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N-(SUBSTITUTED SULFONYL)-AMINOBENZOIC ACIDS

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1

This invention relates to new compounds which are valuable for use in conjunction with the administration of penicillin to provide an increase in the blood plasma penicillin concentration with a given penicillin dosage level, thereby permitting the use of smaller quantities of penicillin for providing a given blood level, or the provision of very high penicillin blood levels, or permitting the less frequent administration of penicillin while maintaining a penicillin blood level adequate for bactericidal or bacteriostatic purposes.

Penicillin today is a well established therapeutic agent used in the treatment of various bacterial, in particular, coccus infections. For internal use it is commonly administered intravenously, intramuscularly, orally, subiingually, subcutaneously, or rectally. Where high blood levels are required, as in the treatment of acute infections or subacute bacterial endocarditis, or where it is desired to establish a high blood level promptly, intravenous administration, and at times administration by continuous venocylsis, is used. Frequently administration is by intramuscular injection, in which case, to maintain blood levels adequate for therapeutic purposes, injections are ordinarily given at 3 to 4 hour intervals where the menstruum is aqueous, and at less frequent intervals where the menstruum is oleaginous. Oral administration is also used to a considerable extent, but with oral administration dosages of about four times those required with intramuscular injection are required to establish comparable blood levels and administration is required about as frequently, the cost thus being substantially greater.

The major cause of the difficulties involved in attempting to maintain adequate or high penicillin blood levels follows from the rapid excretion of penicillin by the kidneys. Penicillin is removed, in the kidney, from the blood stream, not only by glomerular filtration but also by selective excretion by the renal tubules, and its removal from the blood stream on passage of the blood through the renal system is almost quantitative. For this reason, frequent administration is necessary to keep any measurable amount of penicillin in the blood stream, and where a high blood level is required it is necessary to use enormous dosages, and to administer penicillin by continuous venoclysis. Thus to maintain blood levels of the order of 10 to 20 units of penicillin per cc. of plasma may require the administration of over 10,000,000 units per day of penicillin, and even with administration at this rate, it is not possible to obtain blood levels as high as

2

may be desirable in many instances without using accessory agents, to be referred to. The maintenance of high blood levels of penicillin is, in many cases, important because, while relatively low concentrations, for example, 0.06 unit per cc., are extremely effective in many cases, in other cases, where, for example, the organisms are resistant to penicillin, much higher concentrations are required to combat the organisms, and the provision of the high concentration of penicillin in the blood stream permits the treatment of infections which are resistant to penicillin in the low concentrations which are obtained when it is administered orally or by intramuscular injection, as is the case with the organism which causes sub-acute bacterial endocarditis, *Streptococcus viridens*.

The problem presented by the rapid elimination of penicillin has been recognized, and various proposals have been made to overcome it. One such proposal involves the administration of penicillin in suspension in an oleaginous material, for example, soya bean or other fatty oil, or a mixture of such an oil with beeswax, the mixture being administered by intramuscular injection. Oleaginous material is absorbed much less rapidly than an aqueous material similarly injected, and therefore the penicillin is disseminated in the blood stream more slowly and some penicillin remains in the blood stream over a longer period of time than when an aqueous menstruum is used. While this proposal is effective in prolonging the time interval between injections, it is subject to the disadvantage that the penicillin is still excreted almost quantitatively from the blood which 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 for the establishment of a given blood level, the effect being merely to permit the injection of a very large quantity of penicillin at one time and provide for its slower and more prolonged absorption into the blood stream.

Penicillin is removed by the kidneys both by glomerular filtration and excretion by the tubules, and apparently is not reabsorbed by the tubules. With a normally functioning kidney about 19% of a crystalloid such as penicillin or any of the other crystalloid materials in the plasma water, is removed by the glomeruli from the blood which flows through the renal system. This removal is considered to be of the nature of a filtration, with the plasma water and its solutes being removed by the glomeruli and passed to the tubules.

