PATENT SPECIFICATION

678,416

Date of Application and filing Complete Specification: July 12, 1950.

No. 17422/50.

Application made in United States of America on Aug. 20, 1949.

Complete Specification Published: Sept. 3, 1952.

Index at acceptance:- Classes 2(iii), C2d43(e: j), C2d43s(2: 3); and 81(i), B11b2(b3: c: d: f: g: h: i: j: l: n: p: q: r: t: u).

COMPLETE SPECIFICATION

Improvements in or relating to Sulphamyl Benzoic Acids

We, SHARP & DOHME, INCORPORATED, a Corporation organised 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 sulphamyl benzoic 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)%.

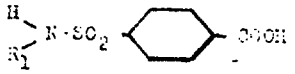
Various proposals have been made to overcome the difficulties due to the rapid elimination of penicillin, such as the administration of it in suspension in an oleaginous material, the mixture being administered by intramuscular injection. While this proposal is effective in prolonging the time interval 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-diiodopyridone-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 favorable 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. Applicant's Specification No. 23728/47, as open to public inspection describes the compound 1-*p*-carboxyphenylsulphonamido-*n*-pentane as an adjuvant for therapeutic use.

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_1 is an *iso*amyl, 2-pentyl or cyclopentyl radical or an alkyl or cycloalkyl radical having six or seven 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 radical represented by R_1 has five or six carbon atoms, such as the para-(*iso*-amylsulphamyl)-benzoic acid, and para-(*n*-hexylsulphamyl)-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 elysis.

In general, oral administration of the adjuvants at the rate of 4 to 16 grams per day is adequate to supress 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 ex-

cretory 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 paracyanobenzenesulphonyl 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 mono-alkyl or mono-cycloalkyl 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 weakly, 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.

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

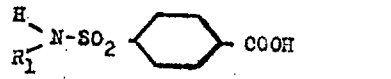
EXAMPLE I.

p-(ISO-AMYLSULPHAMYL)-BENZOIC ACID.

0.1 mole of 4-carboxybenzenesulphonylchloride were added in portions with stirring to a chilled solution of 0.3 mole of *iso*-amylamine in 200 cc. reagent acetone. The mixture was concentrated to about 40 cc. on a steam bath and diluted with cold water. The product which separated was worked thoroughly with dilute hydrochloric acid and the resulting crude product removed by filtration. The product was dissolved in excess aqueous sodium bicarbonate and a small insoluble residue filtered and discarded. After precipitation with acid the product, *p*-(*iso*-amyl-sulphamyl)-benzoic acid, was recrystallized from 50% alcohol after treating with charcoal, yield 69%, m.p. 219—220° C.

By replacing the *iso*-amylamine by an equivalent amount of any other mono-alkyl amine, the allyl radical of which contains six or seven carbon atoms or is a 2-pentyl or cyclopentyl radical and following substantially the same procedure outlined in this example, the corresponding para-(mono-alkyl or mono-cycloalkyl sulphamyl)-benzoic acids are obtained. Examples of other compounds prepared by these methods include those listed in Table A:

TABLE A.



R_1	Yield %	M.p. °C.
2-ethylbutyl	21	206—208
2-pentyl	26	207—208
Cyclopentyl	45	161—162
4-methyl-2-pentyl	31	207—208
n-hexyl	90	204
Cyclohexyl	—	259—260
n-heptyl	50	202.5—203

An alternative method for preparing the compounds of the invention, particularly those derived from the highly branched primary amines, is illustrated by the following example:

EXAMPLE II.

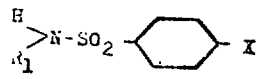
p-(4-METHYL-2-PENTYLSULPHAMYL)-BENZOIC ACID.

