methylpropionylacetamido-2,4,6-triiodobenzoic acid</td>
<td>340</td>
<td></td>
</tr>
<tr>
<td>3-(N-β-hydroxypropionyl-acetamido)-5-N'-methylpropionylacetamido-2,4,6-triiodobenzoic acid</td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>3-(N-β-hydroxyethyl-acetamido)-5-acetamido-2,4,6-triiodobenzoic acid</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>3-(N-β-hydroxypropyl-acetamido)-5-acetamido-2,4,6-triiodobenzoic acid</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>3-(N-β-hydroxypropionyl-acetamido)-5-acetamido-2,4,6-triiodobenzoic acid</td>
<td>210</td>
<td></td>
</tr>
<tr>
<td>3-acetamido-5-acetamidomethyl-2,4,6-triiodobenzoic acid</td>
<td>150</td>
<td></td>
</tr>
</tbody>
</table>

According to a further feature of the present invention we provide a radiological composition containing at least one acid according to the invention or a physiologically compatible salt thereof together with a radiological carrier.

The concentration of the X-ray contrast agent according to the invention in the aqueous medium for administration varies with the particular field of use. In general lower concentrations are required for ventriculography than for myelography while radiography requires still lower concentrations. The preferred concentration and dosage ranges of the compounds for these three applications are as follows:

<table>
<thead>
<tr>
<th>Concentration, mg. Unl.</th>
<th>Dose, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiography</td>
<td>150-350</td>
</tr>
<tr>
<td>Ventriculography</td>
<td>350-350</td>
</tr>
<tr>
<td>Myelography</td>
<td>350-650</td>
</tr>
</tbody>
</table>

The preferred concentration range for cardiovascular visualisation is 150-450 mg. I/mL. The quantity of contrast agent to be administered is preferably such as to stay in the system only for about 2 to 3 hours, although shorter and longer residence periods are normally acceptable. The active material may thus be formulated for cerebrospinal visualisation conveniently in vials or ampoules containing 5 to 15 ml. of an aqueous solution thereof, but for cardiovascular visualisation larger quantities e.g. 10 to 500 ml. will be given.

In our Belgian Pat. No. 645,634 we described compositions containing sodium salts of X-ray contrast acids the toxicity of which was favourably modified by the inclusion of relatively small quantities of substances liberating
calcium and/or magnesium ions. The effect was thought to be connected with the ion balance in the vascular system. We have now found that in the cerebrospinal fluid, although sodium salts of X-ray contrast acids are much more toxic by the intracerebral route than the intravenous route, these toxicities are favorably modified by inclusion of calcium and/or magnesium ions to sodium ions being similar to those observed for the vascular system.

The ratio of calcium to sodium ions is preferably at least 0.00025, advantageously at least 0.0005. Where magnesium ions are present, these are also preferably at least at the above minimum ratios. The ratio of calcium ions to sodium ions is, in fact, preferably in the range 0.005 to 0.10, while the ratio of magnesium ions to sodium ions is preferably in the range 0.002 to 0.05. It is preferred that both calcium and magnesium ions be present.

The calcium and/or magnesium ions may be supplied by adding a calcium and/or magnesium salt of the X-ray contrast acid or by adding or forming in situ another physiologically and chemically compatible water-soluble calcium or magnesium salt. The metal ions should, of course, be in the free state and ions bound by chelating agents, such as ethylene diamine tetracetic acid, are not effective and should not be considered in calculating the respective ion ratios. Particularly useful calcium and magnesium salts for addition to the compositions are the chlorides. Another possibility is to add to a solution of the acid, one or more bases supplying the sodium ions on the one hand and the calcium and/or magnesium ions on the other hand.

The new compounds according to the invention may be prepared in any convenient way, a number of methods being set out hereinafter:

(a) Reaction of a compound of the general formula

\[
\begin{align*}
\text{COOH} \\
\text{I} \\
\text{I} \\
\text{X} \\
\text{N\text{-}Ac}^1
\end{align*}
\]

with a hydroxyalkylating agent to produce a compound of Formula I in which R^1 is a hydroxyalkyl group. The hydroxyalkylating agent may, for example, be a reactive mono-ester derivative of a glycol or polyol, for example a halide, e.g. a chloride or bromide, or a hydrocarbon-sulphonate. For the introduction of a hydroxyethyl group, 2-chloroethanol is one suitable reagent. The reactive derivative is preferably reacted with the acylamido starting material under basic conditions, e.g. in an aqueous alkaline medium, for example containing an alkali metal hydroxide such as sodium or potassium hydroxide or in a non-aqueous medium, e.g. in an alkane such as methanol or ethanol, the base conveniently being an alkali metal alkoxide such as sodium methoxide. It is also possible to react the acylamido compound with an epoxide, for example ethylene oxide, propylene oxide, glycidate etc., also advantageously under the same conditions as those which are used for reactive esters.

(b) Reaction of an amide of Formula II with an allylating agent, e.g. a reactive ester of an allylic alcohol, for example allyl chloride or bromide, to introduce an N-allylic group which is then subjected to oxidation of the double bond thereof, e.g. using a permanganate oxidizing agent, to form a glycol grouping, whereby a compound of Formula I is formed in which R^1 is a dihydroxy alkyl group.

(c) For the production of mono-hydroxyalkyl-bisacylamido-compounds, a compound of the general formula

\[
\begin{align*}
&\text{COOH} \\
&\text{I} \\
&\text{I} \\
&\text{N\text{-}Ac}^1 \\
&\text{AlkOH}
\end{align*}
\]

(where Ac^1 has the above meaning and AlkOH represents a mono- or polyhydroxyalkyl group) may be reacted with an acylating agent to acylate both the primary amino group and the hydroxyl group or groups, followed by hydrolysis of the ester groupings or groupings so formed, e.g. under basic conditions, to yield a mono-hydroxyalkyl compound of the general formula

\[
\begin{align*}
&\text{COOH} \\
&\text{I} \\
&\text{I} \\
&\text{N\text{-}Ac}^1 \\
&\text{AlkOH}
\end{align*}
\]

(where Ac^1, Ac^2 and AlkOH have the above meanings).

The acylating agent may, for example, be an acid anhydride (which can also serve as solvent) together with catalytic amounts of a mineral acid, e.g. sulphuric or perchloric acid, or an acid halide preferably in a polar solvent such as dimethylformamide or dimethylacetamide, acid halides being preferred due to smaller amounts of by-products formed. The basic hydrolysis of the O-acyl grouping may for example, be effected using aqueous alkali metal hydroxide e.g. sodium hydroxide, the reaction preferably being carried out at room temperature. In addition, depending on the acylating agent used, other products may be formed and require separation. When an acyl anhydride such as acetic anhydride is used with concentrated sulphuric acid as catalyst, the primary amino group is often, in part, bis-acylated, although the bis-acylamino group is very readily hydrolysed to acylamido under mild basic conditions, while if a substituted amide or imide solvent such as dimethylacetamide or dimethylformamide is present the hydroxyl group is acylated while the primary amino group is left unreacted.