Most of the water removed by this glomerular filtration and the crystalloids dissolved therein are returned to the blood stream by reabsorption during passage of the filtrate through the lumen of the tubule to maintain the physiological economy of the system, but certain materials, of which penicillin is one, are not so reabsorbed, and therefore whatever penicillin is removed by glomerular filtration is excreted. The epithelial cells of the tubules also serve to remove certain materials from the blood stream as well as to reabsorb selectively substances from the glomerular filtrate and return them to the blood stream. Materials which are so excreted by the tubules are presumably not reabsorbed. The extent to which tubular excretion takes place differs with various materials. 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. The result of this is that the rate of excretion of penicillin from the blood stream is approximately five times the rate of excretion of materials which are excreted by glomerular filtration alone, the tubular excretion accounting for about 80 (81)% and the glomeruli about 20 (19)%; and substantially all of the penicillin in the blood which passes through the renal system is removed in a single circulation through the kidneys. It is for this reason that it is necessary to administer penicillin frequently to maintain any measurable concentration in the blood stream and to administer it in extraordinarily large quantities where it is desired to maintain a blood level in excess of about one unit per cc.

The removal of penicillin and other crystalloids from the blood stream by the glomeruli is thought to be a physical phenomenon involving the simple filtration of plasma water and its crystalloid solutes, as distinguished from protein materials, from the blood stream. The selective excretion by the tubules is thought to be a metabolic process, with the epithelial cells of the tubules functioning physiologically to remove the penicillin from the plasma and transport it to the filtrate in the tubule.

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 the penicillin, a material which, like penicillin, is selectively excreted by the tubules, with the thought that by imposing a sufficient load on the tubule excretion mechanism, it could not function to remove from the blood stream all of the penicillin and all of the added agent, so that the removal of penicillin would be reduced. 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 the removal of penicillin to a substantial extent. Various agents which are removed by tubular excretion, including the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid and hippuric acid, or derivatives or precursors thereof, have been proposed or used for this purpose, and their use has resulted in a reduction in the rate of penicillin excreted and provided for higher plasma concentrations or longer duration of the action from a given dose of penicillin. 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. Thus, while p-aminohippuric acid is effective to reduce the rate of penicillin excretion, its threshold concentration, where an inhibiting effect can be noted, is something over 10 mg. per 100 cc. and substantial inhibition of tubular excretion of penicillin is only obtained at plasma concentrations of 40 to 60 mg. per 100 cc. To maintain such levels, in view of the rapid excretion of the material, it is necessary to use 130 to 250 grams of material per day by intravenous injection. With such materials as the diethanolamine salt of 3,5-diiodo-4-pyridone-N-acetic acid and p-aminohippuric acid the quantity which must be introduced into the blood stream is so large, both because of the high plasma concentrations required and the high rate of excretion involved, that intravenous administration is required, the materials not being well absorbed from the gastro-intestinal tract.

The new compounds of the invention, when administered along with penicillin, operate to block the removal of penicillin from the blood stream by the tubules of the kidneys, without themselves being excreted to any substantial extent by the tubules. The action of the new compounds appears to involve an interference with the normal functioning of the transport mechanism of the epithelial cells of the tubules such that they do not function to remove the penicillin from the blood stream. The new compounds are effective in eliminating or radically reducing tubular excretion of penicillin at plasma concentrations around 10 mg. per 100 cc., which is about the threshold value for agents such as p-amino hippuric acid which inhibit tubular penicillin excretion by competition for the available tubular excretion capacity. By the use of the new compounds, the tubular excretion of penicillin is reduced to almost zero, so that the actual elimination of penicillin from the blood stream becomes that substantially which results from glomerular filtration, that is, about one-fifth the normal rate (ignoring plasma binding).

The new compounds of the invention are sulfonamido carboxy acids, in which there is linked to the sulfur of the sulfonamide group a hydrocarbon or substituted hydrocarbon radical by an aliphatic linkage, and to the nitrogen of the sulfonamido group there is linked a cyclic carboxy acid, that is, a radical in which a carbocyclic or heterocyclic nucleus is linked through a carbon atom to the nitrogen, which nucleus is also linked to a carboxy group which may be the free acid group, or a neutralized group as is the case with salts or an ester group. The compounds may be represented by the formula

$$R_1SO_2NR_2COOY$$
$$\quad\quad\quad

phenyl, or the like, Y is hydrogen, the cation of a base, such as an alkali or alkaline earth metal, an amine, ammonia, or the like, or a lower alkyl radical such as methyl, ethyl or the like, and may be in any of the available positions of the cyclic radical or may be linked thereto through a bridging radical. Where the radical R_2 is phenyl, the carboxy group is advantageously in the para position.

