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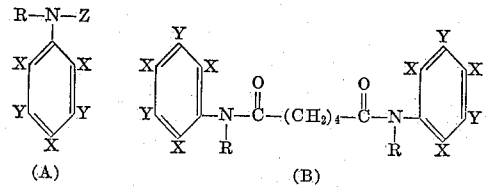
3,178,473

PROCESS FOR THE N-ALKYLATION OF ACYL ANILIDES HALOGEN SUBSTITUTED IN THE NUCLEUS

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5 Claims. (Cl. 260—519)

This invention relates to the preparation of compounds of the general Formulas A and B



(A) (B)

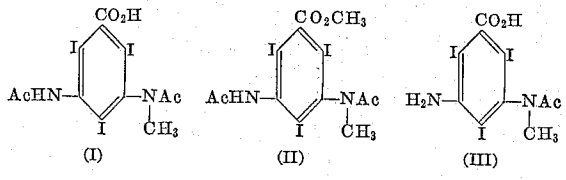
wherein R is a substituted or unsubstituted alkyl group, such as for example methyl, propyl, carboxymethyl, carbalkoxymethyl or hydroxyethyl, X is hydrogen or iodine atoms at least two of them being iodine and, Y designates hydrogen or a desired substituent such as a carboxyl, carbalkoxyl, amino, acylamino or the group



and wherein Z designates the residue of a substituted or unsubstituted aliphatic or aromatic carboxylic acid, for example an acetyl group.

Particularly the invention relates to those compounds of the above general formula in which X is iodine and where R, Y and Z have the meanings given above.

The practical importance of the invention is apparent from the fact that new and valuable compounds can be prepared by the process, especially X-ray contrast agents, in which case the compounds which are acids may be used in the form of their non-toxic salts, and intermediates in their production. Thus, for instance, the new X-ray agent N-methyl-3,5-diacetamido-2,4,6-triiodobenzoic acid (I) is made easily available by means of this invention, and also methyl N-methyl-3,5-diacetamido-2,4,6-triiodobenzoate (II and 3(N-methylacetamido)-5-amino-2,4,6-triiodobenzoic acid (III), the latter two compounds (II and III) being important intermediates in processes for the production of (I):



(I) (II) (III)

The novelty and characteristic inventive feature of the process is a simple and efficient method of making compounds of the above general Formula A or B whereby the N-substituted-acylamido group

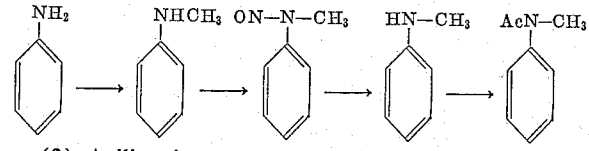


of the above general Formula A or B is formed.

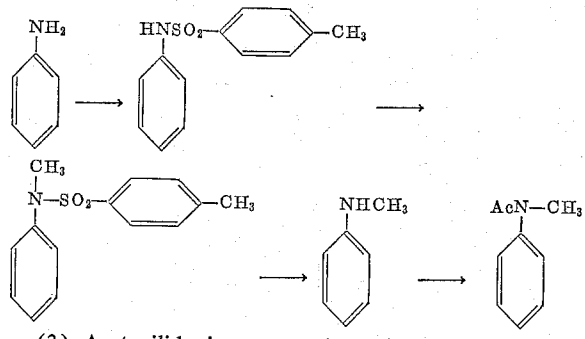
It will be seen that the compounds of the above general Formula A are derivatives of N-alkyl-acylanilides, thus, Compound I for example, is a 2,4,6-triiodo-3-acetamido-5-carboxy-N-methylacetanilide.

The general methods of organic chemistry for making N-alkylacylanilides are the following, as exemplified by N-methylacetanilide:

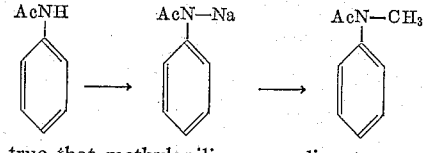
(1) Aniline is methylated by means of a methylating agent (dimethyl sulphate, methyl p-toluene sulphonate, methyl iodide, formaldehyde under reducing conditions, etc.) and the monomethylated aniline separated from unreacted aniline, dimethylaniline and quarternary salts of trimethylaniline via its nitroso derivative from which monomethyl aniline is recovered by reduction or hydrolysis, and finally converted to the desired product by acetylation:



(2) Aniline is reacted with p-toluenesulphonic acid chloride (or benzene-sulphonic acid chloride), the p-toluenesulphonanilide formed is methylated, the N-methylated reaction product hydrolysed under drastic conditions (strong mineral acid, heat) yielding N-methylaniline, which is finally acetylated:

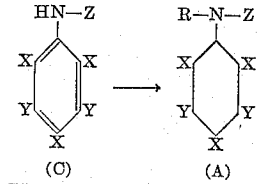


(3) Acetanilide is converted to the sodium salt by heating it with powdered metallic sodium in a high boiling inert solvent, for example Xylene, followed by treatment of the sodium salt with a methylating agent (for example methyl iodide):



It is true that methylaniline according to procedure 1 above can technically be separated from the other reaction products and from unreacted aniline by fractional distillation or by fractional crystallization of the hydrochlorides, but these are special separation procedures not generally applicable and are in any case irrelevant for the present analysis.