Using an acyl halide in a substituted amide or imide solvent, however, the reaction to form the N,O-bisacyl compound is greatly predominant and this method is preferred.

The starting material of Formula III can be prepared, of course, by the processes (a) and (b) above, using compounds wherein X is an amino group.

(d) A further method for producing N-alkylated monohydroxyalkyl bisacylamido compounds comprises reaction of a compound of the general formula

\[
\begin{align*}
&\text{COOH} \\
&\text{I} \\
&\text{I} \\
&\text{N\text{-}Ac}^1 \\
&\text{AlkOH}
\end{align*}
\]

with an alkylating agent, e.g. a reactive ester of an alkylol, for example an alkyl chloride, bromide, iodide, tosylate or mesylate or a dialkyl sulphate, whereby a corresponding compound of Formula I is formed in which X is an N-alkylacylamino group.

The compounds of Formula II used as starting materials may be prepared by conventional methods which depend on the nature of the group X.
The compounds of Formula II in which X is NH₂, a particularly important group of intermediates, may be prepared by acylation of 3-amino-4-nitro-benzoic acid, followed by reduction of the nitro group to amino e.g. by catalytic hydrogenation, for example using palladium or platinum, followed by iodination e.g. with sodium iodide. Compounds of Formula II in which X is N-alkyl acylamido may be prepared by acylation of 3-nitro-5-sulphanilomonoacid as described in our South African Pat. No. 68/6,797 e.g. using a reactive ester of an alkano, preferably in the presence of an acid binding agent, followed by acid hydrolysis of the sulphanilamino group to produce an alkylamino group which may then be acylated as described previously to form a 3-N-alkyl acylamido-5-nitrobenzoic acid which on reduction, for example hydrogenation yields the 5-amino compound; this can then be iodinated, e.g. with NaICl₂ and acylated by the above method to introduce an acyl group, which may be the same or different from that already present, to form the desired 5-acylamino compound.

For the preparation of compounds of Formula I in which X is a group CONR²R⁴ and wherein at least one of the group R³, R⁴ and R⁵ is hydroxyl, a 5-nitroisophthalic acid ester halide may be reacted with ammonia or a primary or secondary amine NHRR⁴ to form the desired 3-carbamoyl group, followed by hydrogenation of the ester grouping e.g. under basic conditions, for example using aqueous alkali, and reduction of the nitro group to an amino group, e.g. by catalytic hydrogenation using, for example palladium or platinum; iodination, e.g. using an iodinating agent such as NaICl₂, yields the corresponding 2,4,6-triiodobenzoic acid which may then be subjected to acylation, e.g. using an acylating agent such as an anhydride or acid halide. The product is thus a compound of Formula I in which AcO⁻ is acyl, R² is hydrogen and X is CONR²R⁴ and it is possible for a hydroxylalkyl group or even two hydroxylalkyl groups to be present in the molecule in the carbamoyl grouping rather than in the acetamido grouping by using an amine in which at least one of R³ and R⁴ is hydroxylalkyl. If desired the product can be subjected to further hydroxyalkylation by reaction with a hydroxylating agent and if neither of R³ and R⁴ is hydroxylalkyl, such further reaction is indeed necessary to produce a compound of Formula I. Where one or both of R³ and R⁴ are hydroxylalkyl, the initial product in which R⁵ is hydrogen may be reacted to introduce an alkyl group carrying no hydroxy groups.

The nitro compound which is catalytically reduced in the above synthesis may also be prepared by reaction of a half ester of 5-nitro-isophthalic acid with the compound NHRR⁴.

In a further method for the preparation of compounds of Formula I in which X is CONR²R⁴, where R³ and R⁴ have the above meanings, a half-ester of 5-nitroisophthalic acid may be reduced to the corresponding 5-amino compound, e.g. by catalytic hydrogenation, followed by iodination as described above to form the corresponding 2,4,6-triiodophthalic acid ester which may then be acylated to form the corresponding 5-acylamino compound; this is then converted into the ester halide, e.g. by reaction with a reagent serving to convert a carboxyl group into an acid halide group, for example a sulphonyl chloride or phosphorus trichloride. The ester halide may then be reacted with the compound NHRR⁴ followed finally by conversion of the esterified carboxyl group into carboxyl, for example by aminolysis. Where none of R³, R⁴ and R⁵ is hydroxylalkyl the product must then be reacted with a hydroxyalkylating agent to introduce a hydroxyalkyl group at the 5-acylamino grouping and/or the carbamoyl group (where one or both of R³ and R⁴ is hydrogen). Where one or both of R³ and R⁴ is hydroxylalkyl the product may be acylated as described above to form the corresponding 5-N-alkyl-acylamidom-compound.

Where it is intended that R¹ should be an alkyl group carrying a substituent of formula

![Chemical Structure]

the compound of Formula II may be reacted with a bifunctional alkane derivative such as an α,α-dihaloalkane alkane or a bisepoxy-alkane, e.g. 1,3-diphenyl diene dioxide.

The isolation of the hydroxyalkylated product from other water-soluble products such as inorganic salts may give rise to difficulty. In cases where the desired product is especially soluble, the residue from the reaction mixture may be dissolved in water and extracted, preferably several times, with for example 3–4 extractions with 3/4–3 vol. of 90% aqueous phenol. The combined phenol extracts may then be re-extracted with water to remove inorganic salts and diluted with a water-immiscible liquid such as diethylether. Further extraction with water then extracts the desired product into the aqueous phase which, after removal of residual phenol, can be evaporated to dryness.

The following examples are given by way of illustration only:

**EXAMPLE 1**

3-amino-5-(N,N-hydroxyethyl-acetamido)-2,4,6-triiodobenzoic acid

Procedure 1: 3-acetamido-5-amino-2,4,6-triiodobenzoic acid (5.72 g) was dissolved in water (16 ml) by adding 5 N sodium hydroxide (8 ml). Then 2-chloroethanol (1.35 ml) was added under vigorous stirring at room temperature. After six hours, the solution was neutralized and treated with charcoal at room temperature overnight. The charcoal was filtered off and the acid liberated by adding 6 N hydrochloric acid. Yield: 5.7 g (93%).

