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3,173,944

# SUBSTITUTED AMONOMETHANE-PHOSPHONIC ACIDS

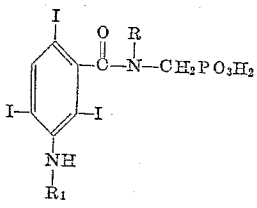
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7 Claims. (Cl. 260—500)

This invention relates to certain new and useful substituted aminomethanephosphonic acids, their non-toxic salts, and to methods of preparing said acids and non-toxic salts.

It is an object of the present invention to provide new compounds which are substituted aminomethanephosphonic acids and the non-toxic pharmaceutically acceptable salts thereof. It is a further object of the present invention to provide substituted aminomethanephosphonic acids which possess relatively low toxicity for human bodies. Another object of the present invention is to provide improved contrast media for X-ray diagnosis. Other objects will be partly obvious and partly apparent from what follows hereinafter.

Surprisingly, it has now been found that aminomethanephosphonic acids of the general formula



wherein R represents alkyl, preferably alkyl with 1 to 8 carbon atoms, or aralkyl, preferably benzyl; and $R_1$ represents lower acyl, preferably acetyl;

and the non-toxic salts thereof, preferably the alkali metal salts, such as sodium, potassium, ammonium, etc. salts are valuable X-ray contrast agents of remarkably low toxicity.

The compounds of the present invention are, therefore, useful in radiologic studies for the visualization of certain anatomic structures of the mammalian system, such as e.g., the urinary tract.

As X-ray contrast agents, the compounds of the present invention may be used in solution, for example in aqueous solution. Advantageously, the non-toxic salts of the substituted aminomethanephosphonic acids may be used. The di- and monosodium salts, for example, are useful. Also useful are the di-diethanolamine salts. Aqueous solutions of the non-toxic salts may be used in concentrations of 20 to 80 weight parts per 100 parts by volume of solution. Volumes of 0.2 to 1.0 ml. per kilogram of body weight may be used for visualization of organs, such as the urinary tract.

Many iodinated organic compounds in the past have been proposed as X-ray contrast agents; however, relatively few of these have been seen to have practical value. Many compounds may possess the requisite opacity to X-rays and/or the required solubility so that concentrations sufficient for X-ray analysis can be circulated in human body fluids. However, a considerable number of these compounds are unsuitable for X-ray diagnosis because of their relatively high toxicity.

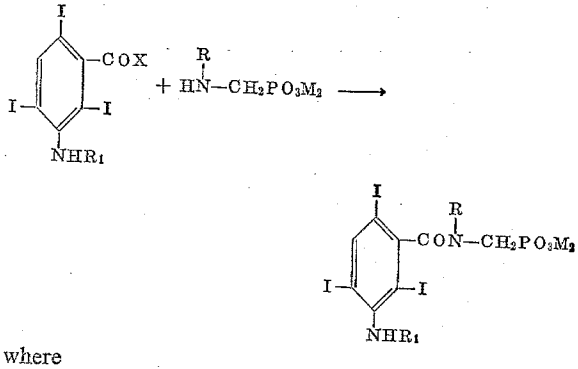
Among those compounds proposed for use as X-ray contrast agents are the iodinated derivatives of benzoic acid. Unfortunately, many of these compounds have been found to fail as X-ray contrast agents, either because they were not sufficiently soluble or because they were



too toxic to permit their use in sufficiently high quantities for good results.

In contrast thereto, the compounds of the present invention have been found to have an $L.D._{50}$ of well over 5000 mg./kg. for male and female mice of from 14 to 23 grams body weight, the $L.D._{50}$ being the lethal dose at which at least 50% of the subjects died.

The substituted aminomethanephosphonic acids of the present invention are conveniently prepared according to the following reaction:



where

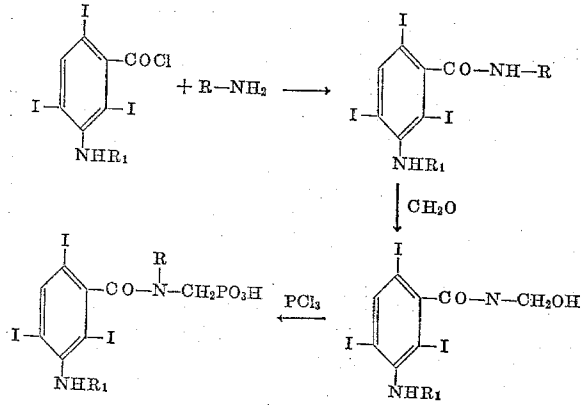
X is a halogen atom, preferably a chlorine or bromine atom, and

M is an alkali metal atom, preferably sodium, or the ammonium ($NH_4$) group, or hydrogen.