The present invention is characterised by the discovery that the N-substituted acylanilides of the above general Formulas A or B are prepared by N-substitution in alkaline aqueous solution (for example sodium hydroxide solution), alkaline aqueous—organic solution (for example alkaline aqueous methanolic solution) or organic solution in the presence of a base (for example ethoxide in ethanol) of the acylanilides of the general Formula C according to the general reaction:



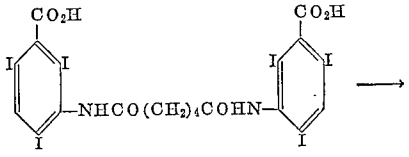
(C) (A)

in which R, X, Y and Z have the meanings given above. The substituting agent can be any ordinary alkylating agent (for example, dimethyl sulphate, methyl p-toluensulphonate, methyl iodide, ethyl iodide, propyl iodide,

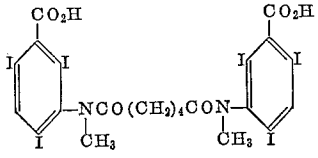
bromoacetic acid, ethyl bromoacetate, ethylenebromohydrin, etc.).

We have thus found that while acylanilides in general are not alkylated in solution in the presence of alkali or sodiumalkoxides, this is the case when two or more halogens are introduced into the ortho and para positions relative to the nitrogen atom of the anilide.

This may appear the more surprising when one considers the steric hindrance known to operate in the neighboring positions of aromatic bound halogens and which is quite formidable in the case of iodine. It is furthermore noteworthy that reaction mechanism studies indicate that the alkylation reaction is proceeded by enolization and ionization of the acylamido group of the anilide to be alkylated, in spite of the work of Neudert and Röpke (Chem. Ber., 87, 659–667 (1954)) who found no indication of a tendency of enolisation or dissociation of the acetamido group in their ultraviolet absorption studies on adipoyl - bis - (2,4,6-triiodo-3-carboxy-anilide) (IV) which is easily methylated in aqueous alkali according to the invention to the N,N'-dimethyl derivative (V)



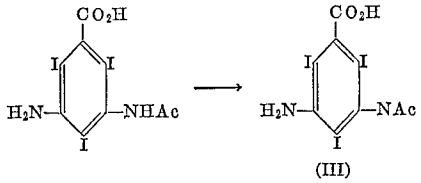
(IV)



(V)

Furthermore we have found that the general method (method 3 above) of alkylating anilides by successive treatment with metallic sodium and an alkylating agent is not generally applicable on the polyhalo-anilides of the invention (general Formula C above). It has thus for instance not been possible in our hands to N-alkylate methyl 3,5-diacetamido-2,4,6-triiodobenzoate by successive treatment with metallic sodium and methyl iodide (or dimethyl sulphate) in boiling xylene (or dioxan) although the alkylation proceeds rapidly at room temperature and below in aqueous alkali.

We have also found that an ordinary alkylation (according to method 1 above) of amino-nitrogen prior to the introduction of the acyl group of the compounds of the general Formula C is not generally applicable and has failed completely in our hands for example in the case of 3,5-diamino-2,4,6-triiodobenzoic acid which could not be N-methylated by means of methyl iodide or dimethyl sulphate. This is taken advantage of in the present invention according to which compounds of the general Formula C in which one Y is an amino group and the other Y is an acetamido group can be alkylated exclusively on the amido-nitrogen as in the following reaction:



(III)

where no trace is found of a derivative carrying a methyl group on the amino nitrogen, and where the yield of the desired Compound III is nearly quantitative. This reaction is of great importance because the intermediate (III) can easily by acetylation be converted to the valuable N-

methyl-3,5-diacetamido - 2,4,6 - triiodobenzoic acid mentioned above.

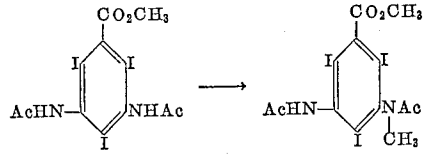
Method 2 above is not generally feasable because of the extraordinary resistance to hydrolysis of polyhalogen substituted anilides, and would of obvious reasons constitute an unnecessary and laborious complication.

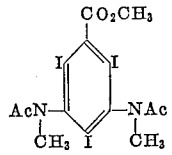
The present invention therefore is founded on the discovery that acyl anilides of the above general Formula C

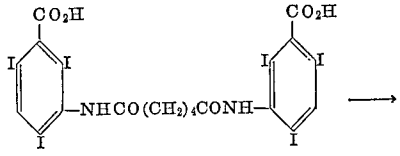
(1) Can be N-alkylated in alkaline aqueous or organic solution as easily as sulphonanilides, contrary to other ordinary acylanilides and that

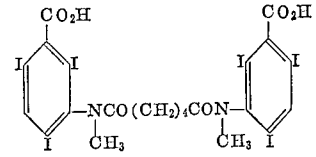
(2) The ordinary method of N-alkylation of anilides is not generally applicable to the compounds of the invention.