20.1 grams of (0.1 mole) of *p*-cyanobenzenesulphonyl chloride was added to 20.2 grams (0.2 mole) of 4-methyl-2-pentylamine in 50 milliliters 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 yellow oil precipitated which soon solidified. The solid was removed by filtration and air-dried, yielding 24 grams of *p*-(4-methyl-2-pentyl-sulphamyl)-benzonitrile. After repeated recrystallizations from isopropyl ether, the nitrile melted at 79—80° C. (Yield 90%). 21 grams of the crude nitrile was heated in 150 milliliters of 10% sodium hydroxide under reflux until no more ammonia was evolved (approximately two hours). The solution was treated with decolorizing carbon, and filtered and the product precipitated from the filtrate with an excess of hydrochloric acid. The *p*-(4-methyl-2-pentylsulphamyl)-benzoic acid thus obtained was dissolved in dilute sodium bicarbonate solution and precipitated with dilute hydrochloric acid. Three recrystallizations from dilute alcohol gave 13.5 grams of product; m.p. 207—208° C.

By replacing the 4-methyl-2-pentylamine of Example II by any other mono-alkyl or mono-cycloalkyl amine, the alkyl or cycloalkyl radical of which contains six or seven carbon atoms or is an *iso*-amyl, 2-pentyl or cyclopentyl radical and following substantially the same procedure outlined in the example, corresponding para-(mono-alkyl or mono-cycloalkyl sulphamyl)-benzoic acids are obtained having an alkyl or cycloalkyl group of the type disclosed for R_1 in the general formula in the eighth paragraph of the specification. Among the compounds prepared by the method illustrated in Example II are those listed in Table B:

TABLE B.



	X = cyano		X = carboxyl	
R_1	Yield %	Mp. C.	Yield %	Mp. C.
2-ethylbutyl	100	56—57	55	206—208
2-pentyl	oil		48	208—209

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.

10,000 grams of lactose and 100,000 grams of the adjuvant, para-(2-pentylsulphamyl)-benzoic acid, are uniformly mixed and wetted with sufficient water to permit their ready granulation. 2,000 grams of dried cornstarch, 500 grams of karaya gum powder, 2,500 grams of talc, and 1,000 grams of calcium stearate are intimately mixed and then mixed together uniformly with the 110,000 grams of the mixture of the granulated adjuvant and lactose. The final mixture is then tabletted (using ½ inch die standard curvature punches) yielding 200,000 tablets of 0.58 gram each, and each containing 0.5 gram of the adjuvant.

By replacing the quantity of the adjuvant in the above example by the same quantity of any other selected adjuvant embraced within the scope of the general formula above, tablets of the same individual weight and same content of any of the other adjuvants are obtained.

Measured amounts of the composition of Example (d) containing any selected adjuvant, or merely the adjuvant alone, can be filled into hard gelatine, telescopic capsules, each holding 0.5 grams of adjuvant.

Alternatively, the selected adjuvant may be homogeneously dispersed in an equal quantity of corn oil, and the composition encapsulated in known manner in soft, elastic sheet gelatine, hermetically sealed capsules each containing one gram of the adjuvant-oil composition.

EXAMPLE B.

AMPOULE.

10 kilos of the adjuvant, para-(2-pentylsulphamyl)-benzoic acid, are suspended in very nearly 50 liters of distilled water and 1481 grams of sodium hydroxide are added to help in the dissolution of the adjuvant. 390 grams of monopotassium phosphate are added and distilled water added to make the volume of solution up to 50 liters (pH is about 7.4). The solution is then filled into ampoules for 5 cc. liquid content each, which are then flame-sealed and autoclaved at 15 pounds pressure for 20 minutes.

EXAMPLE C.

COMPRESSED TABLET CONTAINING PENICILLIN.

10,000 grams of lactose are mixed with 100,000 grams of the adjuvant, para-(2-pentylsulphamyl) - benzoic acid, and granulated as in example (a). 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 tabletted with the same die as in example (a) yielding 200,000 tablets weighing 0.6 gram and each containing 0.5 gram of adjuvant 25,000 units penicillin (plus 10% excess).

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

EXAMPLE D.

DRY FILLED CAPSULE WITH PENICILLIN.

Under atmosphere controlled as in example (c), 25 kilos of the adjuvant, para-(2-pentylsulphamyl) - 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 0.52⅔ gram of mixture containing 0.5 gram of adjuvant and 25,000 units penicillin (plus 10% excess).

EXAMPLE E.

SOFT ELASTIC CAPSULE WITH PENICILLIN.