The N-alkyl phosphonate intermediate is conveniently prepared as follows:

$$R{-}NH_2 + X{-}CH_2PO_3M_2 \rightarrow R{-}NH{-}CH_2PO_3M_2$$

The substituted aminomethanephosphonic acids of the present invention may also be prepared by the following series of reactions:



The preparation of acylamidomethanephosphonic acids has been described by Kosolapoff (Organophosphorus Compounds, J. Wiley and Sons, New York, 1950, page 125).

Any suitable alkylamine may be used as starting material, e.g. methylamine, ethylamine, propylamine, butylamine, amylamine, hexylamine, heptylamine, octylamine. Any suitable aralkyl amine may be used, e.g. benzylamine and substituted benzylamines, such as alkylbenzyl amines, alkoxybenzylamines, halobenzylamines, nitrobenzylamines, etc.

Any suitable triiodo-m-aminobenzoyl halide may be used according to the present invention. The acyl derivatives, e.g. the acetylaminobenzoyl halides are especially useful. A method for the preparation of the substituted aminomethanephosphonic acids of the present invention is illustrated in Example I hereinbelow. This example

illustrates the use of a triiodo-m-nitrobenzoyl halide in the preparation of the compounds of the present invention. The free anilino-compound so-obtained may be acylated according to known methods to produce the compounds of the present invention.

The following examples are illustrative of the present invention, but there is no intention to limit the same thereto. In the examples, temperatures are in degrees centigrade and parts are parts by weight, unless otherwise stated. The relationship of parts by weight to parts by volume is as that of grams to cubic centimeters.

## EXAMPLE I

*Preparation of N-(3-acetylamino-2,4,6-triiodobenzoyl)-N-methyl-aminomethanephosphonic acid via m-nitrobenzoyl chloride*

A solution of disodium N-methylaminomethanephosphonate is prepared by dissolving 16.0 parts of sodium hydroxide and 25.0 parts (0.2 mole) of N-methylaminomethanephosphonic acid in 50 parts by volume of water. (The N-methylaminomethanephosphonic acid may be prepared according to Pikl in U.S. Patent 2,328,358).

The solution of 33.8 parts (0.20 mole) of disodium methylaminomethanephosphonate in 50 parts by volume of water is cooled at 20° and a solution of 40.8 parts (0.22 mole) of m-nitrobenzoyl chloride in 100 parts by volume of dioxane is added dropwise keeping the temperature at 20–30° and maintaining the pH at 10–11 by the addition of alkali. The reaction mixture is stirred for one hour and then let stand overnight. The addition of 100 parts by volume of water results in a clear solution which is then acidified to pH of 1 by the addition of 40 parts by volume of concentrated hydrochloric acid. An oil separates which on cooling crystallizes. The product is separated by filtration, washed with 50 parts by volume of acetone and 50 parts by volume of ether and air dried yielding 28.6 parts (52% yield) of N-(m-nitrobenzoyl)-N-methylaminomethanephosphonic acid.

| Analysis: | N.E. |
|---|---|
| Calc. | 274 |
| Found | 282 |

A slurry of 27.4 parts (0.1 mole) of N-(m-nitrobenzoyl)-N-methylaminomethanephosphonic acid in 550 parts by volume of methanol is shaken under hydrogen pressure in the presence of 1.0 part of palladium on charcoal catalyst (10%) until the theoretical amount of hydrogen is absorbed. The slurry is then filtered and the solid washed two times with 200 parts by volume of hot methanol. The combined filtrate and washings are taken to dryness on a steam bath under reduced pressure leaving a yellow solid. The methanol insolubles are dissolved in water and filtered to remove the catalyst. The aqueous solution is added to the flask containing the residue from the methanol distillation. The yellow solid seems to dissolve and a white solid separates which does not redissolve on the addition of 200 parts by volume of water or when heated. The slurry is concentrated by the removal of about 200 parts by volume of water under vacuum. The residue is cooled, filtered, washed with 50 parts by volume of methanol and dried in vacuo over phosphoric anhydride. In this manner 18.5 parts (76% yield) of N-(m - aminobenzoyl) - N - methylaminomethanephosphonic acid are obtained. M.P. 149–159°.