In general, the quantity of the compound which is administered in conjunction with penicillin is from about 8 to about 24 grams per day, which is quite comparable to dosages commonly used with the sulfonamides and is adequate to suppress the rate of penicillin excretion to an extent such that the blood levels with a given dosage of penicillin administered orally or intramuscularly in aqueous solution will be increased to as much as four times or more the level obtained without the use of any blocking agent and will permit either the use of a very much smaller quantity of penicillin to provide a given blood level or the provision of higher penicillin blood levels as compared with those obtainable with the administration of penicillin by the routes ordinarily used today. In general, quantities of penicillin ranging from 1500 to 7500 units per gram of a compound of the invention are used with advantage, and in administering penicillin along with these materials, due account should be taken of the property of the material of markedly increasing the amount of penicillin in the blood stream when a given quantity of it is administered.

The compounds of the invention may be administered in admixture with penicillin or separately therefrom. Thus, when the penicillin is intended for oral administration, tablets containing one or more of the new compounds and the penicillin may be prepared and both materials administered simultaneously. Where the penicillin is to be administered intravenously, one of the new compounds and penicillin may be included in a single ampul and at the time of use dissolved in the menstruum, e. g., water or saline, and administered. Ordinarily where the penicillin is to be administered intramuscularly or subcutaneously its administration with a dissolved compound of the type of the invention is not desirable because of the limitations on the size of the injection and the fact that most of the new compounds are not sufficiently soluble in water to dissolve in the quantity of liquid which can be used, unless administration is by continuous intravenous injection.

The penicillin and one of the compounds of the invention may be administered separately, the penicillin being administered in any of the forms commonly used today, orally or parenterally, and the blocking agent of the invention being administered separately, advantageously orally in the form of tablets, capsules or the like, although parenteral administration may be used if desired. In such cases, it is frequently advantageous to administer one of the compounds of the invention before the penicillin is administered to establish a substantial concentration of it in the blood and inhibit the excretion of penicillin from the very beginning. In any event, the quantity of the selected compound administered should be such as to provide a concentration in the blood stream adequate to block substantially the excretory mechanism of the tubules. Most of the compounds of the invention exert a maximum effect with blood plasma concentrations of about 5 to 15 mg. per 100 cc., obtainable at dosage levels of about 8 to 24 grams per day orally and somewhat less than this intravenously.

The compounds which are included in the invention are those having the structure given in the foregoing formula. Among the compounds which are included in the invention and which are effective to prevent the excretion of pencillin by the tubules of the kidneys are—