Procedure 2: 3-acetamido-5-amino-2,4,6-triiodobenzoic acid (1036 g) was suspended in water (3.1 l) and dissolved by adding 10 N sodium hydroxide (740 ml). The solution was heated at 70⁰C (in the reaction flask) and 2-chloroethanol (250 ml) added during an hour. The mixture was heated at 70⁰C for an additional half an hour. After cooling, the solution was neutralized and stirred with charcoal overnight. The charcoal was filtered off and the acid precipitated by adding 6 N hydrochloric acid after dilution of the reaction solution with water (9 l). Yield: 1048 g (94%).

Procedure 3: 3-acetamido-5-amino-2,4,6-triiodobenzoic acid (57.2 g) was dissolved in the solvent (150 ml) as sodium salt by adding sodium hydroxide or sodium methoxide. Then the ethylene oxide was led into the bottom of the cylindrical reaction flask through a delivery tube. Table 1 describes a number of preparations using this procedure under various conditions.
The chromatograms showed small amounts of ester.

### EXAMPLE 2

**N-(β-hydroxyethyl)-3,5-diactetamido-2,4,6-triodobenzoic acid**

Procedure 1: 3 - amino - 5 - (N - β - hydroxyethylacetamido) - 2,4,6 - triiodobenzoic acid (462 g) was dissolved in a mixture of acetic anhydride (1400 ml) and concentrated sulphuric acid (14 ml) and heated on a steam bath for forty-five minutes. Then water (185 ml) was added through a dropping funnel. When the anhydride was hydrolyzed, the solution was concentrated in vacuo and half of the volume. The mixture was diluted with water (4 l) and acidified with 6 N hydrochloric acid. The next day, the mixture was decanted and the precipitate dissolved in water (900 ml) by adding 10 N sodium hydroxide to pH 7. More than 10 N sodium hydroxide (365 ml) was added and the solution heated on a steam bath for forty-five minutes. After cooling, the acid was liberated by means of 6 N hydrochloric acid. Yield: 326 g. The product was dissolved in methanol (650 ml) by heating on a steam bath. After cooling, the ammonium salt was precipitated by adding concentrated ammonia (81 ml). The mixture was cooled down to —20 °C and filtered. Yield: 138 g. The salt was suspended in water (280 ml) and acidified with 6 N hydrochloric acid. Yield: 127 g. This procedure was repeated three times. Yield: 76 g. Then, the product was recrystallized from dioxane (charcoal). Yield: 66 g. The procedure with precipitation of the ammonium salt from methanol and liberating of the acid in aqueous solution was repeated three times. Yield: 52 g. The acid was dissolved in water as sodium salt by adding 10 N sodium hydroxide, treated with charcoal, filtered, and the acid precipitated by adding 6 N hydrochloric acid. Yield: 37 g. (7%); M.P.: 247-263 °C (Found: C, 24.18; H, 2.20; N, 56.3; N, 4.36; E, 665. Calcd. for C_{16}H_{18}N_{2}O_{6}: C, 23.73; H, 1.99; I, 57.9; N, 4.26; E, 658.)

Procedure 2: 3 - amino - 5 - (N - β - hydroxyethylacetamido) - 2,4,6 - triiodobenzoic acid (62 g) was dissolved in N,N'-dimethylacetamide (150 ml) and acetyl chloride (34 ml) added. After one hour at room temperature, the solution was diluted with water (20 ml). Then the solution was evaporated in vacuo and the residue dissolved in water (50 ml) by adding 10 N sodium hydroxide (10 ml excess). The solution was heated on a steam bath for half an hour, then cooled and neutralized with glacial acetic acid. Ammonium chloride (22 g) was added and the mixture stirred overnight. The precipitate was suspended in water (500 ml) and the acid liberated by adding 6 N hydrochloric acid. Yield: 45 g. This acid was dissolved in methanol (90 ml) and precipitated by adding concentrated ammonia (11 ml). The precipitate was suspended in water and the acid liberated by means of hydrochloric acid. Yield: 34 g. This procedure was repeated once. Yield: 30 g. After recrystallisation from dioxane, the acid melted at 232-263 °C. Dec. Yield: 24 g. (36%). A mixed melting point of the substances from the two procedures gave no depression. The IR spectra were identical.

### EXAMPLE 3

**N,N'-di(β-hydroxyethyl)-3,5-dibutyramido-2,4,6-triodobenzoic acid**

3,5 - dibutyramido - 2,4,6 - triiodobenzoic acid (13.4 g, 0.02 mole) was dissolved in methanol (120 ml) by adding 5 N sodium methoxide (16 ml, 0.08 mole). Then 2-chloroethanol (2.8 ml, 0.04 mole) was added at room temperature in one portion with vigorous stirring. After twenty-four hours 5 N sodium methoxide (8 ml, 0.04 mole) and 2-chloroethanol (2.8 ml, 0.04 mole) were added. The mixture was stirred for twenty-four hours before the latter addition was repeated. The next day the reaction mixture was diluted with water (120 ml) and neutralized with acetic acid and concentrated in vacuo to half the original volume. The reaction product was precipitated by adding 6 N hydrochloric acid. After filtration, the acid was redissolved in water (120 ml) by adding 10 N sodium hydroxide and treated with charcoal at room temperature overnight. The product was liberated by means of 6 N hydrochloric acid. Yield: 12.2 g. (81%). The product was redissolved in water (50 ml) as sodium salt, treated with charcoal overnight and the acid precipitated by adding 6 N hydrochloric acid. Yield: 11 g. Melting point: 203-270 °C. Dec. (Found: C, 29.63%; H, 3.38%; I, 49.2%; N, 3.86%; N.E., 771. Calcd. for C_{16}H_{18}N_{2}O_{6}: C, 30.10; H, 3.25; I, 50.21; N, 3.70; N.E., 758.)