| Analysis: | N.E. |
|---|---|
| Calc. | 135 |
| Found | 148 |

A solution of 27.2 parts (0.167 mole) of iodine monochloride in 25 parts by volume of acetic acid is added dropwise with stirring to a boiling solution of 15.0 parts (0.056 mole) of N-(3-aminobenzoyl)-N-methylaminomethanephosphonic acid in 150 parts by volume of glacial acetic acid. After the addition, the dark wine colored reaction mixture is cooled to room temperature and 400 parts by volume of water added to dissolve a dark tarry material. Forty grams of sodium sulfite is added in an attempt to decolorize the solution, but the color is not improved appreciably. All of the volatile material is then removed under reduced pressure in a water bath. The residue is extracted with 200 parts by volume of hot methanol, filtered and air dried. This material weighs 18.5 parts and is a mixture of sodium sulfite and the monosodium salt of N-(3-amino-2,4,6-triiodobenzoyl)-N-methylaminomethanephosphonic acid. Purification is accomplished by slurrying 0.5034 part in 10 parts by volume of 1N hydrochloric acid, filtering and washing well with water. After drying, the residue weights 0.157 part and titrates for the expected N-(3-amino-2,4,6-triiodobenzoyl)-N-methylaminomethanephosphonic acid.

| Analysis: | N.E. |
|---|---|
| Calc. | 311 and 622 |
| Found | 320 and 640 |

If the so-obtained substituted aminomethanephosphonic acid is acetylated with excess quantities of acetic anhydride in the presence of sulfuric acid, there is produced the N-(3-acetylamino-2,4,6 - triiodobenzoyl)-N-methylamino-methanephosphonic acid of the present invention.

Likewise, acetyl chloride may be used. Other lower acyl derivatives may be prepared from the corresponding lower acyl chloride. For example, the propionyl derivatives may be prepared from propionyl chloride, etc.

## EXAMPLE II

*Preparation of N-(3-acetylamino-2,4,6-triiodobenzoyl)-N-methylaminomethanephosphonic acid*

To a solution of 50 parts (0.087 mole) of 3-acetylamino-2,4,6-triiodobenzoyl chloride in 150 parts by volume of dimethylformamide is added a solution of 14.7 parts (0.087 mole) of disodium N-methylaminomethanephosphonate in 100 parts by volume of water, said solution being obtained by dissolving 10.9 parts (0.087 mole) of N-methylaminomethanephosphonic acid and 6.95 parts (0.174 mole) of sodium hydroxide in 100 parts by volume of water and the N-methylaminomethanephosphonic acid being obtained in the same manner as described in Example I. The addition requires about fifteen minutes and the temperature is allowed to rise to 60°. As the aqueous solution is added to the dimethyl-formamide solution some of the acid chloride precipitates, but as the reaction proceeds it redissolves. After all the disodium aminomethanephosphonate is added, 5N sodium hydroxide is added portion-wise to maintain the pH above 10. When the pH no longer drops, stirring is continued for 1½ hours and the solution is acidified to pH 2 with concentrated hydrochloric acid and about one-third of the solvent is removed under vacuum until a solid begins separating. The pH is then lowered to 1.0 and a heavy precipitate forms. After cooling in an ice bath, the precipitate is removed by filtration, washed with water and acetone and dried in vacuo over phosphoric anhydride. In this manner 35.0 parts of a white powdery N-(3 - acetylamino - 2,4,6 - triiodobenzoyl) - N - methylaminomethanephosphonic acid melting with decomposition at 220–225° is obtained.

| Analysis | N.E. | C | H | I | Acetyl |
|---|---|---|---|---|---|
| Calc. for $C_{11}H_{12}N_2PI_3O_5$ | 664 | 19.98 | 1.82 | 57.35 | 6.45 |
| Found | 664 | 19.76 | 1.46 | 57.31 | 6.63 |

The disodium salt of N-(3-acetylamino-2,4,6-triiodobenzoyl)-N-methylaminomethanephosphonic acid is obtained when 66.4 parts (0.1 mole) of the free acid is dissolved in water and 8.0 parts (0.2 mole) of sodium hydroxide is admixed therewith. The disodium salt is isolated by evaporation of the water.