Under atmosphere controlled as in example (c), 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-(2-pentylsulphamyl)-benzoic acid, similarly dispersed in the oil, and the resulting composition encapsulated in known manner in soft, elastic, sheet gelatin, hermetically sealed capsules, yielding 100,000 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 F.

FLAME-SEALED AMPOULE CONTAINING PENICILLIN.

12.5 kilos of the adjuvant, para-(2-pentylsulphamyl) - benzoic acid are stirred into very nearly 30 liters of sterile, pyrogen-free, distilled water and 1831 grams of sodium hydroxide are added to aid in the dissolution of the adjuvant. Then 300 grams of monopotassium phosphate are added and, under atmospheric conditions as in example (c), 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 liters. 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 G.

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 the mixture is still sufficiently liquid, and under atmosphere conditions as in example (c), 10 kilos of the adjuvant, para - (2-pentylsulphamyl-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 (g) contains its respective specific adjuvant, each of them may be prepared with any other suitable, effective adjuvant, i.e. any other adjuvants embraced by the general formula above.

In addition, in those 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 the 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 or 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-amino-salicylic acid.

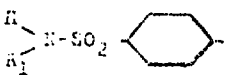
The compositions of the invention may also include an antacid material, such as aluminium hydroxide, magnesium trisilicate, trisodium citrate, calcium carbonate, magnesium oxide, or other antacid substances suitable for administration for the purpose of neutralizing gastric acidity. The amount of antacid 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 or glycerin, may be included in proportions commonly used in preparing tablets of this nature.

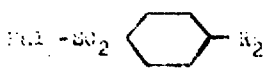
If the compositions are produced in the form of suspensions or solutions in an edible oily material, there are available various substances which may be used for this purpose. Corn oil or other suitable oil is used with advantage.

What we claim is:—

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



which process comprises reacting an amine having the general formula $R_1 - NH_2$ with a compound having the general formula

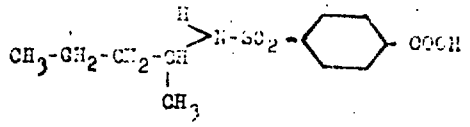


wherein R_1 is an *iso*amyl, 2-pentyl or cyclopentyl group or an alkyl or cycloalkyl group having 6 or 7 carbon atoms; Hal is a halogen atom; and R_2 is a carboxyl group or a nitrile group; and where necessary hydrolysing the nitrile group to the carboxyl group.

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 claims 1—3, wherein a mono-2-pentylamine is reacted with a para-carboxybenzenesulphonylhalide to produce a para-(2-pentylsulphamyl)-benzoic acid having the formula

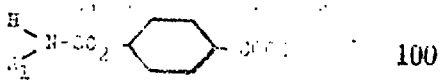


5. A process as claimed in any one of the preceding claims wherein the sulphamyl benzoic acid thus produced is mixed with a medicinal agent such as penicillin or a salt thereof to form a composition of matter suitable for therapeutic use, the sulphamylbenzoic acid constituent of said composition upon 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.

6. A process as claimed in claim 5, wherein there is also included a proportion of an antacid substance.

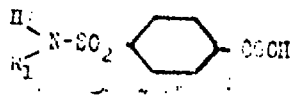
7. A process as claimed in claim 6, wherein the antacid substance is magnesium trisilicate.

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



where R_1 is an *iso*amyl, 2-pentyl or cyclopentyl group or an alkyl or cycloalkyl group having 6 or 7 carbon atoms substantially as described with reference to the specific examples hereinbefore set forth.

9. As an adjuvant for therapeutic use a para-sulphamylbenzoic acid of the general formula



The penicillin used may be any of the forms available for use, such as the calcium, sodium, potassium or 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-amino-salicylic acid.

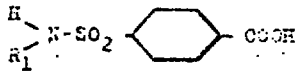
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As to binders and lubricants used in making the tablets, such materials as lactose, corn starch, gum karaya, talc, calcium stearate, gelatin, ethyl cellulose, mineral oil, propylene glycol or glycerin, may be included in proportions commonly used in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

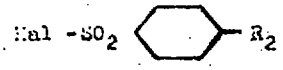
If the compositions are produced in the form of suspensions or solutions in an oleaginous material, there are available various substances which may be used for this purpose. Corn oil or other suitable oil is used with advantage.