As to the interpretation of the general Formulae A and C it should be stated clearly that they are intended to cover also compounds which contain two or more acylanilido groups in the same or in different aromatic nuclei, thus the following compounds and reactions fall within this invention:

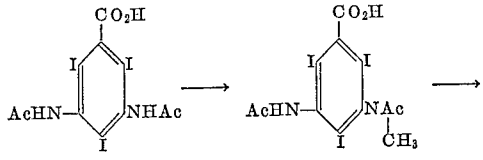


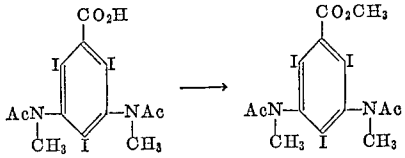






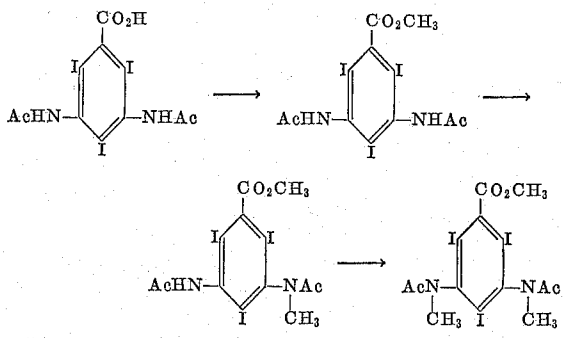
It has furthermore been found that certain compounds of the general Formula C of the invention can be further alkylated when suitable groups (for example carboxyl groups) are present as substituents, and that in such cases it is usually possible to lead the reaction so as to give the one or the other reaction product. It is thus possible according to the invention to methylate 3,5-diacetamido-2,4,6-triiodobenzoic acid to either the N-monomethyl acid, the N,N'-dimethyl acid or the N,N'-dimethyl-methyl ester as illustrated by the following formula:





and while this reaction sequence takes place in aqueous media, N-alkylation taking place more rapidly than esterification, the following sequence is predominant in non-

aqueous media, esterification taking place more rapidly than N-methylation:



In some such cases it may be an advantage to carry the reaction to the completely N-methylated ester stage and then convert the N-methylated ester to the acid if the latter compound is desired.

It has furthermore been found that in the cases where the N-methylated acylanilides of the invention carry an iodine atom in both ortho positions to the acylamido group a new type of isomerism occurs which is due to restricted rotation of the acyl group around the axis connecting the carbonyl carbon atom with the nitrogen atom, making two thermodynamically preferred orientations of the acyl group possible, one in which the carbonyl of the acyl group points inwards towards the aromatic nucleus (endo form) and another in which it points outwards away from the aromatic nucleus (exo form), the two forms adopting their thermodynamical equilibrium rapidly above 70° C.

The process of the invention is very simple and is carried out in the following way. The acyl-polyhalo-anilide is dissolved in aqueous alkali eventually by the help of an organic solvent (for example acetone, methanol, dioxan etc.), or it is dissolved in an organic solvent to which is added strong alkali or an alkali alkoxide or some other suitable base, and the alkylating agent (for example dimethyl sulphate, methyl p-toluene sulphonate, propyl iodide etc.) is added preferably in portions with stirring, dissolved in some solvent which will give a homogeneous solution. Stirring and cooling are usually advantageously employed in the case of the very reactive alkylating agents.

The compounds of Table II below are examples of compounds which can be prepared according to the invention, those of Table I comprise those which have actually been prepared.

TABLE I

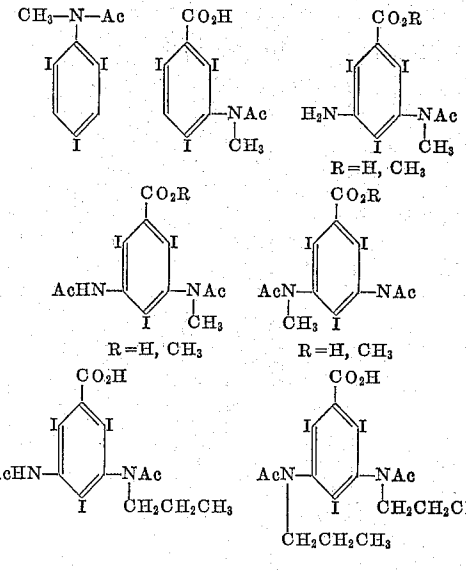
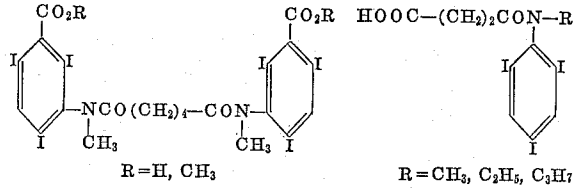
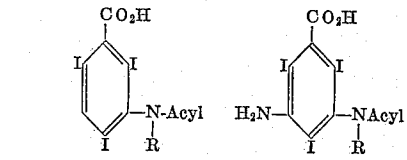
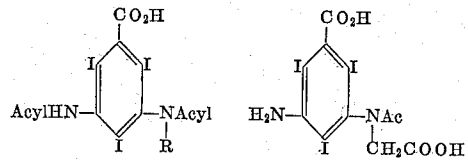
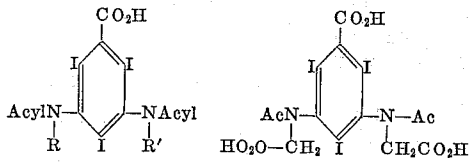


TABLE I—Continued









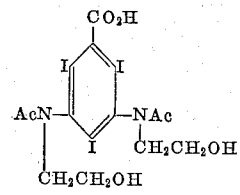
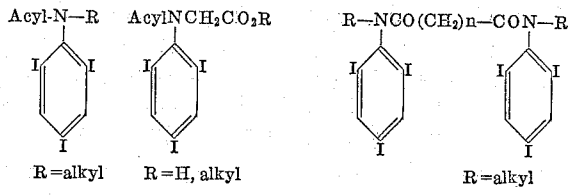
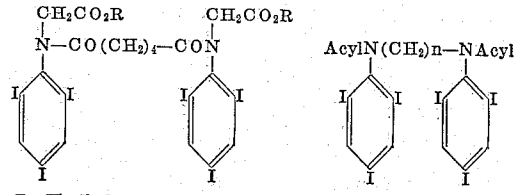
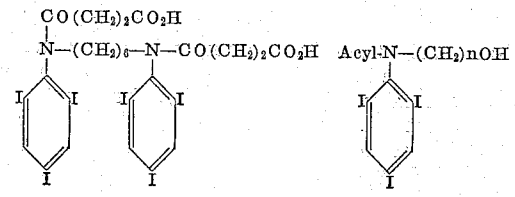