In a similar manner the other alkali metal hydroxides, e.g. potassium hydroxide may be employed to produce the

salts of the free substituted phosphonic acid. If only one mole of sodium hydroxide is mixed with one mole of free acid, the monosodium salt is obtained.

The di-diethanolamine salt of N-(3-acetylamino-2,4,6-triiodobenzoyl)-N-methylaminomethanephosphonic acid is obtained as a 30% aqueous solution as follows: 4.47 parts (6.74 millimole) of the aminomethanephosphonic acid is added to 6.74 parts by volume of a 2 Normal diethanolamine solution and 3.29 parts of water. The resulting clear solution has a pH of 8.0.

## EXAMPLE III

*Preparation of N-(3-acetylamino-2,4,6-triiodobenzoyl)-n-octylaminomethanephosphonic acid*

A mixture of 64.6 parts (0.5 mole) of n-octylamine, 43.5 parts (0.25 mole) of disodium chloromethanephosphonate, prepared by dissolving chloromethanephosphonic acid with 2 equivalents of sodium hydroxide, about 270 parts by volume of water and 200 parts by volume of ethyl cellosolve, is refluxed while stirring under a nitrogen atmosphere for 24 hours. The pH of the solution is then raised from 8.5 to 11.5 and then said solution is extracted with ether. When the aqueous layer is lowered to pH of 2.5–3.0, the product crystallizes. N-(n-octyl)-aminomethanephosphonic acid is separated by filtration, washed with water until the washings are free of chloride ion and dried in vacuo. The product weighs 7.6 parts (13.6% yield).

| Analysis | N.E. | C | H |
|---|---|---|---|
| Calc. for $C_9H_{22}O_3NP$ | 223 | 48.5 | 9.88 |
| Found | 221 | 48.26 | 10.14 |

To a solution of 5.75 parts (0.01 mole) of N-acetylamino-2,4,6-triiodobenzoyl chloride in 60 parts by volume of acetone is added a solution of 2.67 parts (0.01 mole) of disodium N-n-octyl-aminomethanephosphonate in 10 parts by volume of water, prepared from the phosphonic acid and two equivalents of sodium hydroxide in water. The reaction mixture is stirred for one hour at room temperature and then warmed at 30–35° for one hour during which time 0.4 part (0.01 mole) of sodium hydroxide in 10 parts by volume of water is added to maintain the pH and then stirred for an additional hour. The solution is poured into 200 parts by volume of water, treated with charcoal, filtered and made acid to pH 1. An oil separates which on standing overnight solidifies. The solid is removed by filtration, washed well with water, triturated with acetone and dried in vacuo. The product, N-(3-acetylamino - 2,4,6-triiodobenzoyl) - n - octylaminomethanephosphonic acid, weighs 2.3 parts (30% yield). Further purification is accomplished by dissolving in warm acetone, filtering from a small amount of insoluble material and evaporating the solvent.

| Analysis | C | H | N | I |
|---|---|---|---|---|
| Calc. for $C_{18}H_{26}O_5N_2PI_3$ | 28.4 | 3.41 | 3.67 | 50.0 |
| Found | 28.14 | 3.83 | 3.43 | 49.90 |

In the same manner, if 5.89 parts (0.01 mole) of N-propionylamino-2,4,6-triiodobenzoylchloride or 6.03 parts (0.01 mole) of n-butyrylamino-2,4,6-triiodobenzoyl chloride is used then the corresponding substitued aminomethanephosphonic acid is obtained.

Likewise, the mono- and disodium salts of the free acid are prepared when one or two moles of sodium hydroxide is mixed with the free substituted aminomethanephosphonic acid in water and the water afterwards removed by evaporation.

