PATENT SPECIFICATION

674,298

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COMPLETE SPECIFICATION

Improvements in or relating to Sulphamylbenzoic Acids

We, SHARP & DOHME, INCORPORATED, a Corporation organized and existing under the laws of the State of Maryland, United States of America, of 640, North Broad Street, Philadelphia, Pennsylvania, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to sulphamylbenzoic acids which are effective as adjuvants for use in conjunction with the administration of penicillin to provide an increase in the blood plasma penicillin concentration with a given dose of penicillin, thereby making possible very high penicillin blood levels, or permitting the use of smaller quantities of penicillin for providing a given blood level, or permitting the less frequent administration of penicillin while maintaining a penicillin blood level adequate for bactericidal or bacteriostatic purposes. The invention also relates to the preparation of various dosage forms in which one or more of the new compounds are incorporated for administration by various routes.

Penicillin today is a well established therapeutic agent used in the treatment of bacterial, in particular coccus infections. For internal use, it is commonly administered intravenously, or intramuscularly, or orally. Where high blood levels are required intravenous administration or administration by continuous venoclysis, is used.

The major cause of the difficulties involved in attempting to maintain adequate or high penicillin blood levels follows from the fact that substantially all of the penicillin in the blood is removed in a single circulation through the kidneys.

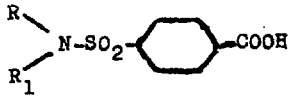
Penicillin appears to be almost quantitatively excreted from the blood by the epithelial cells of the tubules at least within plasma concentrations which have been explored, with the result that its rate of excretion from the blood stream is approximately five times that of materials which are excreted by glomerular filtration alone, the tubular excretion accounting for about 80 (81)% and the glomeruli about 20 (19)%.

Various proposals have been made to overcome the difficulties due to the rapid elimination of penicillin, such as the administration of it in suspension in an oleaginous material, the mixture being administered by intramuscular injection. While this proposal is effective in prolonging the time interval between injections, its disadvantage is that the penicillin is still excreted almost quantitatively when the blood passes through the renal system, and therefore does not permit the maintenance of high blood levels nor does it permit the use of smaller quantities of penicillin to obtain a given blood level.

The second proposal which has been made to provide for the reduction in the rate of excretion of penicillin has been to use, in conjunction with it, a material which, like penicillin, is selectively excreted by the tubules. By having the ratio of the added agent to the penicillin sufficiently large, this concept provides for a substantial reduction in the rate of excretion of penicillin by the tubules and thus slows down its removal to a substantial extent. Various agents including "Diodrast" (Registered Trade Mark) (the diethanolamine salt of 3,5-diodo-4-pyridone-N-acetic acid) and hippuric acid, or derivatives or precursors thereof, have been proposed or used for this purpose. Such agents do not, however, seem to afford a solution to the problem of value except in extreme cases, because as the

reduction in the rate of penicillin excretion is a reflection of the degree of overloading of the tubules with materials which they function to remove from the blood, it is necessary to maintain a very high concentration of the agent in the blood stream to afford a favourable partition ratio between the agent and the penicillin and, in addition, because the agents are themselves rapidly removed from the blood stream, it is necessary to administer them in large quantities to maintain the necessary high plasma concentrations. This presents an additional problem since in order to maintain the high concentration of these agents they must be administered intravenously as they are not well absorbed from the gastro-intestinal tract.

The present invention is based upon the discovery that removal of penicillin from the blood stream by the kidney tubules can be effectively blocked by the adjuvants of this invention, having the general formula



and their salts, wherein R and R_1 respectively is an alkyl radical; the alkyl radicals represented by R and R_1 having a combined total of at least five and no more than eight carbon atoms. Sulphamylbenzoic acid derivatives wherein the carboxyl group is in para-position have been found to be particularly effective adjuvants, and within this group, those in which the alkyl radicals represented by R and R_1 have a combined total of five or six carbon atoms, such as the para-(di-*n*-propylsulphamyl) - benzoic acid and para - (di-isopropylsulphamyl) - benzoic acid, have been found to be outstandingly effective in inhibiting the renal excretion of penicillin.