1. 4'-carbethoxy-phenylmethanesulfonanilide.
2. 4'-carboxy-phenylmethanesulfonanilide.
3. Mono - sodium - 4'-carboxy-phenylmethanesulfonanilide.
4. Disodium - 4'-carboxy-phenylmethansulfonanilide.
5. N - methyl - 4'-carboxy-phenylmethanesulfonanilide.
6. 2 - chloro - 4' - carbethoxy-phenylmethanesulfonanilide.
7. 2 - chloro - 4' - carboxy-phenylmethanesulfonanilide.
8. 4 - nitro - 4' - carbethoxy-phenylmethanesulfonanilide.
9. 4 - nitro - 4' - carboxy-phenylmethanesulfonanilide.
10. 4 - amino - 4' - carbethoxy-phenylmethanesulfonanilide.
11. 4 - amino - 4' - carboxy-phenylmethanesulfonanilide.
12. 3 - nitro - 4' - carbethoxy-phenylmethanesulfonanilide.
13. 3 - amino - 4' - carbethoxy - phenylmethanesulfonanilide.
14. 4' - carbethoxy - β - phenylethanesulfonanilide.
15. 4'-carboxy-β-phenylethanesulfonanilide.
16. 4 - nitro - 4' - carbethoxy - β - phenylethanesulfonanilide.
17. 4 - amino - 4' - carbethoxy - β-phenylethanesulfonanilide.
18. 4 - amino - 4' - carboxy-phenylmethanesulfonanilide hydrochloride.
19. 4' - carbethoxy-β-phenylethenesulfonanilide.
20. 4'-carboxy-β-phenylethenesulfonanilide.
21. p-Carbethoxy-ethanesulfonanilide.
22. p-Carboxy-ethanesulfonanilide.
23. p-Carbethoxy-1-propanesulfonanilide.
24. p-Carboxy-1-propanesulfonanilide.
25. p-Carbethoxy-1-pentanesulfonanilide.
26. p-Carboxy-1-pentanesulfonanilide.
27. p-Carboxy-1-heptanesulfonanilide.
28. 3'-carboxy-phenylmethanesulfonanilide.
29. 2' - carbomethoxy-phenylmethanesulfonanilide.
30. 2 - phenylmethanesulfonamido - 4-carbethoxythiazole.
31. 2 - phenylmethanesulfonamido - 4-carboxythiazole.
32. 2 - phenylmethanesulfonamido - 4 - methyl-5-carbethoxymethylthiazole.
33. 2 - phenylmethanesulfonamido - 4 - methyl-5-carboxymethylthiazole.
34. Ethyl p - phenylmethanesulfonamidohippurate.
35. p-Phenylmethanesulfonamidohippuric acid.
36. 4' - carbomethoxy - phenylmethanesulfonanilide.

The preparation of these compounds will be illustrated in the following examples, but the invention is not limited thereto.

Example 1.—4'-carbethoxy-phenylmethanesulfonanilide.—Ethyl p-aminobenzoate was dissolved in dry pyridine (3 g. per 4 cc.) and then an equimolar portion of phenylmethanesulfonyl chloride

was added in small portions with cooling as necessary, to keep the temperature less than 35° C. and with agitation after each addition. The reaction mixture was allowed to stand at room temperature overnight after which it was diluted with alcohol (1 cc. per cc. of pyridine used) and an equal volume of concentrated hydrochloric acid added with cooling and stirring. The acidified mixture was cooled in the refrigerator for two hours during which time the product crystallized. The product was filtered, washed with water and dried. Yields varied from 50 to 70% of product. M. P. 139–141°. Recrystallization from 50% aqueous isopropanol raised the melting point to 143–145°.

Example 2.—4'-carboxy-phenylmethanesulfonanilide.—The 4'-carbethoxy-phenylmethanesulfonanilide was dissolved in 5 cc. of 5% sodium hydroxide solution per gram of ester and then heated for one hour on the steam-bath. The solution was treated with decolorizing carbon and filtered. About 10% of alcohol was added to the solution which was then acidified with acetic acid. After cooling, the product was filtered and washed well with water. The residue was dissolved in a minimum of 5% sodium hydroxide solution, again treated with decolorizing carbon, filtered and reprecipitated as above. This process was repeated until a pure white product resulted. Yields were about 90% of product. M. P. 228–30°. Recrystallization from 50% aqueous alcohol raises the melting point to 229–230°.

Example 3.—Mono-sodium salt of 4'-carboxy-phenylmethanesulfonanilide.—A solution of 5.2 g. (0.13 mole) of sodium hydroxide dissolved in 20 cc. of water was added to 37.8 (0.13 mole) of 4' - carboxy - phenylmethanesulfonanilide dissolved in 350 cc. of alcohol. A precipitate resulted which dissolved when the mixture was refluxed for fifteen minutes. The solution was then evaporated to dryness in a stream of air on the steam-bath. The residue was finally dried in vacuo at 100° C. and 2–5 mm. pressure to constant weight. The yield was 31.5 g.

Example 4.—Disodium salt of 4'-carboxy-phenylmethanesulfonanilide. — Ten g. (0.035 mole) of 4'-carboxy-phenylmethanesulfonanilide was dissolved in 25 cc. of 10% sodium hydroxide. Alcohol was added to the solution until the product had precipitated. The crude product was dissolved in 50 cc. of 50% aqueous alcohol, treated with decolorizing carbon and filtered. The solution was diluted to 200 cc. with alcohol and the product allowed to crystallize. The yield was 5 g.