## EXAMPLE IV

*Preparation of N-(3-acetylamino-2,4,6-triiodobenzoyl)-N-benzylaminomethanephosphonic acid*

A mixture of 53.5 parts (0.5 mole) benzylamine, 43.5 parts (0.25 mole) disodium chloromethanephosphonate prepared from the phosphonic acid and two equivalents of sodium hydroxide in water, 270 parts by volume of water and 100 parts by volume of ethyl cellosolve, is refluxed while stirring under a nitrogen atmosphere until analysis shows that 250 milliequivalents of chloride ion are liberated. The clear solution is then cooled, washed two times with 250 parts by volume of ether and the pH of the aqueous layer is lowered to 2.0. The product which separates is removed by filtration, washed with water and dried in vacuo. In this manner, 17.0 parts (34% yield) of N-benzylaminomethanephosphonic acid is obtained.

| Analysis | C | H | N.E. |
|---|---|---|---|
| Calc for $C_8H_{12}O_3NP$ | 47.7 | 5.98 | 201 |
| Found | 47.64 | 6.47 | 200.5 |

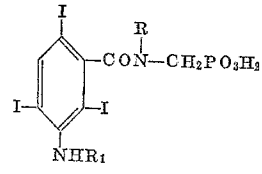
To a solution of 5.75 parts (0.01 mole) of N-acetylamino-2,4,6-triiodobenzoyl chloride in 50 parts by volume of acetone is added a solution of 2.45 parts (0.01 mole) of disodium N-benzylaminomethanephosphonate in 20 parts by volume of water. The reaction mixture is stirred and maintained at 40° for one hour during which time the pH is maintained at 10.5–11.5 by the dropwise addition of 0.4 part (0.01 mole) of sodium hydroxide in 20 parts by volume of water. The clear solution is allowed to cool, diluted with 200 parts by volume of water, the pH adjusted to 4.0 and a small amount of insoluble material removed by filtration. The pH of the solution is then lowered to 1.0 and the solid which separates is removed by filtration, washed with water and dried in vacuo. The crude product weighs 5.0 gm. The purification is accomplished by washing with acetone and 2.8 parts of pure N-(3-acetylamino-2,4,6-triiodobenzoyl)-N-benzylaminomethanephosphonic acid is obtained.

| Analysis | C | H | I | N.E. |
|---|---|---|---|---|
| Calc. for $C_{17}H_{16}O_5N_2PI_3$ | 27.6 | 2.16 | 51.5 | 370 |
| Found | 27.32 | 2.52 | 51.69 | 372 |

In the same way, if one or two moles of sodium hydroxide is mixed with the foregoing substituted aminomethanephosphonic acid in water and the water subsequently evaporated, the mono- or disodium substituted aminomethanephosphonate is obtained.

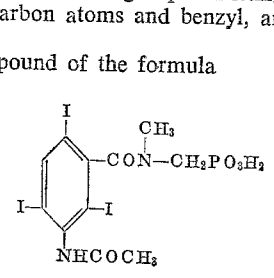
What is claimed is:

1. A compound selected from the class consisting of the aminomethanephosphonic acids of the formula.

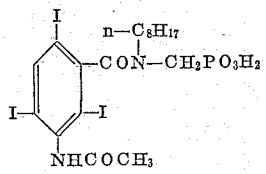


and the non-toxic pharmaceutically acceptable salts thereof with alkali metals and with amines, wherein R is a member selected from the group consisting of alkyl with from 1 to 8 carbon atoms and benzyl, and $R_1$ is lower alkanoyl.

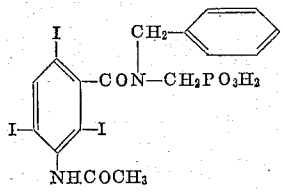
2. The compound of the formula



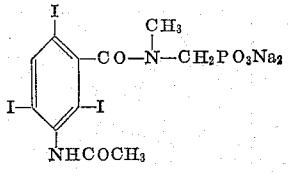
3. The compound of the formula



4. The compound of the formula

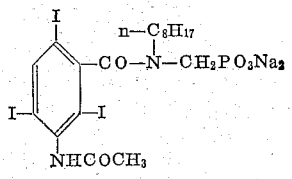


5. The compound of the formula

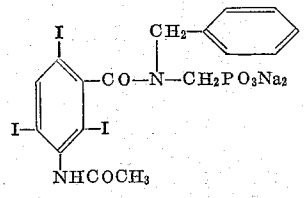




6. The compound of the formula



7. The compound of the formula



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