TABLE II







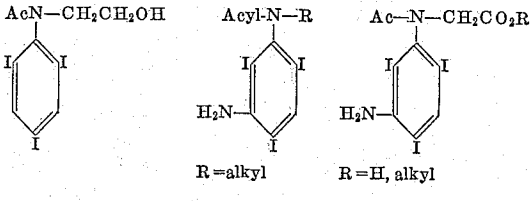
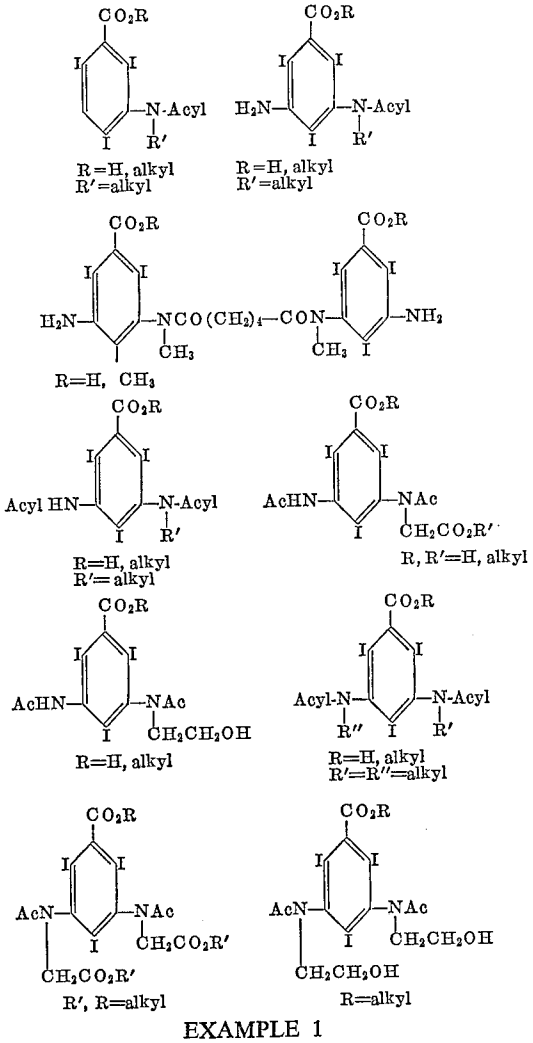


TABLE II—Continued



EXAMPLE 1

N-methyl-2,4,6-triiodoacetanilide

Triiodoacetanilide (3.9 mmol., 2 g.) was suspended in 20 ml. of ethanol and brought into solution by means of 2 ml. of 5 N methanolic sodium hydroxide. Dimethyl sulphate (6.4 mmol., 0.6 ml.) was added while stirring and placed on a water bath at 60° C. After about 15 minutes N-methyl-2,4,6-triiodoacetanilide crystallised and was filtered after 12 hours standing and washed on the filter with 5 ml. of ethanol. The pistol dried product (0.6 g., 78% of theory) melted at 183–190° C. (Mixture of the acetexo and acetendo forms.)

EXAMPLE 2

N-methyl-3-acetamido-2,4,6-triiodobenzoic acid

3-acetamido-2,4,6-triiodobenzoic acid (0.147 mol., 82 g.) was dissolved in a mixture of water (80 ml.) and 5 N sodium hydroxide (3.7 eqv., 110 ml.). The solution was cooled to about 15° C. and dimethyl sulphate (1.2 eqv.), dissolved in acetone (17 ml.) was added with stirring at a relatively slow rate. After 45 minutes stirring the N-methyl-3-acetamido-2,4,6-triiodobenzoic acid was precipitated by addition of hydrohcloric acid (1:1) to pH about 0.5. The moist acid, containing the exo and endo isomers in about equal proportions was dissolved as their ammonium salts in about 400 ml. of water and the solution kept in boiling water bath for about 45 minutes in order to convert the thermodynamically less stable isomer (endo compound) into the more stable (exo compound), whereafter the solution was treated with active carbon, filtered, cooled and precipitated by means of hydrochloric acid (1:1), stirred for about 1 hour, filtered, washed with water and dried. Exo-N-methyl-3-acetamido-2,4,6-triiodobenzoic acid was obtained in 94% yield (79 g.).

EXAMPLE 3

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

3-acetamido-5-amino-2,4,6-triiodobenzoic acid (2 g.) was suspended in water (2 ml.) and dissolved by adding 5 N potassium hydroxide (2.6 ml.). Dimethyl sulphate (0.6 ml.; 1.82 eqv.) dissolved in acetone (0.8 ml.) was added in portions with stirring. After a few minutes the solution became homogeneous. Stirring was continued for one hour after which dilute hydrochloric acid (1:1) was added to pH about 0.5, the precipitate filtered, washed with water and dried in vacuo. 5-amino-3-(N-methylacetamido)-2,4,6-triiodobenzoic acid (2.0 g.; 97% yield) was collected as a colourless powder, melting point 275° C.