Example 5.—N - methyl - 4' - carboxy - phenylmethanesulfonanilide.—Twenty - nine g. (0.1 mole) of 4'-carboxy-phenylmethanesulfonanilide was dissolved in 200 cc. of 5% sodium hydroxide and cooled to 5° C. The solution was stirred vigorously while 25 g. (0.2 mole) of dimethyl sulfate was added dropwise, care being taken to maintain strongly alkaline conditions throughout the reaction. The reaction mixture was stirred for three hours after which an insoluble precipitate was removed. This solid weighed 10 g., M. P. 111–115°. This product proved to be N - methyl - 4' - carbomethoxyphenylmethanesulfonanilide which when purified weighed 8.5 g., M. P. 114–116°. Acidification of the filtrate with acetic acid yielded 17.5 g. of acid product, M. P. 191–194°. The above ester was hydrolyzed by heating for half an hour in 25 cc. of 10% sodium hydroxide. Acidification of the solution gave 6.7 g. of product, M. P. 191–194°. The two batches of acid were combined and recrystallized from alcohol, M. P. 195–197°.

Example 6.—2 - chloro-4'-carbethoxy-phenylmethanesulfonanilide.—A benzene solution of the reaction product from the chlorination-oxidation of the Bunte salt of 0.3 mole of o-chlorobenzyl chloride was added to 40 g. (0.25 mole) of ethyl p-aminobenzoate dissolved in 50 cc. of pyridine. After standing overnight about one half of the solvent was removed in vacuo and the residue was acidified with excess hydrochloric acid. The crude product was crystallized from alcohol to give 23 g. (25%) of product, M. P. 135–142°. A sample recrystallized from isopropanol or benzene melted at 154–156°.

Example 7.—2 - chloro - 4' - carboxy - phenylmethanesulfonanilide.—Twenty-one grams (0.06 mole) of the crude ester was dissolved in 150 cc. of 5% sodium hydroxide and heated on the steam-bath for one-half hour. The product was precipitated by acidification with acetic acid. The yield was 8.5 g. (50%) of product, M. P. 217–220°. After recrystallization from 50% aqueous alcohol the yield was 6.9 g., M. P. 218–220°.

Example 8.—4 - Nitro - 4 - carbethoxy-phenylmethanesulfonanilide.—To 33 g. (0.2 mole) of ethyl p-aminobenzoate in 50 cc. of anhydrous pyridine, 46.5 g. (0.2 mole) of p-nitrophenylmethanesulfonyl chloride was added in portions with cooling and agitation. The solution was allowed to stand at room temperature overnight. The solution was then diluted with 30 cc. of alcohol and acidified with concentrated hydrochloric acid to the Congo red end-point. A tacky precipitate resulted which was triturated with 100 cc. of cold isopropanol and the mixture filtered. The residue was dissolved in boiling isopropanol, treated with charcoal and filtered hot. On cooling, 26.2 g. (35%) of product, M. P. 187–189°, crystallized from solution. Recrystallization from isopropanol or 90% aqueous alcohol gives a product melting at 189–190°.

Example 9.—4 - nitro - 4' - carboxy - phenylmethanesulfonanilide.—Twenty grams of the above ester was hydrolyzed in 150 cc. of 5% sodium hydroxide by heating for one-half hour on the steam-bath. Acidification with acetic acid gave 12 g. of product, M. P. 251–253°. Recrystallization from alcohol did not change the melting point.

Example 10.—4-amino-4'-carbethoxy-phenylmethanesulfonanilide.—Nineteen g. (0.057 mole) of the nitro ester and 3 g. of 10% palladium on charcoal catalyst in 150 cc. of the methyl ether of ethylene glycol and 15 cc. of concentrated hydrochloric acid were shaken in an atmosphere of hydrogen until absorption of gas ceased. The amount of hydrogen absorbed was 97% of the calculated quantity. Some product had crystallized on the catalyst so that the solution was made basic with sodium hydroxide, filtered and reacidified with acetic acid. The solvent was removed and the residue dissolved in dilute sodium hydroxide. After treatment with charcoal, the product was reprecipitated with acetic acid. The yield of product was 14.5 g., M. P. 144°, with effervescence. Repeated recrystallization of the product from alcohol raised the melting point to 157° with effervescence.