### EXAMPLE 4

**3-(N-β-hydroxyethyl-acetamido)-5-propionamido-2,4,6-triodobenzoic acid**

3 - amino - 5 - (N - β - hydroxyethyl - acetamido)-2,4,6-triodobenzoic acid (138 g) was dissolved in a mixture of propionionic anhydride (415 ml) and concentrated sulphuric acid (4.1 ml) and heated on a steam bath for one hour. Then water (56 ml) was added through a dropping funnel. The solution was concentrated in vacuo to about half the volume and water added to the residue until further addition gave no more precipitate and the mixture acidified with 6 N hydrochloric acid. The residue was dissolved in water (550 ml) by adding 10 N sodium hydroxide to pH 7, then more 10 N sodium hydroxide (138 ml) was added and the solution heated on a steam bath for forty-five minutes. After cooling, the solution was neutralized with glacial acetic acid and treated with charcoal overnight. The charcoal was filtered off and the acid liberated by means of 6 N hydrochloric acid. After decantation, the precipitate was dissolved in water as sodium salt and recrystallized from methanol (700 ml). Yield: 64 g. The substance was dissolved in ethanol (150 ml) by adding concentrated ammonia (16 ml) by heating on a steam bath. After cooling, the ammonium salt precipitated and was filtered. The salt was dissolved in water (340 ml) by adding 10 N sodium hydroxide and precipitated by adding 6 N hydrochloric acid. This procedure was repeated twice. Yield: 40 g. (27%); M.P.: 246-259 °C. Dec. (Found: C, 24.76; H, 2.29; I, 56.9; N, 4.22; E, 665.)
EXAMPLE 5

3-acetimidomethyl-5-(N-β-hydroxyethyl-acetamido)-2,4,6-triodobenzoic acid

3 - acetamido - 5 - acetimidomethyl-2,4,6-triodobenzoic acid (62.8 g; 0.1 mole) was dissolved in methanol (500 ml.) by adding 5 M sodium methoxide (80 ml.; 0.44 M NaOCH₃) (935 ml.) was added through a dropping funnel during one hour. After heating for three and a half hours after the addition, the mixture was cooled and filtered. The product was suspended twice in acetic acid. Yield: 238 g. (50%).

EXAMPLE 10

3-(N-β-hydroxyethyl-acetamido)-5-(N-methyl-propionamido)-2,4,6-triodobenzoic acid

3 - acetamido - 5-(N-methyl-propionamido)-2,4,6-triodobenzoic acid was prepared by acetylation of 3-acetamido-5-(N-methyl-propionamido)-2,4,6-triodobenzoic acid with acetic anhydride with concentrated sulphuric acid as catalyst.

EXAMPLE 11

N-(β-hydroxyethyl)-N'-methyl-3,5-diacetamido-2,4,6-triodobenzoic acid

Procedure 1: N-(β-hydroxyethyl)-3,5-diacetamido-2,4,6-triodobenzoic acid (6.6 g.) was dissolved in a mixture of water (20 ml.) and 10 N sodium hydroxide (4 ml.). Then the solution was cooled in ice-water and dimethyl sulphate (1.9 ml.) added in portions. Half an hour after the addition, the reaction solution was neutralized and heated on a steam bath for fifteen minutes. After cooling, the mixture was acidified with 6 N hydrochloric acid. Yield: 4.4 g. (65%).

The paper chromatogram of the reaction solution before heating showed three spots with Rₜ values 0.35, 0.48 and 0.58 in a ratio of about 5:5:1 in order of increasing Rₜ values. The paper chromatogram of the heated reaction solution showed the same three spots in a ratio of about 3:7:1 in order of increasing Rₜ values. The paper chromatogram of the precipitated product showed two spots with Rₜ values 0.48 and 0.58 in a ratio of about 9:1 in order of increasing Rₜ values. When the precipitate was dissolved in water as ammonium salt and the solution heated on a steam bath for twenty minutes, the spot with Rₜ value 0.48 reappeared in an amount of about 15%. It may be mentioned that the starting material has Rₜ value 0.35.

Procedure 2: N-methyl-3,5-diacetamido-2,4,6-triodobenzoic acid (6.3 g.) was dissolved in a mixture of water (10 ml.) and 10 N sodium hydroxide (6 ml.). Then 2-bromoethanol (2.1 ml.) was added at room temperature. The solution was kept for five hours and then acidified with 6 N hydrochloric acid. Yield: 5.6 g. (82%). The paper chromatogram of the product showed one spot with Rₜ value 0.48.
EXAMPLE 13

N'-(2,3-di(hydroxypropyl))-N'-methyl-3,5-di(acetamido)-2,4,6-triodobenzoic acid via the corresponding N-allyl derivative

(1) Allylation derivative:

(1) Allylation N-methyl-3,5-diacetamido-2,4,6-triodobenzoic acid (6.3 g.) was suspended in water (15 ml.), dissolved by addition of 10 N sodium hydroxide solution (6 ml.) and the solution was heated to 50° C. before allyl bromide (4 ml.) was added by stirring. The stirring was continued at 50° until the solution became clear (abt. 30 minutes). The solution was cooled to room temperature and acidified with hydrochloric acid (1:1) to a pH of about 0.5. The precipitated product was filtered, suspended in water (about 50 ml.) and sodium bicarbonate was added to pH about 7. Undissolved byproduct (0.4 g. (probably ester)) was filtered off and the desired N-allyl compound precipitated with concentrated hydrochloric acid, filtered, washed with water and dried in vacuo at about 60° C. Yield: 4.8 g., 72%; M.P. 220-224° C.; percent I. calc. 57.0; found: 55.7%. Paper chromatography in the solvent system n-BuOH: EtOH: NH₄OH (25%): H₂O = 4:1:2:1. Rₖ value: 0.66.

(2) Oxidation: The N-allyl compound from (1) above (200 gm.) was suspended in water and sodium carbonate was added to give a clear alkaline solution to which potassium permanganate solution was then added (2.6 ml., 0.3 mmol/ml.). Manganese dioxide was filtered off and the filtrate was acidified with concentrated hydrochloric acid to pH about 0.5. The precipitated product was filtered, washed with water and dried. A paper chromatogram revealed about 30% of the desired di(hydroxypropyl) compound.

EXAMPLE 14

3-aminom-5-N-(β-hydroxyethyl-propionamido)-2,4,6-triodobenzoic acid

3-aminom-propionamido-2,4,6-triodobenzoic acid (117 g.) was suspended in water (300 ml.) and dissolved by addition of 10 N sodium hydroxide solution (80 ml.). 2-chloroethanol (27 ml.) was added dropwise with stirring at 70° C. in the course of 30 minutes. After stirring for altogether 1½ hours, the solution was cooled to room temperature and the pH was adjusted to about 6 by the addition of concentrated hydrochloric acid. The solution was treated with charcoal (3 g. charcoal), filtered and acidified with concentrated hydrochloric acid to pH about 0.5. The precipitated product was filtered, washed with water and dried in vacuo at about 50° C. Yield: 117 g. (93%). M.P.: 150-155°.