EXAMPLE 4

Methyl 5-amino-3-(N-methylacetamido)-2,4,6-triiodobenzoate

3-acetamido-5-amino-2,4,6-triiodobenzoic acid (2 g.) was suspended in water (2 ml.) and dissolved by adding 7.8 ml. of 5 N potassium hydroxide. Dimethyl sulphate (1.8 ml.) dissolved in acetone (1.8 ml.) was added in portions with stirring at 50° C. The insoluble methyl 5-amino - 3 - (N-methylacetamido) - 2,4,6-triiodobenzoate which precipitated was filtered, washed with dilute acetic acid and with water and dried (2.0 g.).

EXAMPLE 5

Methyl N-methyl-3,5-diacetamido-2,4,6-triiodobenzoate

Methyl 3,5-diacetamido-2,4,6-triiodobenzoate (50 g.; 0.08 mol.) was suspended in water (150 ml.) and dissolved by adding 5 N potassium hydroxide (38 ml.; 2.4 eqv.). Acetone (5 ml.) was added with stirring followed by dimethyl sulphate (8 ml.; 1.05 eqv.) dissolved in acetone (10 ml.) slowly at about 15° C. After 1½ hours insoluble methyl N,N'-dimethyl-3,5-diacetamido-2,4,6- triiodobenzoate (2.9 g.) was separated by filtration. The filtrate was acidified by means of concentrated hydrochloric acid (about 20 ml.) and the precipitated material filtered, washed with water, redissolved in strong alkali to a concentration of about 10% ester, filtered from a small amount of N,N'-dimethyl-methylester, the filtrate reacidified and the practically pure methyl N-methyl-3,5-diacetamido-2,4,6-triiodobenzoate filtered, washed with water and dried.

EXAMPLE 6A

N-methyl-3,5-diacetamido-2,4,6-triiodobenzoic acid

502.4 g. (0.8 mol.) of methyl 3,5-diacetamido-2,4,6-triiodobenzoate is dissolved in 800 ml. 5 N aqueous potassium hydroxide (4 mol.) by mechanical agitation and gentle heating. All material dissolves and the solution is cooled to room temperature whereafter 1600 ml. of molar methanolic methylsulphuric acid is added with stirring. The mixture is heated on boiling water bath for 10 minutes under reflux cooling. Then the heating continues on the boiling water bath with descending condenser. After about 2 hours about 1420 ml. has distilled over at 72–82°. Some solid substance has precipitated, and a further 200 ml. (1 mol.) 5 N potassium hydroxide and 22 g. of solid (85%) potassium hydroxide are added, after which heating on boiling water bath continues with descending cooler. After 80 minutes a sample of the mixture gives, after addition of glacial acetic acid to pH about 4.5, no longer any precipitate. Altogether about 1560 ml. distillate has been collected.

The heating is suspended and to the dark—brown mixture is added 500 ml. of water. After cooling to room temperature, the precipitated substance is filtered by suction on a glass filter and washed with 250 ml. of water.

The two filtrates are combined and filtered. To this clear, brown, filtered liquid (1920 ml.) is added with mechanical stirring 970 ml. of dilute hydrochloric acid (1:2) to pH about 4. After standing over night the solution is filtered from a voluminous, chocolate-brown precipitate, which is washed with 400 ml. water. Filtrate and washings are combined and 70 g. of carbon (index 35) added, heated to boiling and filtered. The filtrate is washed with about 1000 ml. of water and the two filtrates combined. To the tea-coloured solution is added about 250 ml. dilute hydrochloric acid (1:2) with mechanical stirring to pH 1–0.5. After agitation over night it is filtered on a sintered plate (G4) and the precipitate washed twice with water (500 ml. and 300 ml.), and dried to constant weight over phosphorous pentoxide in vacuum. The slightly yellowish substance weighs 378 g. (76.6%) and consists of approx. 85% N-methyl-3,5-diacetamido-2,4,6-triiodobenzoic acid, admixed with about 5% 3,5-diacetamido-2,4,6-triiodobenzoic acid and about 15% N,N'-dimethyl-3,5-diacetamido-2,4,6-triiodobenzoic acid. 3 g. of this product is extracted twice with pyridine-containing alcohol. The undissolved pyridine salt is treated with diluted hydrochloric acid, washed and dried, whereby 56% chromatographically pure N - methyl - 3,5 - diacetamido-2,4,6-triiodobenzoic acid is obtained. By processing of the alcoholic mother liquors the yield of this compound can be increased.

EXAMPLE 6B

N-methyl-3,5-diacetamido-2,4,6-triiodobenzoic acid

3,5-diacetamido-2,4,6-triiodobenzoic acid (10 g.) is suspended in water (10 ml.), 5 N potassium hydroxide (4.3 eqv.) is added and the mixture cooled to about 15° C. Dimethyl sulphate (0.5 eqv.) dissolved in an equal volume of acetone is added drop by drop while stirring. After the reaction mixture has been stirred for about 1 hour hydrochloric acid (1:1) is added, with stirring to pH about 0.5. The precipitate is filtered, washed and suspended moist in 4 parts of water, concentrated ammonia is added to pH about 7 and the ammonium salt solution is isomerized at 90–100° C. for about half an hour whereafter additional ammonia is added to pH about 9 followed by solid ammonium chloride (about 10% weight/volume) and the solution stirred over night and the excess of 3,5-diacetamide-2,4,6-triiodobenzoic acid recovered as ammonium salt on the filter. The filtrate is precipitated by means of hydrochloric acid (1:1) at pH about 0.5 and the N-methyl-3,5-diacetamido-2,4,6-triiodobenzoic acid collected on a filter, washed and dried.