The sulphamyl benzoic acids of the invention are relatively non-toxic, they are soluble in blood plasma and operate, when carried by the blood stream into contact with the tubules, to prevent their normal action in removing penicillin from the blood stream. The adjuvants themselves are not excreted to any substantial extent by the tubules, and the available evidence indicates that on coming into contact with the epithelial cells of the tubules, they operate to block their action by interference with the normal functioning of the epithelial cells and do not inhibit the excretion of the penicillin by competing with it within the tubular functional capacity. Thus, the adjuvants are effective in eliminating or very radically reducing tubular excretion of penicillin in plasma concentrations around 10 mg. per 100 cc., which is about the threshold value for agents such as *p*-aminohippuric acid or "Diodrast" (Registered Trade Mark) which inhibit tubular penicillin excretion by competition for the available tubular excretion capacity. The highly effective adjuvants of this invention will reduce the excretion of penicillin by the tubules, at a blood plasma concentration of about 10 mg. per 100 cc. to almost zero, so that the actual elimination of penicillin from the blood stream becomes substantially that resulting from glomerular filtration, that is, about one-fifth the normal rate (ignoring plasma binding). The adjuvants are also eliminated by the glomeruli.

The adjuvants may be administered orally or, when dissolved in an aqueous solution, they may be administered intravenously or intramuscularly. This last method has not yet proven desirable for single injection of the material, because in general, administration of more than 2 cc. per single injection intramuscularly is inadvisable, and the quantities of adjuvant desirable to use, i.e., 4 to 16 grams per day, are such as to make injection by this route impractical. However, the sulphamylbenzoic acids or their salts are well adapted for continuous intramuscular or subcutaneous dosis.

In general, oral administration of the adjuvants at the rate of 4 to 16 grams per day is adequate to suppress the rate of penicillin excretion to an extent such that the blood level with a given dose of penicillin administered orally or intramuscularly in aqueous solution will be increased to as much as four times the level obtained without the use of the adjuvant, and will permit either the use of a very much smaller quantity of penicillin to provide a given blood level, for example, permitting the penicillin doses to be about one-fourth of those commonly used, or permitting the provision of penicillin blood levels several times as great as those obtainable with the administration of penicillin by the routes ordinarily used today.

The adjuvants of the invention or a suitable salt of any one of them may be administered in admixture with the penicillin, or separately therefrom. In any event, whether the adjuvant is administered in admixture with or separately from the penicillin, the quantity used should be such as to provide a concentration in the blood stream of adjuvant adequate to block substantially the excretory mechanism of the tubules. Maximum effect will be

obtained with blood plasma concentrations of about 5 to 15 mg. per 100 cc., obtainable at dosage levels of about 4 to 16 grams per day orally and somewhat less than this intravenously.

The adjuvants may be prepared in any convenient dosage form, either alone or admixed with penicillin, such as in a compressed tablet, a dry filled capsule or a soft elastic capsule. It is to be understood, of course, that other ingredients, such as binders, diluents, excipients, antacid substances, or other inert or therapeutically active compounds may be incorporated into any selected dosage form along with the adjuvant or adjuvant plus penicillin, provided the added ingredient does not destroy the activity of either the adjuvant or penicillin. Similarly, the adjuvant and, if desired, the penicillin may be dispersed in an oleaginous base either alone or along with other suitable substances and filled into soft elastic capsules or an aqueous solution may be prepared and filled into ampoules. Other suitable dosage forms will be readily apparent to those skilled in the art, and it is not the purpose of this discussion to limit the mode of packaging or administration to those specifically described herein.

The new sulphamyl benzoic acids of the invention wherein the carboxyl radical is in para-position in relation to the sulphonyl radical on the benzene nucleus are generally made by first preparing a para-carboxybenzenesulphonyl halide by oxidation of para-toluenesulphonyl halide, or by preparing para-cyanobenzenesulphonyl halide by treating para-sulphamyl benzoic acid with phosphorus pentachloride. The para-carboxybenzenesulphonyl halide or para-cyanobenzenesulphonyl halide thus formed is reacted with the appropriate di-alkyl amine, advantageously using an excess, for example, two to three equivalents, of the amine, and when the cyanobenzenesulphonyl halide reactant is used, hydrolyzing the product thus formed to the corresponding carboxyl derivative. The reaction is preferably carried out in the presence of a solvent, such as acetone or pyridine or in aqueous sodium hydroxide, and preferably with cooling. Any by-product formed during the reaction is removed by treating the reaction medium with a weak, alkaline substance, such as an aqueous sodium bicarbonate solution, filtering off the precipitated by-product, and then recovering the desired sulphamyl benzoic acid from the filtrate by acidification.