What we claim is:—

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



which process comprises reacting an amine having the general formula $R_1—NH_2$ with a compound having the general formula

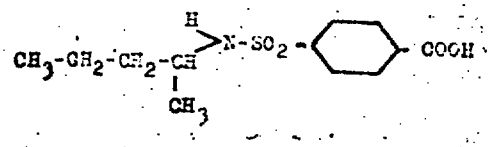


wherein R_1 is an *iso*amyl, 2-pentyl or cyclopentyl group or an alkyl or cycloalkyl group having 6 or 7 carbon atoms; Hal is a halogen atom; and R_2 is a carboxyl group or a nitrile group; and where necessary hydrolysing the nitrile group to the carboxyl group.

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 claims 1—3, wherein a mono-2-pentylamine is reacted with a para-carboxybenzenesulphonylhalide to produce a para-(2-pentylsulphamyl)-benzoic acid having the formula

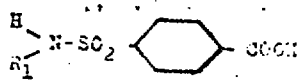


5. A process as claimed in any one of the preceding claims wherein the sulphamyl benzoic acid thus produced is mixed with a medicinal agent such as penicillin or a salt thereof to form a composition of matter suitable for therapeutic use, the sulphamylbenzoic acid constituent of said composition upon 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.

6. A process as claimed in claim 5, wherein there is also included a proportion of an antacid substance.

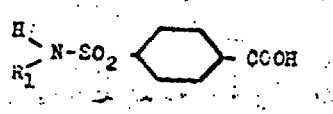
7. A process as claimed in claim 6, wherein the antacid substance is magnesium trisilicate.

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



where R_1 is an *iso*amyl, 2-pentyl or cyclopentyl group or an alkyl or cycloalkyl group having 6 or 7 carbon atoms substantially as described with reference to the specific examples hereinbefore set forth.

9. As an adjuvant for therapeutic use a para-sulphamylbenzoic acid of the general formula



where R, represents an *iso*amyl, 2-pentyl or cyclopentyl group or an alkyl or cycloalkyl group having 6 or 7 carbon atoms.

10. As an adjuvant for therapeutic use, para - (2-pentylsulphamyl)-benzoic acid.

Dated this 12th day of July, 1950.

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ERRATA

SPECIFICATION No. 678,416

Page 2, line 20, *after* " 23728/47 " *insert* " (Serial No. 666,475)."
Page 3, line 53, *for* " derivatives " *read* " derivative "
Page 3, line 91, *for* " allyl " *read* " alkyl "
Page 3, line 119, *for* " of 0.1 mole) " *read* " (0.1 mole "
Page 4, line 20, *for* " precipitated " *read* " re-precipitated "
Page 5, line 37, *after* " 0.52 " *delete* " % "

THE PATENT OFFICE,
9th October, 1952.

* C L M S *

CORRECTION OF CLERICAL ERRORS

SPECIFICATION NO. 678,416

The following corrections are in accordance with the Decision of the Superintending Examiner, acting for the Comptroller-General, dated the tenth day of September, 1953.

Page 3, *delete* line 91,
insert "alkyl or mono-cycloalkyl amine, the alkyl or cycloalkyl radical of which".

Attention is also directed to the following Printer's errors:-

Page 2, line 20, *after* "23728/47" *insert* "(Serial No. 666,475)."
Page 3, line 53, *for* "derivatives" *read* "derivative".
Page 3, line 91, *for* "allyl" *read* "alkyl".
Page 3, line 119, *for* "of 0.1 mole)" *read* "(0.1 mole)".
Page 4, line 20, *for* "precipitated" *read* "re-precipitated".
Page 5, line 37, *after* "0.52" *delete* "%".

THE PATENT OFFICE,
9th November, 1953

DB 37236/1(6)/3527 150 11/53 R

PUBLISHED BY :-
THE PATENT OFFICE,
25, SOUTHAMPTON BUILDINGS,
LONDON, W.C.2.