EXAMPLE 15

5-(N-(9-hydroxyethyl-acetamido)-2,4,6-triido-N-methylsophthalamic acid

5-acetamido-2,4,6-triido-N-methyl-isophthalamic acid (122.8 g. 0.2 mole) was dissolved in methanol (1200 ml.) by adding 5 M sodium methoxide (160 ml. 0.8 mole). Then 2-chloroethanol (28 ml. 0.4 mole) was added under stirring. After twenty-four hours, 5 M sodium methoxide (40 ml. 0.2 mole) and 2-chloroethanol (14 ml. 0.2 mole) were added under stirring. After twenty-four hours, the reaction solution was diluted with water (700 ml.), neutralized with glacial acetic acid and evaporated in vacuo to about one third of its volume. The product was precipitated by adding 6 N hydrochloric acid. After filtration, the product was redissolved in water (1.2 l.) as sodium salt by adding 10 N sodium hydroxide and treated with charcoal overnight. Then the product was precipitated by means of 6 N hydrochloric acid. Yield: 11.5 g. (87%). Melting point: 258-280° dec. (Found: I, 57.4; E. 666. Calcd. for C₁₂H₁₃N₂O₅: I, 57.9; E. 658.) Rₖ value: 0.26.
EXAMPLE 16

3-acetamido-2,4,6-triiodo-(N-β-hydroxyethyl)-isophthalic acid

(a) Methoxycarbonyl 5-nitrobenzoyl chloride was prepared according to the method of Høey et al., J. Med. Chem. 6, 24 (1963).

(b) Methyl 5-nitro-(N-β-hydroxyethyl)-isophthalanate: The product from (a) above (100 g, 0.41 mole) was dissolved in 55 min. added to a well stirred solution of ethanolamine (27.5 g., 0.45 mole) and sodium bicarbonate (69.0 g., 0.82 mole) in water (500 ml). After stirring for 2 hours at 0-5°C, the reaction mixture was allowed to reach room temperature. The stirring was continued for 1 hour. After standing overnight the reaction mixture was filtered, the undissolved material washed with sodium bicarbonate solution and then with water, and finally dried. Yield: 88 g. (80%), M.P. 124-129°C.

(c) 5-nitro-(N-β-hydroxyethyl)-isophthalic acid: Sodium carbonate (29.6 g) was added in portions to a heated mixture of the product from (b) above (75 g) in methanol (100 ml) and water (900 ml). After filtration and acidification with hydrochloric acid, crude III precipitated. The product was collected, washed and dried. Yield: 51.8 g. (73%), M.P. 135-138°C.

(d) 5-amino-(N-β-hydroxyethyl)-isophthalic acid: The crude product from (c) above (20 g) was hydrogated at atmospheric pressure in methanolic solution (500 ml) with Pd/C (2 g., 10%) as catalyst. When the reaction was complete, the solid material was filtered, extracted with methanol, the extraction solution combined with the filtrate and the solvent removed under reduced pressure to give a white residue of IV. The crude product was crystallized from ethanol, M.P. 169-170°C. Neutralisation equivalent 256.5 (calcd. 254.2).

EXAMPLE 18

3-acetamido-5-(N-methyl-N-(β-hydroxyethyl)-carbamyl)-2,4,6-triiodobenzoic acid

(a) 3-amino-5-methoxycarbonylbenzoic acid: 3-methoxycarbonyl-5-nitrobenzoic acid (25 g.) was hydrogenated in methanol (500 ml.) using palladium oxide on charcoal (2.5 g. 10%) at atmospheric pressure. When the exothermic reaction was completely catalysed the catalyst was filtered off. After cooling the solution at -20°C. for 2½ hours, 12.7 g. product was isolated. An additional 6.5 g. was isolated by concentrating the mother liquor.

The product (100 µg.) showed one spot only (Rf 0.4) when chromatographed on thin layer (Silicagel, CHCl3/ Et2O: MeOH: HCOOH = 55:25:10:10)

EXAMPLE 17

N,N'-di(β-hydroxyethyl)-3-acetamido-5-propanoamide-3,4,6-triiodobenzoic acid

3-acetamido-5-propionamide-2,4,6-triiodobenzoic acid (62.8 g. 0.1 mole) was dissolved in methanol (600 ml.) by adding 5 N sodium methylate (80 ml. 0.4 mole). Then 2-chloroethanol (14 ml. 0.2 mole) was added at room temperature in one portion under stirring. After twenty-four hours, 5 N sodium methylate (40 ml. 0.2 mole) and 2-chloroethanol (14 ml. 0.2 mole) were added under stirring. After twenty-four hours, the latter addition was repeated. The next day, the reaction mixture was diluted with water (600 ml.), neutralized with glacial acetic acid and concentrated in vacuo to half the original volume. The reaction product was precipitated by adding 6 N hydrochloric acid. The product was redissolved in water (600 ml.) by adding sodium hydroxide, treated with charcoal overnight, and precipitated by means of 6 N hydrochloric acid. After filtration, the latter procedure was repeated. Yield: 48 g. (67%). Melting point: 234-236°C.

N,N'-di(β-hydroxyethyl)-3,5-dipropionamido-2,4,6-triiodobenzoic acid

3,5-dipropionamido-2,4,6-triiodobenzoic acid (64.2 g., 0.1 mole) was hydroxylated and purified as described above. Yield: 52 g. (71%). M.P. 193-195°C.

EXAMPLE 19

N,N'-di(β-hydroxyethyl)-3,5-dipropionamido-2,4,6-triiodobenzoic acid (64.2 g., 0.1 mole) was hydroxylated and purified as described above. Yield: 52 g. (71%). M.P. 193-195°C.

(c) 3-amino-5-methoxycarbonylbenzoic acid: 3-methoxycarbonyl-5-nitrobenzoic acid (25 g.) was hydrogenated in methanol (500 ml.) using palladium oxide on charcoal (2.5 g. 10%) at atmospheric pressure. When the exothermic reaction was completely catalysed the catalyst was filtered off. After cooling the solution at -20°C. for 2½ hours, 12.7 g. product was isolated. An additional 6.5 g. was isolated by concentrating the mother liquor.

The product (100 µg.) showed one spot only (Rf 0.4) when chromatographed on thin layer (Silicagel, CHCl3/ Et2O: MeOH: HCOOH = 55:25:10:10)

EXAMPLE 18

3-acetamido-5-(N-methyl-N-(β-hydroxyethyl)-carbamyl)-2,4,6-triiodobenzoic acid

(a) 3-amino-5-methoxycarbonylbenzoic acid: 3-methoxycarbonyl-5-nitrobenzoic acid (25 g.) was hydrogenated in methanol (500 ml.) using palladium oxide on charcoal (2.5 g. 10%) at atmospheric pressure. When the exothermic reaction was completely catalysed the catalyst was filtered off. After cooling the solution at -20°C. for 2½ hours, 12.7 g. product was isolated. An additional 6.5 g. was isolated by concentrating the mother liquor.