It is possible in some instances to prepare the dialkyl derivatives by alkylation of a mono-alkylsulphamylbenzoic acid, preferably in the presence of a solvent, such as in aqueous alkali.

The preparation of the compounds of the invention is illustrated by, but not restricted to the following examples:

EXAMPLE I.

p-(DI-*n*-BUTYLSULPHAMYL)-BENZOIC ACID.

To 38.7 grams (0.3 mole) of di-*n*-butylamine dissolved in 300 millilitres of dry acetone, contained in an open flask provided with a stirrer, 22.1 grams (0.1 mole) of *p*-carboxy-benzenesulphonyl chloride was added in portions with cooling and stirring. The reaction was stirred for one-half hour after which the suspension was concentrated over a steam bath to about one-third the original volume. The residue was poured into 250 millilitres of cold water, the solution made acid with dilute hydrochloric acid, and the crude product removed by filtration. The crude product was dissolved in dilute sodium bicarbonate solution. The solution was treated with decolourising charcoal and filtered. The product, after precipitation from the solution by an excess of dilute hydrochloric acid, was recrystallised from 50% aqueous alcohol. The yield was 20 grams (64%), m.p. 163—164° C.

EXAMPLE II.

p-(DI-*n*-PROPYLSULPHAMYL)-BENZOIC ACID.

24.0 grams (0.11 mole) of *p*-carboxybenzenesulphonyl chloride was added in small portions to a suspension of 20.0 grams (0.146 mole of di-*n*-propylamine in 100 millilitres of 10% sodium hydroxide with vigorous stirring at a temperature of 15—25° C. Stirring was continued for fifteen minutes after the final addition. The clear solution was treated with decolourizing carbon and filtered. The product was precipitated by the addition of an excess of hydrochloric acid. The crude product was purified by reprecipitation from bicarbonate solution and recrystallization from dilute alcohol. The yield was 20.0 grams (64%) melting at 194—196° C.

By replacing the di-*n*-butylamine of Example I or the di-*n*-propylamine of Example II by an equivalent amount of another di-alkyl amine and following substantially the same procedure outlined in either example, the corresponding para-(di-alkyl sulphamyl)-benzoic acids are obtained. An example of another compound prepared by these methods is *p*-(di-*iso*butylsulphamyl)-benzoic acid which was obtained in a 17% yield and melted at 200—201.5° C.

An alternate method for preparing the compounds of the invention, particularly those derived from the highly branched

secondary amines, is illustrated by the following example:

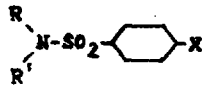
Example III.

p-(di-sec-butylsulphamyl)-benzoic acid.

30.3 grams (0.15 mole) of *p*-cyanobenzenesulphonyl chloride was added to 19.35 grams (0.15 mole) of di-sec-butylamine in 50 millilitres of dry pyridine with cooling and stirring. The reaction was allowed to stand at room temperature overnight after which it was poured into 50 cc. of concentrated hydrochloric acid and 500 grams of crushed ice. A dark oil precipitated which soon solidified. The solid was removed by filtration and air-dried, yielding 22.5 grams (75%) of *p*-(di-secbutylsulphamyl)-benzonitrile, melting at 88—91° C. After repeated recrystallizations from isopropyl ether, the nitrile melted at 97—99° C. 20 grams (0.68 mole) of the crude nitrile was heated in 150 millilitres of 10% sodium hydroxide under reflux until no more ammonia was evolved (approximately four hours). The solution was treated with decolourizing carbon, and filtered and the product precipitated from the filtrate with an excess of hydrochloric acid. The *p*-(di-sec-butylsulphamyl) - benzoic acid thus obtained was dissolved in dilute sodium bicarbonate solution and reprecipitated with dilute hydrochloric acid. The yield was 14 grams of product; m.p. 175—179° C. Three recrystallizations from dilute alcohol gave 7.5 grams (18%) of product; m.p. 185° C.

By replacing the di-secondary butylamine of Example III by another dialkyl amine and following substantially the same procedure outlined in the example, corresponding para-(di-alkylsulphamyl)-benzoic acids are obtained having an alkyl group of the type disclosed for R and R' in the general formula in the eighth paragraph of the specification. Among the compounds prepared by the method illustrated in Example III are those listed in Table A:

Table A.