Example 11.—4 - amino - 4' - carboxy - phenylmethanesulfonanilide.—Fourteen and one-half g. (0.048 mole) of the ester was heated in 100 cc. of 5% sodium hydroxide on the steam-bath for fifteen minutes. Acidification with acetic acid precipitated 10.3 g. of a product, M. P. 160°

with effervescence. Recrystallization from absolute alcohol gives a product, M. P. 168–169° with effervescence. When excess hydrochloric acid was added to a solution of the amino acid, the hydrochloride precipitated. M. P. 198° with effervescence. When the amino acid was heated with acetic anhydride, the acetyl derivative was formed; M. P. 248–250° with effervescence.

Example 12.—3 - nitro - 4'-carbethoxy-phenylmethanesulfonanilide. — m - Nitrophenylmethanesulfonyl chloride condensed with ethyl p-aminobenzoate in pyridine to give about a 50% yield of 3-nitro-4'-carbethoxy-phenylmethanesulfonanilide. It was recrystallized from alcohol; M. P. 202–204°.

Example 13.—3-amino-4'-carbethoxy-phenylmethanesulfonanilide.—Catalytic reduction of the nitro compound gave high yields of product. M. P. 161–163°.

Example 14.—3 - amino - 4' - carboxy - phenylmethanesulfonanilide.—Hydrolysis of the ester in an excess of 5% sodium hydroxide by heating on the steam-bath for fifteen minutes gave this product in about 60% yield. M. P. 210–212°.

Example 15.—4'-carbethoxy-β-phenylethanesulfonanilide.—Twenty g. (0.1 mole) of phenylethanesulfonyl chloride was reacted with 16.5 g. (0.1 mole) of ethyl p-aminobenzoate in 50 cc. of pyridine. The reaction mixture was heated for one-half hour on the steam-bath after which it was diluted to 200 cc. with cold water and acidified with hydrochloric acid. The solid which precipitated was triturated with a little cold alcohol and dried. The yield was 10 g. of product; M. P. 168–172°. When recrystallized from alcohol, there was 8 g. of product melting 173–175°.

Example 15.—4'-carboxy-β-phenylethanesulfonanilide.—The ester (23.3 g., 0.07 mole) was heated for fifteen minutes on the steam-bath in 150 cc. of 5% sodium hydroxide. The solution was treated with charcoal, filtered and acidified with acetic acid to precipitate the product. The crude material, M. P. 220–223°, was recrystallized from 70% aqueous alcohol to give 20.8 g., M. P. 223–225°.

Example 16.—4-nitro-4'-carbethoxy-β-phenylethanesulfonanilide.—Twenty-six grams (0.1 mole) of p-nitrophenylethanesulfonyl chloride was added to 16.5 g. (0.1 mole) of ethyl p-aminobenzoate dissolved in 25 cc. of dry pyridine. After standing overnight, 30 cc. of alcohol was added and the mixture acidified with concentrated hydrochloric acid. The yield was 28 g. of product; M. P. 169–174°. Recrystallization from isopropanol gave 17 g. (46%) product; M. P. 178–180°.

Example 17.—4-amino-4'-carbethoxy-β-phenylethanesulfonanilide.—Twenty grams (0.053 mole) of the nitro compound dissolved in 350 cc. of the methyl ether of ethylene glycol was hydrogenated in the presence of 5 g. of 10% palladium on charcoal catalyst and 15 cc. of concentrated hydrochloric acid. When 0.16 mole of hydrogen had been absorbed the reaction had stopped. The catalyst was filtered out and the solvent removed in vacuo. The yield of crude product was 18 g. (98%) M. P. 130–133°. No suitable solvent was found from which to recrystallize the product.