The product (100 µg.) showed one spot only (Rf 0.4) when chromatographed on thin layer (Silicagel, CHCl3/ Et2O: MeOH: HCOOH = 55:25:10:10)

(b) 3 - Amino - 5 - methoxycarbonyl - 2,4,6 - triiodobenzoic acid: The amine compound from (a) (12.0 g.) was suspended in water (280 ml.), dissolved by addition of concentrated hydrochloric acid (7.1 ml.) and glacial acetic acid (28.5 ml.). At 60-70°C. NaICl solution (73 ml., 58.7 g. ICl/I100 ml.) was added dropwise while stirring in the course of about 3 hours. The reaction mixture was heated at 80-90°C., for additional 3 hours while stirring. After cooling to room temperature the mother liquor was decanted and the residue dissolved as ammonium salt in water (80 ml.). The ammonium salt was precipitated by adding NHCl (2.4 g.) and cooling to 0°C. The ammonium salt was filtered off and dissolved in water (140 ml.), charcoal twice at 80°C. and the acid was precipitated at room temperature by addition of hydrochloric acid and was filtered off. The crude product was dissolved in ethyl acetate (100 ml.) and the solution was washed 3 times with hydrochloric acid (2 N). By evaporating the solvent, 19 g. iodinated product was isolated. TLC on Silica gel using BuOH/ EtOH/H2O/NH3=30:5:5:10 showed one spot only with Rf 0.35 (starting material Rf 0.27), M.P. 170-176°C.

(c) 3-amino-5-methoxycarbonyl-2,4,6-triiodobenzoyl chloride: A mixture of 3-amino-5-methoxycarbonyl-2,4,6- triiodobenzoic acid (198 g.) and thionyl chloride (400 ml.) was heated while stirring at 70°C. for 16 hours. The solid material dissolved slowly. Thionyl chloride was evaporated in vacuo, the residue dissolved in chloroform (1000 ml.), the solution washed with water (80 ml. each), twice with saturated sodium bicarbonate, then 5
times with 2 N sodium hydroxide solution and finally with water to neutral. The solution was dried with CaCl₂, filtered and evaporated to dryness. The product was dried at 50°C, 64°C (yield: 210 g. M.P. 45-60°C). 

(d) 3 - acetamido - 5 - methoxycarbonyl-2,4,6-triodobenzoyl chloride: To the acid chloride from (c) (53 g.) was added acetic anhydride (106 ml.). After stirring at room temperature for 20 min. then insoluble material was filtered off (3-4 g.). To the filtrate was added concentrated sulfuric acid (0.3 ml.) whereupon a yellowish product started to precipitate. The temperature reached about 50°C. The product was isolated after storing in refrigerator overnight. Yield: 39 g. M.P. 210-215. Found: Cl, 54.8%. Calcd. for C₁₃H₁₁Cl₂N₂O₂: Cl, 66.2%. 

(e) Methyl 5 - acetamido - 2,4,6-triiodo-(N-methyl-N-(β-hydroxyethyl))-isophthalamide: The acetylated product (36 g.) was dissolved in a mixture of dioxan (400 ml.) and dimethylformamide (20 ml.). In the course of 2 hours this solution was added dropwise to a solution of N-methyl-ethanolamine (5.0 ml., 10% excess) and triethylamine (8.7 ml.) in dioxan. The stirring was continued for about 4 hours. A sticky precipitate was filtered off. The filtrate was evaporated to dryness in vacuo. The residue was triturated with aqueous sodium bicarbonate, filtered off and mixed with first fraction. The combined solids were then suspended in aqueous sodium bicarbonate filtered off washed with water and dried in vacuo. Yield: 23 g. M.P. 201-212°C. Found: I, 54.4%. Calcd. for C₁₃H₁₁N₂O₄: I, 56.6%. 

(f) 5 - acetamido - 2,4,6 - triido-(N-methyl, N-(β hydroxyethyl))-isophthalamic acid: The isophthalamic acid from (e) (21.8 g.) was mixed with fresh distilled ethanolamine (4 ml.) and stirred at 70°C for 9 hours. The excess ethanolamine was removed in vacuo at 50-60°C. The residue was dissolved in water, and charcoal at pH 5-5.5. The crude product was precipitated with hydrochloric acid (pH 0.5) and filtered after stirring for 2 hours. At 0°C, 7.6 g. of this acid were dissolved in ethanol (13.3 ml.) and dissolved by addition of concentrated ammonia (1.54 ml.). The ammonium salt started to precipitate in the course of about 30 min. and was isolated after stirring for 2 hours. The salt was dissolved in water (30 ml.), filtered and the acid was precipitated with hydrochloric acid (pH 0.5). After stirring at 0°C for 2 hours, the product was filtered off and dried in vacuo Yield: 5.7 g. Found: I, 55.8%. Calcd. for C₁₃H₁₁N₂O₂: I, 57.86%; N, 6.64% (theor. 6.68%). 

5 - acetamido - 2,4,6 - triido - (N,N-di-(β-hydroxyethyl))-isophthalamic acid was prepared from 3-acetamido - 5 - carboxymethyl - 2,4,6 - tridoobenzoyl chloride by reaction with diethanolamine according to the procedure described above. 

(g) 5 - (N - β - hydroxyethyl) - acetamido-2,4,6-triido - (N - β - hydroxyethyl)-isophthalamic acid: 5-acetamido - 2,4,6-triido - (N - β - hydroxyethyl)-isophthalamic acid (34.0 g.) was suspended in methanol (295 ml.) and dissolved by addition of 3 N sodium hydroxide to the mixture and left at room temperature for 4 days. After being neutralized the solution was concentrated to 150 ml. and acidified to pH about 0.5. After stirring at 0°C the precipitated product was isolated by filtration (28.18 g.). 10 g. of this product was suspended in methanol (30 ml.) and the add in a mixture chloroform (2 g.), charcoal, filtered and acidified (pH 0.8). After stirring at 0°C 3 g. was isolated. Found: I: 54.24% (Caled. 55.34%). N.E.: 681 (theor. 688). Found: C, 27.34; H, 2.86; N, 3.67; I, 54.32. Calcd. for C₁₃H₁₁N₂O₂: C, 24.44; H, 2.20; N, 4.07; I, 55.34. 