R	R'	X = cyano Yield %	X = cyano M.p. °C.	X = carboxyl Yield %	X = carboxyl M.p. °C.
n-propyl	*n*-propyl	80	53—54	45	193—195
isopropyl	isopropyl	100	117—118	30	209—210
isobutyl	isobutyl	100	95—96.5	57	200—201.5
sec-butyl	sec-butyl	75	97—98	18	185

The invention is further illustrated by, but not restricted to, the following various dosage forms of different compositions for administration by various routes.

Example (*a*).

Compressed tablet containing penicillin.

10,000 grams of lactose are uniformly mixed with 100,000 grams of the adjuvant, para-(di-*n*-propylsulphamyl)-benzoic acid, and wetted with sufficient water to permit their ready granulation, 3375 grams of sodium penicillin (1630 units per mg.), 2625 grams dried cornstarch, 500 grams karaya gum powder, 2500 grams talc and 1000 grams calcium stearate are mixed together in an atmosphere controlled at 10% relative humidity at 21° C., and then under the same conditions mixed with the granulation of the adjuvant and the lactose and tableted (using ½ inch die standard curvature punches) yielding 200,000 tablets weighing 0.6 gram and each containing 0.5 gram of adjuvant and 25,000 units penicillin (plus 10% excess).

Any other selected adjuvant may replace the above adjuvant in equal amount to obtain tablets of the same weight and same content of any of the other adjuvants.

Example (*b*).

Dry filled capsule with penicillin.

Under atmosphere controlled as in example (*a*), 25 kilos of the adjuvant, para - (di-*n*-propyl-sulphamyl) - benzoic

acid, 850 grams of crystalline penicillin sodium (as used above), and 150 grams of dried cornstarch are intimately and uniformly mixed and the mixture filled into capsules, yielding 50,000 capsules, each holding 0.52 gram of mixture containing 0.5 gram of adjuvant and 25,000 units penicillin (plus 10% excess).

EXAMPLE (*c*).

SOFT ELASTIC CAPSULE WITH PENICILLIN.

Under atmosphere controlled as in example (*a*), 1.69 kilos of the same crystalline penicillin sodium are homogeneously dispersed in 48.31 kilos of corn oil and 50 kilos of the adjuvant, para-(di-*n*-propylsulphamyl)-benzoic acid, similarly dispersed in the oil, and the resulting composition encapsulated in known manner in soft, elastic, sheet gelatin, hermetically sealed capsules, yielding 10,000 capsules, each holding one gram net of the composition and containing 0.5 gram of adjuvant with 25,000 units penicillin (plus 10% excess).

EXAMPLE (*d*).

FLAME-SEALED AMPOULE CONTAINING PENICILLIN.

12.5 kilos of the adjuvant, para-(di-*n*-propylsulphamyl) - benzoic acid, are stirred into very nearly 30 litres of sterile, pyrogen-free, distilled water and 1831 grams of sodium hydroxide are added to aid in the dissolution of the adjuvant. Then 390 grams of monopotassium phosphate are added and, under atmospheric conditions as in example (*a*), 169 grams of the same crystalline penicillin sodium are added and stirred into solution and sufficient water added to bring the total volume of solution to 30 litres. 12 cc. of this solution are then filled into each of the required number of 20 cc. total volume ampoule-vials. The contents of the vials are then quickly frozen by rotating them in a bath of methyl "Cellosolve" (Registered Trade Mark) chilled with "Dry-Ice" to −70° C., and desiccated under high vacuum for 48 hours by the method and apparatus as in British Specification No. 536,293 and rubber stoppers inserted in the neck of each of the containers while the vacuum is still being maintained. The vacuum is then broken and the containers removed from the apparatus and the extension of the glass neck beyond the top of the stoppers is flame-sealed. The contents of the flame-sealed ampoule-vial is then restored with sterile, pyrogen-free, distilled water shortly before the product is to be used. When thus restored to 20 cc. liquid volume, the resulting solution is buffered at pH 7.4 and contains 100,000 units penicillin (plus the 10% excess) and 25% of the adjuvant.

EXAMPLE (*e*).

AMPOULE OIL SUSPENSION WITH PENICILLIN.

3 kilos of USP white wax are mixed into 35.127 kilos of purified peanut oil heated sufficiently to melt and permit homogeneous dispersion of the white wax. While this mixture is still sufficiently liquid, and under atmosphere conditions as in example (*a*), 10 kilos of the adjuvant, para-(di-*n*-propylsulphamyl)-benzoic acid, and 1873 grams of calcium penicillin (734 units/mg.) are added and the mixture stirred to homogeneity. Each cc. of the resulting oil suspension contains 25,000 units of penicillin (plus 10% excess) and 0.2 gram of adjuvant. It is put up in flame-sealed ampoules containing suitable volume of the suspension which is as stable as the ordinary penicillin in peanut oil preparations.