Example 18.—4 - amino - 4' - carboxy - phenyl methanesulfonanilide hydrochloride.—Seventeen grams (0.05 mole) of the ester was heated in 100 cc. of 5% sodium hydroxide on the steam-bath for half an hour after which it was treated with charcoal and filtered. Addition of 100 cc. of concentrated hydrochloric acid precipitated the product. The yield was 12 g. (67%) of product; M. P. 225°, with effervescence. This was redissolved in water, decolorized and the product (6 g.) reprecipitated with a large excess of concentrated hydrochloric acid; M. P. 256°, with effervescence. When repeatedly recrystallized from water and hydrochloric acid, the melting point was raised to 271° with effervescence.

Example 19.—4'-carbethoxy-β-phenylethanesulfonanilide.—Phenyl-ethanesulfonyl chloride (36 g., 0.18 mole) prepared by procedure of Bordwell and Suter (JACS, 68, 139 (1946)) was added to 29.7 g. (0.18 mole) of ethyl p-aminobenzoate dissolved in 50 cc. of dry pyridine. The reaction mixture was allowed to stand overnight after which 60 cc. of concentrated hydrochloric acid was added and the mixture was diluted to 500 cc. with cold water. An oil precipitated which soon solidified. A small sample when repeatedly recrystallized from benzene melted at 143–145°. It behaved as solvate when plunged into the bath at 120°, melting, resolidifying and then remelting at 143–145°. When dried at 100° in vacuo for three hours, however, it melted only at 143–145°.

Example 20.—4' - carboxy - phenylethenesulfonanilide.—The crude ester from above was heated on the steam-bath for one hour in 600 cc. of 5% sodium hydroxide. The solution was then treated with decolorizing carbon and filtered. When the solution was acidified with acetic acid, 40 g. (74%) of product; M. P. 240–243° was obtained. Recrystallization from acetone-water gave 31.1 g., melting at 243–245° to a clear oil which then decomposes violently to a red solid. A dilute solution of the product in acidified aqueous acetone decolorizes a potassium permanganate solution quite rapidly.

Example 21.—p-Carbethoxy-ethanesulfonanilide.—Fifty-one g. of the ethanesulfonyl halide resulting from the chlorination-oxidation of the Bunte salt from ethyl bromide was added to a solution of 55 g. of ethyl p-aminobenzoate in small portions. The reaction mixture was allowed to stand for four hours after which it was acidified with 100 cc. of concentrated hydrochloric acid and diluted to about a liter with cold water. An oil precipitated which solidified. A sample after repeated recrystallization from 30% aqueous alcohol melted 150–152.°

Example 22.—p-Carboxy-ethanesulfonanilide.—The above crude ester was hydrolyzed in 700 cc. of 5% sodium hydroxide solution by heating one-half hour on the steam-bath. The solution was treated with decolorizing carbon, acidified with acetic acid and chilled to precipitate 19.4 g. of product melting at 189–191°. Recrystallization from water did not change the melting point.

Example 23.—p-Carbethoxy-1-propanesulfonanilide.—This was prepared by adding crude propanesulfonyl halides (51 g.) from the chlorination of the Bunte salt derived from n-propyl bromide to a solution of 45 g. of ethyl p-aminobenzoate in 65 cc. of dry pyridine. After standing overnight, the reaction mixture was acidified with 75 cc. of concentrated hydrochloric acid and diluted to about a liter with cold water. The oil that precipitated soon crystallized. A sample recrystallized repeatedly from dilute aqueous alcohol had a melting point of 136–137°.

Example 24.—p-Carboxy-1-propanesulfonanilide.—This was obtained by the hydrolysis of the crude ester in 400 cc. of 5% sodium hydroxide solution. Acidification with acetic acid

and chilling gave a red product. This was dissolved in 500 cc. of boiling water, treated with decolorizing carbon and filtered. The product which precipitated (13.5 g.) and a melting point of 184–185°.