EXAMPLE 19 

N-(3-acetamido-5-carboxy-2,4,6-triiodobenzoyl)-N-methylglucamine 

(a) N-(3-methoxy carbonyl - 5 - nitrobenzoyl)-N-methylglucamine: N-methylglucamine (13.9 g.) was dissolved in DMF (400 ml.), then triethylamine (7.14 g.) was added. 2-methoxycarbonyl-5-nitrobenzoyl chloride (14.4 g.) dissolved in dioxan (50 ml.) was added dropwise in the course of 45 min. while stirring. After 3 hours the solution was evaporated to dryness in vacuo. The residue, a yellow oil, was extracted twice with ether and then dissolved in methanol (80 ml.) and water (2 ml.). After storing at -20°C for 16 hours, 22.6 g. (86%) were isolated. M.P. 144-146°C. Recryst. MeOH/H₂O: M.P. 158-164°C. Found: C, 47.91; H, 5.38; N, 7.12. Calcd. for C₁₉H₁₆N₄O₂: C, 47.77; H, 5.51; N, 6.97%.

(b) N-(3-amino - 5 - carboxybenzoyl)-N-methylglucamine: The nitro-ester (4.02 g.) was suspended in water (50 ml.), heated to 60°C and by stirring added sodium carbonate (1.06 g.) in portions in the course of 30 min. The stirring was continued 10 min. after all substance was dissolved. The solution was hydrogenated at room temperature at pH 4 using Pd/C as catalyst 1-4 atm. is convenient. After removal of the catalyst the solution was extracted 5 times with phenol (10 ml. each). The combined phenol extracts were washed 5 times with water (10 ml. each) then diluted with ether (150 ml.) and extracted 5 times with water (10 ml. each). The combined aqueous solution was washed 3 times with ether (15 ml. each), and evaporated to dryness in vacuo. The residue (0.5 g.) melted at 94-97°C. 

(c) N-(3-amino - 5 - carboxy-2,4,6-triiodobenzoyl)-N-methylglucamine: Nitro-ester (20.1 g.) was hydrolyzed and hydrogenated as described above. The product was, however, not isolated. After removal of the catalyst the solution was charcoaled, acidified with HCI (2 N, 25 ml.) and heated to 50°C NaClO₄ solution (41 ml., 4 N, 3.3 eqv.) was added by stirring during a period of 1 hour. The stirring was continued for 3½ hours, the last 2 hours the temperature was 80°C. The solution was treated with Na₂S₂O₄ at 50°C until maximum decolorization and extracted with phenol (1× 100 ml., 3× 50 ml.). The phenol phase was diluted with ether (750 ml.) and extracted with water (4× 70 ml.). The aqueous solution was washed with ether and evaporated to dryness. Residue: 22.6 g. (61%), M.P. 138-147°C. After recrystallization from ethanol (charcoal) the white product melted at 94-140 (cryst. EtOH). 


(d) N-(3-carboxy - 5 - diacetylaminio-2,4,6-triiodobenzoyl)-N-methylglucamine pentaacetaete: The amino compound (21 g.) was peracetylated by suspending it in acetic anhydride (63 ml.) at 60°C using H₂SO₄ conc. (0.2) as a catalyst. The solution was stirred for 1 hour at 80°C before evaporation to dryness. The residue was dissolved in ethyl acetate (200 ml.), washed with water (3× 15 ml.), dried with CaCl₂, evaporated to dryness in vacuo. Yield: 27.2 g. (91.9%), M.P. 126-142°C. 

(e) N-(3-acetamido - 5 - carboxy-2,4,6-triiodobenzoyl)-N-methylglucamine: The peracetylated compound (26.2 g.) was suspended in water and dissolved by addition of 2 N sodium hydroxide solution dropwise until pH 10 became constant (60°C). At room temperature and pH 1 the solution was extracted with phenol as described above. From the final aqueous solution 13.3 g. (67%) of a light brown product was isolated by evaporating to dryness M.P. 174-180°C. Recryst. (EtOH) 195-205°C. 

Found: I, 46.0. Calcd. for C₁₉H₁₆N₄O₂: C, 46.3.

This product was dissolved in water and charcoaled at 100°C. The solution was evaporated to dryness. M.P. 189-194°C. Found: C, 26.77; H, 2.80; N, 3.63; I, 48.5. Calcd. for C₁₉H₁₆N₄O₂: C, 26.23; H, 2.72; N, 3.59.

I, 48.93.
According to procedure a-e was also prepared the corresponding glucoamine derivative:

Step (a)—Yield: 95%; M.P. 159-170°C. (H2O). Found: C; 48.84; H; 5.15; N; 7.09. Calcd. for C12H14N2O5: C; 46.85; H; 5.19; N; 7.21.

Step (b)—M.P. 82-82.9°C. C.

Step (c)—Yield: 78%; M.P. 140-145°C. C.

Step (d)—Yield: 65%; M.P. 125-135°C. C.

Step (e)—Yield: 91% (crude); M.P. 184-192°C. C.

Found: C; 24.92; H; 2.57; N; 3.49; I; 49.44%. Calcd. for C12H14N2O5: C; 25.15; H; 2.51; N; 3.67; I; 49.8%. EXAMPLE 20

N-(3-carboxy-5-N-methylacetamido-2,4,6-triiodobenzoyl)-N-methylglucamine

(a) 3-methoxycarbonyl - 5 - N-methylacetamido-2,4,6-triiodobenzonic acid: 3-amino - 5 - methoxycarbonyl-2,4,6-triiodobenzonic acid (200 g) was acetylated with acetic anhydride (400 ml) at 70°C using concentrated sulphuric acid as catalyst. The excess anhydride was distilled off, the residue suspended in water (500 ml), 10 N sodium hydroxide solution added until the pH became stable at 10 (60°C). The solution was charcoaled at pH 7.5 at 80°C, cooled to room temperature and the product precipitated with conc. hydrochloric acid. Yield: 212.6 g. (98%). M.P. 160-168°C. Found: I; 61.7%. Calcd. for C12H16N2O3: I; 62.3%. This compound (61.5 g) was N-methylated in aqueous alkali with dimethyl sulphate to yield 59.5 g of the desired product. M.P. 160-165°C. Found: C; 23.00; H; 1.97; N; 2.33; I; 59.6%. Calcd. for C12H16N3O3: C; 22.90; H; 1.61; N; 2.23; I; 60.6%

(b) 3-methoxycarbonyl - 5 - N-methylacetamido-2,4,6-triiodobenzyl chloride: The N-methyl derivative (48.0 g) was suspended in thionyl chloride (96 ml) and heated at 60°C while stirring for 30 minutes after acid was dissolved (total 1/2 hours). Excess thionyl chloride was distilled off and the residue crystallised from toluene. Yield: 38.9 (78%). M.P. 205-230°C. Recryst. from toluene, M.P. 206-233°C. Found: Cl; 5.39%. Calcd. for C12H16ClN3O3: Cl; 5.48%

(c) N-(3-carboxy-5-N-methylacetamido-2,4,6-triiodobenzoyl)-N-methyl-glucamine: The acid chloride (22.7 g, 0.035 mol) was dissolved in dioxan (220 ml) and water (45 ml) and potassium bicarbonate (3.86 g, 0.039 mol) was added. N-methylglucamine (8.2 g, 0.042 mol) was added in portions in the course of 30 minutes. The mixture was left while stirring at room temperature for 40 hours, (water 45 ml) was added after stirring for 16 hours. The solution was evaporated to dryness in vacuo, the residue dissolved in hot water (50 ml) and 14.9 g of product, M.P. 120-123°C, was isolated after storage at 3°C. The mother liquor was extracted with phenol, the phenol solution washed with water, diluted with ether, extracted with water, the aqueous solution washed with ether and finally evaporated to dryness in vacuo. Yield: 10.4 g, M.P. 111-110°C. Total yield: 25.3 g (89%). The product was crystallized from water M.P. 170-178°C.