EXAMPLE 7

Methyl N,N'-dimethyl-3,5-diacetamido-2,4,6 triiodobenzoate

50 g. of methyl 3,5-diacetamido-2,4,6-triiodobenzoate is dissolved in a mixture of 50 ml. 5 N potassium hydroxide and 200 ml. of water by careful heating under mechanical stirring. At 48–50° 21.5 ml. of dimethylsulphate is added under constant stirring, 12–16 drops per minute. After the solution has become neutral, it is heated for 5 minutes to 55–65°. The product is filtered off, extracted hot for a few minutes with 2 N potassium hydroxide, cooled, filtered, washed and dried, whereby 50.0 g. (94%) pure N,N'-dimethyl-3,5-diacetamido-2,4,6-triiodobenzoic acid methyl ester is isolated.

EXAMPLE 8

N,N'-dimethyl-3,5-diacetamido-2,4,6-triiodobenzoic acid

3,5-diacetamido-2,4,6-triiodobenzoic acid (10 g.) is suspended in 10 ml. of water and 5 N potassium hydroxide (6 eqv.) added and the mixture cooled to about 15° C. Dimethyl sulphate (1.4 eqv.) dissolved in an equal volume of acetone is added drop by drop with stirring. The product is precipitated by the addition of hydrochloric acid, collected on a filter, resuspended moist in about 4 volumes of water and dissolved by the addition of alkali to pH about 7. The solution is now isomerised by heating to 90–100° C. for about 1 hour, cooled and reprecipitated by means of hydrochloric acid, filtered, washed and dried in the ordinary way, yielding about 10 g. of dry N,N'-dimethyl-3,5-diacetamido-2,4,6-triiodobenzoic acid.

EXAMPLE 9

Propylation of 3,5-diacetamido-2,4,6-triiodobenzoic acid

3,5-diacetamido-2,4,6-triiodobenzoic acid (5 g.; 8.2 mmol.) was suspended in water (5 ml.), and brought into solution by means of the addition of 5 N potassium hydroxide (6.5 ml.; about 4 eqv.). n-Propyl iodide (0.8 ml.; 8.2 mmol.) dissolved in acetone (1 ml.) was added and the mixture heated under reflux and mechanical stirring on the boiling water bath for about 1 hour. The temperature was then decreased to between 60 and 80° C. and the solution was stirred at this temperature for another hour. The mixture was then cooled to room temperature and acidified by means of hydrochloric acid (1:1) to pH about 0.5. The precipitate was filtered, washed with water and dried yielding a product (4.8 g.; 90% yield) having a M.P. 215° C. (decomp.) and which by comparative chromatography of unisomerised and isomerised samples indicated a mixture of about 50% starting material, 30% N-propyl-3,5-diacetamido-2,4,6-triiodobenzoic acid and about 20% of N,N'-dipropyl-3,5-diacetamido-2,4,6-triiodobenzoic acid.

EXAMPLE 10

Propylation of methyl 3,5-diacetamido-2,4,6-triiodobenzoate

Methyl 3,5-diacetamido-2,4,6-triiodobenzoate (5 g.; about 8 mmol.) was suspended in water (5 ml.), and then brought into solution by means of 5 N potassium hydroxide (6.5 ml.; 4 eqv.). Propyl iodide (0.78 ml.; 8.0 mmol.) dissolved in acetone (1 ml.) was added. The mixture was heated under reflux and mechanical stirring on the boiling water bath for about 1 hour. And then for a further hour at 60–80° C. A precipitation occurred during heating and the precipitated methyl N,N'-dimethyl-3,5-diacetamido-2,4,6-triiodobenzoate weighed 1.3 g. and melted at 220° C. (decomp.). A sample was converted to the corresponding acid by means of aminolysis and a chromatogramme showed it to be pure dipropyl compound.

The filtrate was acidified with concentrated hydrochloric acid to pH about 0.5, and filtered, and washed by suspending it twice in 50 ml. each time of 0.5-M sodium carbonate, and filtered a new. After final washing with a little water the methyl N-propyl-3,5-diacetamido-2,4,6-triiodobenzoate weighed dry 3.0 g. and melted at 220° C. (decomp.). A sample of this product was converted to the corresponding acid and chromatographed, the chromatogramme showing that it consisted of the monopropyl compound with only traces of starting material and dipropyl compound present.

EXAMPLE 11

N,N'-dimethyl-adipoyl-bis-(3-carbomethoxy-2,4,6-triiodoanilide)

Adipoyl-bis-(3-carboxy-2,4,6-triiodoanilide) (29.8 g.) was dissolved in potassium hydroxide (60 ml.; 2.5 N) and dimethyl sulphate (18 ml.) added with stirring in the course of 5 minutes. The temperature rose to 40° and the solution became cloudy. Successively more potassium hydroxide (60 ml.; 5 N) and dimethyl sulphate (72 ml.) were added in portions whereby the temperature rose further. After stirring for about 1 hour the N,N'-dimethyl-adipoyl-bis-(3 - carbomethoxy - 2,4,6 - triiodoanilide) (25 g.) was obtained after filtration, washing and drying.