While each of the preceding examples (*a*) to (*e*) contains its respective specific adjuvant, each of them may be prepared with any other suitable, effective adjuvant, for example, any other adjuvants embraced by the general formula above.

In addition, in the compositions containing penicillin, it is advisable, in accordance with customary practice, to include an excess of the penicillin, for example, a ten per cent excess over the label-claimed quantity in accordance with present practice. An excess of penicillin introduces no difficulty save its cost. The penicillin used may be any of the forms available for use, such as the calcium, sodium potassium and procaine salts of amorphous or crystalline penicillin.

The quantity per dose of adjuvant and penicillin will depend upon the blood level and duration of action required for the particular condition encountered in each case. An advantageous ratio of adjuvant to penicillin per tablet or capsule is about one-half gram of the selected adjuvant to 25,000 to 200,000 units of penicillin.

Although the preferred use of the adjuvants described above is to inhibit the excretion of penicillin they are also effective in maintaining a high blood concentration of other medicinal agents such as, for example, para-aminosalicylic acid.

The compositions of the invention may also include an antacid material, such as aluminium hydroxide, magnesium trisilicate, trisodium citrate, calcium carbonate, magnesium oxide, or other antacid substances suitable for administration for the purpose of neutralizing gastric acidity. The amount of antacid material is limited only to that which is desirable to use in connection with penicillin or

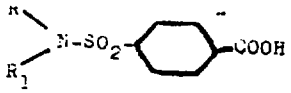
which can be physically incorporated in a tablet or capsule of suitable size for administration.

As to binders and lubricants used in making the tablets, such materials as lactose, corn starch, gum karaya, talc, calcium stearate, gelatin, ethyl cellulose, mineral oil, propylene glycol and glycerin, may be included in proportions commonly used in preparing tablets of this nature.

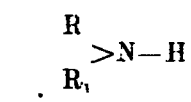
If the compositions are produced in the form of suspensions or solutions in an oleaginous material, there are available various substances which may be used for this purpose. Corn oil or other suitable oil is used with advantage.

What we claim is:—

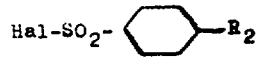
1. A process for the preparation of a sulphamylbenzoic acid of the general formula



which process comprises reacting a compound having the general formula



with a compound having the general formula

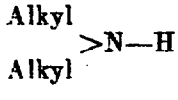


wherein R and R_1 respectively is an alkyl group, the alkyl groups represented by R and R_1 having a combined total of at least 5 and not more than 8 carbon atoms; Hal is a halogen atom; and R_2 is a carboxyl group or a nitrile or an ester group; and where necessary hydrolysing the nitrile or ester group to a carboxyl group.

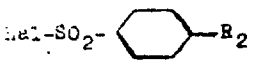
2. A process as claimed in claim 1, wherein the reaction is carried out in the presence of an inert solvent.

3. A process as claimed in claim 1 or claim 2, wherein there is used an excess of the amine reactant.

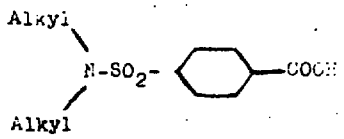
4. A process as claimed in any one of the preceding claims wherein a compound having the general formula



wherein the alkyl radicals have a combined total of at least 5 and not more than 8 carbon atoms, is reacted with a compound having the general formula



thereby producing a compound of the formula



5. A process as claimed in claim 4, wherein a dipropylamine is reacted with a para-carboxybenzenesulphonyl halide to produce a para - (di - propylsulphamyl)-benzoic acid.

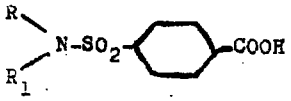
6. A process as claimed in claim 4, wherein a dipropylamine is reacted with a para - cyanobenzenesulphonyl halide, and the para - (di - propylsulphamyl)-benzonitrile thus formed is hydrolyzed to the para - (di - propylsulphamyl)-benzoic acid.

7. A process as claimed in any one of the preceding claims wherein the sulphamylbenzoic acid thus produced is mixed with a medicinal agent, such as penicillin or a salt thereof to form a composition of matter suitable for therapeutic use, the sulphamylbenzoic acid constituent of said composition upon administration functioning substantially to block the excretion of the medicinal agent by interfering with the normal functioning of the transport mechanism of the kidney tubules.