(d) N-(3-carboxy - 5 - N - methylacetamido-2,4,6-triiodobenzoyl)-N-methyl-glucamine: The ester prepared according to (c) (30 g) was amidolyised by adding ethanolate (60 ml) and heating while stirring at 70°C under nitrogen for 4 hours. The ethanolate was distilled off under high vacuum, the residue dissolved in water (200 ml) acidified to pH 1, charcoaled at room temperature for 1 hour and extracted with phenol (5×50 ml). The phenol layer was washed with water (6×59 ml), diluted with ether (600 ml) and extracted with water (4×70 ml). The aqueous solution obtained was washed with ether (2×30 ml), charcoaled at room temperature for 16 hours and evaporated to dryness. The residue (24.4 g, 83% M.P. 145-155°C) was crystallised from isopropanol/ethyl acetate, then dissolved in water, charcoaled for 20 minutes at 100°C and evaporated to dryness in vacuo. M.P. 150-170°C. Found: C; 27.77; H; 3.13; N; 3.54; I; 47.6%. Calcd. for C14H23N2O7: C; 27.30; H; 2.92; N; 3.54; I; 48.0%

EXAMPLE 21

5-(N'-β-hydroxyethyl-acetamido) - 2,4,6 - triiodo-N-acetamido-2,4,6-triiodobenzoic acid (36.85 g) was suspended in water for injection (about 70 ml) and titrated in solution by adding strong sodium hydroxide solution. Calcium disodium ethylenediamine tetracetate (15 mg), calcium chloride dihydrate (68 mg) and magnesium chloride hexahydrate (62 mg) were dissolved in the solution, the volume adjusted to 100 ml, the pH adjusted to 7.4; and the solution filtered, ampouled and autoclaved at 120°C for 20 minutes resulting in a composition containing 200 mg. I/ml and the ratios of calcium ions and magnesium ions to sodium ions being 0.015 and 0.006 respectively.

The intracerebral LD50 in mice of this solution was 625 mg. I/kg, body weight as compared to 425 I/kg, when no calcium and magnesium were added.

EXAMPLE 22

5-(N'-β-hydroxyethyl-acetamido) - 2,4,6 - triiodo-N-methylisophthalamic acid (34.6 g), calcium oxide (25 mg), magnesium oxide (12 mg) and calcium disodium ethylenediamine tetracetate (15 mg.) was suspended in water for injection (about 70 ml). The remaining acid which was not neutralized by the alkaline earth metal oxides was neutralized by addition of strong sodium hydroxide solution. The resulting solution was treated as above resulting in a composition equivalent to that described above with regard to iodine concentration and ionic ratios.

The intracerebral LD50 in mice was 580 mg. I/kg, as compared to 400 mg. I/kg, when no calcium and magnesium were added.

We claim:

1. A compound of the formula

\[
\begin{align*}
\text{COOH} & \\
\text{X} & \\
\text{N-Ac}^2 & \\
\end{align*}
\]

wherein:

Ac\(^1\) is a lower alkanyl group having 1 to 4 carbon atoms;

R\(^1\) is selected from the group consisting of hydrogen atom, an alkyl group having 1 to 6 carbon atoms, and an alkyl group having 1 to 6 carbon atoms substituted with at least one hydroxyl group;

X is selected from the group consisting of a group of the formula

\[
\begin{align*}
\text{CON} & \\
\text{R}^2 & \\
\text{R}^3 & \\
\end{align*}
\]

wherein R\(^2\) and R\(^3\) are each a hydrogen atom, an alkyl group having from 1 to 6 carbon atoms, or an alkyl group having from 1 to 6 carbon atoms substituted by at least one hydroxyl group, provided that there is at least one N-hydroxylalkyl group in the molecule; and their sodium, calcium, and mag-
nesium salts or their salts with ethanolamine or N-methylglucamine.

2. The compound of claim 1 wherein R\(^2\) is a hydroxyalkyl group and X is the

\[
-N^--\text{R}^3
\]

3. The compound of claim 1 wherein X is the group CONHOR\(^4\) and at least one of R\(^1\), R\(^2\) and R\(^4\) is a hydroxyalkyl group.

4. The compound of claim 1 in which the hydroxyalkyl group is \(\beta\)-hydroxyethyl.

5. A compound as claimed in claim 1 selected from the group consisting of

- (N-\(\beta\)-hydroxyethyl-acetamido)-5'-N'-methylacetamido-2,4,6-triiodobenzoic acid,
- (N-\(\beta\)-dihydroxypropyl-acetamido)-5'-N'-methylacetamido-2,4,6-triiodobenzoic acid,
- (N-\(\beta\)-hydroxyethyl-acetamido)-2,4,6-triiodo-N-methylisophthalamic acid,
- (N-\(\beta\)-hydroxyethyl-propionamido)-5'-N'-methylacetamido-2,4,6-triiodobenzoic acid,

6. A compound as claimed in claim 1 which is selected from the group consisting of 3-acetamido-2,4,6-triiodo-N-hydroxyethyl-isophthalamic acid and its calcium, sodium and magnesium salts or its salts with ethanolamine or N-methylglucamine.

References Cited

UNITED STATES PATENTS

3,076,024 1/1963 Larsen 260—518 A
3,178,473 4/1965 Holtermann et al. 260—518 A
3,476,802 11/1969 Holtermann et al. 260—518 A

LORRAINE A. WEINBERGER, Primary Examiner

L. A. THAXTON, Assistant Examiner

U.S. Cl. X.R.

260—247.2 R, 293.88, 519; 424—248, 267, 316, 317
Disclaimer


Disclaimer filed July 9, 1974, by the assignee, Nyegaard & Co. A/S.

Hereby enters this disclaimer to all claims of said patent.

[Official Gazette May 27, 1975.]