EXAMPLE 12

N,N'-dimethyl-adipoyl-bis-(3-carboxy-2,4,6-triiodoanilide)

Adipoyl-bis-(3 - carboxy-2,4,6-triiodoanilide) (1.28 g.) was dissolved in water (2 ml.) and acetone (1 ml.) and potassium hydroxide (2 ml.; 5 N) added. Dimethyl sulphate (0.28 ml.; 1.4 eqv.) was added with stirring, whereby the temperature rose from 21–31° C. in the course of about 30 seconds. After about 20 minutes the reaction product was precipitated by means of strong hydrochloric acid (pH 0.5), filtered, washed and dried, whereby 1.15 g. of chromatographically pure N,N'-dimethyl-adipoyl-bis-(3-carboxy - 2,4,6 - triiodoanilide) was obtained as a completely colourless product.

EXAMPLE 13

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

3,5-diacetamido-2,4,6-triiodobenzoic acid (24 g.) was suspended in warm water (70 ml.) and dissolved by adding 10 N sodium hydroxide (30 ml.). Ethylenebromohydrin (16 ml.) was added to the still warm solution and left at room temperature over night.

The acid was then precipitated by means of concentrated hydrochloric acid to pH about 0.5, filtered, washed with water, dried and crystallised from ethanol/ethylacetate.

Yield 17.5 g. (64%).
Melting point 196–197° C.
Toxicity in mice LD_{50}:17.0 g. acid/kg.

EXAMPLE 14

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

The compound was prepared from 3-acetamido-2,4,6-triiodobenzoic acid according to Example 13. The product was crystallised from ethanol/water. Melting point 121.5–122.5° C.

The following compounds were prepared according to Example 2:

Example	Compound	Alkylating agent	React. temp., ° C.	React. time, hrs.	Yield, Percent	Melting point, ° C.
15	N-ethyl-3-acetamido-2,4,6-triiodobenzoic acid.	Ethyl iodide	65	2½	66	210–235
16	N-n-propyl-3-acetamido-2,4,6-triiodobenzoic acid.	n-Propyl iodide	90	1	95	132–140
17	N-n-butyl-3-acetamido-2,4,6-triiodobenzoic acid.	n-Butyl iodide	80–90	2		

At these reaction temperatures the conversion of the less stable isomers is not necessary.

The following compounds were prepared according to Example 3:

Example	Compound	Alkylating agent	React. temp., ° C.	React. time, hrs.	Yield, Percent	Melting point, ° C.
18	5-amino-3-(N-ethyl acetamido)-2,4,6-triiodobenzoic acid.	Ethyl iodide	65	1½	92	200–250
19	5-amino-3-(N-n-propyl-acetamido)-2,4,6-triiodobenzoic acid.	n-Propyl iodide	90	1½	100	240–262d
20	5-amino-3-(N-n-butyl-acetamido)-2,4,6-triiodobenzoic acid.	n-Butyl iodide	90	2	80	155–160
21	5-amino-3-(N-n-pentyl-acetamido)-2,4,6-triiodobenzoic acid.	n-Pentyl iodide	90	2	47	141
22	5-amino-3-(N-methyl propamido(-2,4,6-triiodobenzoic acid.	Dimethyl sulphate	15	1	95	156–160
23	5-amino-3-(N-ethyl-propamido)-2,4,6-triiodobenzoic acid.	Ethyl iodide	65	1½	95	
24	5-amino-3(N-n-propyl-propamido)-2,4,6-triiodobenzoic acid.	n-Propyl iodide	90	1½	75	
25	5-amino-3(N-methyl-butyramido)-2,4,6-triiodobenzoic acid.	Dimethyl sulphate	15	1	97	

From these compounds the following diacyl-derivatives have been prepared:

Example	Compound	Yield, percent	Melting point, ° C.
18a	N-ethyl-3,5-diacetamido-2,4,6-triiodobenzoic acid.	79	276–286
19a	N-n-propyl-3,5-diacetamido-2,4,6-triiodobenzoic acid.	80	265–270
19b	3-(N-n-propylacetamido)-5-propamido-2,4,6-triiodobenzoic acid.	92	254–257
20a	N-n-butyl-3,5-diacetamido-2,4,6-triiodobenzoic acid.	78	200–265
20b	3-(N-n-butyl acetamido)-5-propamido-2,4,6-triiodobenzoic acid.	89	158–161
21a	N-n-pentyl-3,5-diacetamido-2,4,6-triiodobenzoic acid.	75	168–171
22a	N-methyl-3,5-dipropamido-2,4,6-triiodobenzoic acid.	91	288–295d
22b	3-(N-methylpropamido)-5-acetamido-2,4,6-triiodobenzoic acid.	90	280–290
23a	N-ethyl-3,5-dipropamido-2,4,6-triiodobenzoic acid.	61	
23b	3-(N-ethylpropamido)-5-acetamido-2,4,6-triiodobenzoic acid.	69	
24a	3-(N-n-propylpropamido)-5-acetamido-2,4,6-triiodobenzoic acid.	95	

EXAMPLE 26

N,N'-diethyl-3,5-diacetamido-2,4,6-triiodobenzoic acid

3,5-diacetamido-2,4,6-triiodobenzoic acid (20 g.) was suspended in water (20 ml.) and 10 N sodium hydroxide

(22.8 ml.) added and the mixture heated to about 65° C. Ethyl iodide (8.1 ml.) was added with stirring. After 1½ hours at 65° C. the solution was cooled and the product precipitated by means of hydrochloric acid (1:1) to pH about 0.5, filtered, washed with water and dried.

Yield 18.3 g. (83.5%). Melting point 248–253° C.