8. A process as claimed in claim 7, wherein there is also included a proportion of an antacid substance.

9. A process as claimed in claim 8, wherein the antacid substance is magnesium trisilicate.

10. A process for the preparation of a sulphamylbenzoic acid of the general formula



where R and R_1 is an alkyl group, the alkyl groups represented by R and R_1 having a combined total of between 5 and 8 carbon atoms substantially as described with reference to the specific examples hereinbefore set forth.

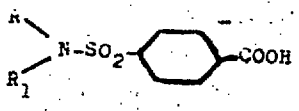
which can be physically incorporated in a tablet or capsule of suitable size for administration.

As to binders and lubricants used in making the tablets, such materials as lactose, corn starch, gum karaya, talc, calcium stearate, gelatin, ethyl cellulose, mineral oil, propylene glycol and glycerin, may be included in proportions commonly used in preparing tablets of this nature.

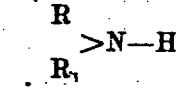
If the compositions are produced in the form of suspensions or solutions in an oleaginous material, there are available various substances which may be used for this purpose. Corn oil or other suitable oil is used with advantage.

What we claim is:—

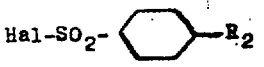
1. A process for the preparation of a sulphamylbenzoic acid of the general formula



which process comprises reacting a compound having the general formula



with a compound having the general formula

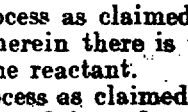


wherein R and R_1 respectively is an alkyl group, the alkyl groups represented by R and R_1 having a combined total of at least 5 and not more than 8 carbon atoms; Hal is a halogen atom; and R_2 is a carboxyl group or a nitrile or an ester group; and where necessary hydrolysing the nitrile or ester group to a carboxyl group.

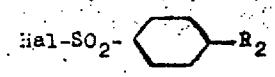
2. A process as claimed in claim 1, wherein the reaction is carried out in the presence of an inert solvent.

3. A process as claimed in claim 1 or claim 2, wherein there is used an excess of the amine reactant.

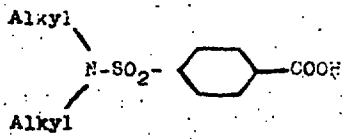
4. A process as claimed in any one of the preceding claims wherein a compound having the general formula



wherein the alkyl radicals have a combined total of at least 5 and not more than 8 carbon atoms, is reacted with a compound having the general formula



thereby producing a compound of the formula



5. A process as claimed in claim 4, wherein a dipropylamine is reacted with a para-carboxybenzenesulphonyl halide to produce a para - (di - propylsulphamyl)-benzoic acid.

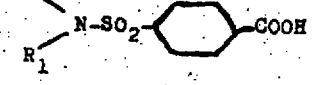
6. A process as claimed in claim 4, wherein a dipropylamine is reacted with a para - cyanobenzenesulphonyl halide, and the para - (di - propylsulphamyl)-benzonitrile thus formed is hydrolyzed to the para - (di - propylsulphamyl)-benzoic acid.

7. A process as claimed in any one of the preceding claims wherein the sulphamylbenzoic acid thus produced is mixed with a medicinal agent, such as penicillin or a salt thereof to form a composition of matter suitable for therapeutic use, the sulphamylbenzoic acid constituent of said composition upon administration functioning substantially to block the excretion of the medicinal agent by interfering with the normal functioning of the transport mechanism of the kidney tubules.

8. A process as claimed in claim 7, wherein there is also included a proportion of an antacid substance.

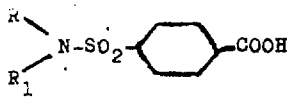
9. A process as claimed in claim 8, wherein the antacid substance is magnesium trisilicate.

10. A process for the preparation of a sulphamylbenzoic acid of the general formula



where R and R_1 is an alkyl group, the alkyl groups represented by R and R_1 having a combined total of between 5 and 8 carbon atoms substantially as described with reference to the specific examples hereinbefore set forth.

11. As an adjuvant for therapeutic use a parasulphamyl - benzoic acid of the general formula



where R and R_1 each represents an alkyl group, the alkyl groups represented by R and R_1 having a combined total of at least 5 and not more than 8 carbon atoms.

12. As an adjuvant for therapeutic use para - (di - *n* - propylsulphamyl) - benzoic acid.

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