EXAMPLE 27

N,N'-dimethyl-3,5-dipropamido-2,4,6-triiodobenzoic acid

Sodium 3,5-dipropamido-2,4,6-triiodobenzoate (15 g.) dissolved in water (30 ml.) was added 5 N sodium hydroxide (18 ml.). Dimethyl sulphate (6.5 ml.) dissolved in acetone (10 ml.) was added the cooled solution with stirring. After 1 hour the product was precipitated with concentrated hydrochloric acid, filtered, washed with water and dried.

Yield: 15 g. (96%), melting point 230–232° C.

EXAMPLE 28

N,N'-dipropyl-3,5-dipropamido-2,4,6-triiodobenzoic acid

This compound was prepared as described in Example 27 by using propyl iodide as alkylating agent and the reaction temperature being 90° C.

Yield 53%, melting point 265–270° C.

EXAMPLE 29

N-carboxymethyl-3-acetamido-2,4,6-triiodobenzoic acid

3-acetamido-2,4,6-triiodobenzoic acid (1 g.) was suspended in water (1 ml.) and 5 N sodium hydroxide (3 ml.) added. Bromoacetic acid (1.01 g.) dissolved in water (1 ml.) was added drop by drop with stirring to the solution which had been heated to 50° C. After about 30 min. at 50–60° C. the product was precipitated by means of concentrated hydrochloric acid to pH about 0.5, filtered, washed with water and dried.

Yield 82%, melting point 255° C.

EXAMPLE 30

N,N'-dicarboxymethyl-3,5-diacetamido-2,4,6-triiodobenzoic acid

This compound was prepared from 3,5-diacetamido-2,4,6-triiodobenzoic acid as described in Example 29.

Yield: 26%, melting point 150–180° C.

EXAMPLE 31

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

This compound was prepared from 3-acetamido-5-amino-2,4,6-triiodobenzoic acid as described in Example 29.

Yield: 90%, melting point: 160–161° C.

EXAMPLE 32

N-methyl-2,4,6-triiodo-β-carboxypropanilide

5.70 g. 2,4,6-triiodo-β-carboxypropanilide was dissolved in 24 ml. of a mixture of ethanol: 5 N KOH=1:1 and 3.80 ml. dimethyl sulphate was added in the course of 10 minutes.

After stirring for 1 hour concentrated hydrochloric acid was added (pH 0.5–1.0). The mixture was left over night, filtered, and washed with water. Weight: 5.15 g. (88%).

The acid was dissolved as sodium salt in 40 ml. of water and precipitated by adding concentrated hydrochloric acid (pH 0.5–1.0). Weight: 4.7 g.

The acid was crystallised from 60 ml. benzene. Weight: 4.0 g. Melting point: 160–163.5° C.

EXAMPLE 33

N-ethyl-2,4,6-triiodo-β-carboxypropanilide

The compound was prepared as described in Example 32, using ethyl iodide as the alkylating agent. The reaction temperature was 70° C.

Yield: 77%, melting point: 146–149° C.

EXAMPLE 34

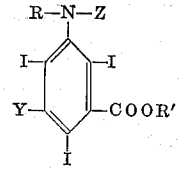
N-n-propyl-2,4,6-triiodo-β-carboxypropanilide

The compound was prepared as described in Example 32. Using n-propyl iodide as the alkylating agent. The reaction temperature was 90° C.

Yield: 85%, melting point 167–178° C.

We claim:

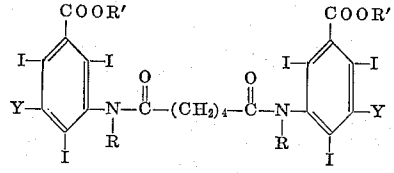
1. A compound selected from the group consisting of a compound of the formula



in which R is a member selected from the group consisting of lower carboxyalkyl, lower carbalkoxyalkyl and lower hydroxyalkyl, Z is lower alkanoyl, Y is a member selected from the group consisting of hydrogen, amino, lower alkanoylamido and



and R' is a member selected from the group consisting of hydrogen and lower alkyl; a compound of the formula

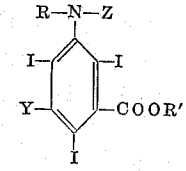


in which Y, R and R' have the same meaning as above; and nontoxic salts of the compounds of both of said formulas in which R' is hydrogen.

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

3. N-(β-hydroxyethyl) - 3 - acetamido - 2,4,6 - triiodobenzoic acid.

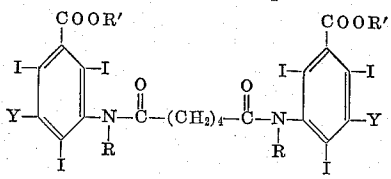
4. A process for the preparation of a compound selected from the group consisting of a compound of the formula



in which R is a member selected from the group consisting of lower carboxyalkyl, lower carbalkoxyalkyl and lower hydroxyalkyl, Z is lower alkanoyl, Y is a member selected from the group consisting of hydrogen, amino, lower alkanoylamido and



and R' is a member selected from the group consisting of hydrogen and lower alkyl and a compound of the formula



in which Y, R and R' have the same meaning as above, comprising reacting the corresponding compound in which

R is hydrogen with a compound selected from the group consisting of lower haloalkanoic acids, lower alkyl esters of lower haloalkanoic acids and lower alkylene halohydrins in the presence of an aqueous alkaline medium.

5. The process of preparing N,N'-di(β-hydroxyethyl)-3,5-diacetamido-2,4,6-triiodobenzoic acid, comprising reacting 3,5 - diacetamido - 2,4,6 - triiodobenzoic acid with ethylenebromohydrin in the presence of an aqueous solution of sodium hydroxide.

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