Example 25.—p-Carbethoxy-1-pentanesulfonanilide.—The crude oil that resulted from the chlorination-oxidation of the Bunte salt formed from 0.4 mole of 1-pentyl bromide and sodium thiosulfate was used after drying in ethereal solution and removal of the ether. This was considered to be 1-pentanesulfonyl bromide. This oil (41 g.) was added to 32 g. (0.2 mole) of ethyl p-aminobenzoate dissolved in 50 cc. of dry pyridine. After standing overnight, acidification of the mixture with hydrochloric acid and dilution to 500 cc. with cold water precipitated in oil that solidified to a tacky mass. This was removed, washed with hexane and dried. The yield of crude product was 14.8 g. (25%). A sample when repeatedly recrystallized from a 2:1 mixture of hexane-isopropyl ether had a melting point of 76–78°.

Example 26.—p-Carboxy-1-pentanesulfonanilide.—The crude oily ester (13 g.) was dissolved in 75 cc. of 5% sodium hydroxide and heated on the steam-bath for an hour. The product was precipitated from solution with hydrochloric acid. The yield of product after crystallization from 30% aqueous alcohol, was 9.3 g., (75%) M. P. 191–193°.

Example 27.—p-Carboxy-1-heptanesulfonanilide.—Crude 1-heptanesulfonyl bromide (45 g.) was reacted with 29.7 g. of ethyl p-aminobenzoate in 50 cc. of dry pyridine. By acidification and dilution a low melting solid was obtained which after repeated recrystallization melted 75–95°. The intermediate crude ester was hydrolyzed by heating in 250 cc. of 5% sodium hydroxide. Acidification with acetic acid precipitated a product which was filtered and recrystallized from 50% aqueous alcohol which weighed 17 g., M. P. 193–195°. Repeated recrystallization of a sample raised the melting point to 194–196°.

Example 28. — 3' - carboxy - phenylmethane - sulfonanilide.—By using methyl m-aminobenzoate in place of the p-aminobenzoate in the reaction with phenylmethanesulfonyl chloride, there was isolated from the reaction mixture an oil that solidified on standing. When reprecipitated from alkaline solution with excess hydrochloric acid, a product was obtained; M. P. 202–204°, which proved to be the acid instead of the expected intermediate ester. Recrystallization from alcohol raised the melting point to 204–206°.

Example 29. — 2 - carbomethoxy - phenyl - methanesulfonanilide.—When methyl anthranilate was condensed in a similar manner with phenylmethanesulfonyl chloride, yields of about 50% of product were obtained; M. P. 104–106°.

Example 30. — 2' - carboxy - phenylmethane - sulfonanilide.—The ester was hydrolyzed in high yields by heating in excess 5% sodium hydroxide. Acidification of the alkaline solution with acetic acid precipitated a product; M. P. 215–217°. The melting point was unchanged by recrystallization from alcohol.

Example 31.—2-phenylmethanesulfonamido-4-carbethoxythiazole.—Eighteen grams (10% excess) of phenylmethanesulfonyl chloride was added in portions with stirring to a solution of 12.12 g. (0.086 mole) of 2-amino-4-carbethoxythiazole in 80 cc. pyridine. The solution became colored and considerable heat was evolved. The mixture was added to 300 cc. water and ice and concentrated hydrochloric acid added until the mixture was acid to Congo red. The mixture was chilled. The oily precipitate was separated by decantation and then worked with cold dilute hydrochloric acid until it solidified; 20 g., 71% yield. A small sample was purified by recrystallization from 50% alcohol after treating with charcoal. The crystalline solid was solvated and melted at 88–93°. After rigid drying, melting point was 130–131°, corr.

Example 32.—2-phenylmethanesulfonamido-4-carboxythiazole.—Twenty grams of 2-phenylmethanesulfonamido - 4 - carbethoxythiazole was dissolved in 110 cc. 10% sodium hydroxide and warmed gently. After standing a half-hour the solution was treated with charcoal and the product precipitated with excess hydrochloric acid, 14.12 g. This material was found to be a sodium salt and was warmed in dilute hydrochloric acid to give the free acid, 12.3 g. This was purified by recrystallization from 50% alcohol after treating with charcoal; M. P. 222–3°, corr.

Example 33.—2-phenylmethanesulfonamido-4-methyl - 5 - carbethoxymethylthiazole. — Twenty-one grams (10% excess) of phenylmethanesulfonyl chloride was added in portions with stirring to solution of 20 g. (0.1 mole) of 2-amino-4-methyl-5-carbethoxymethylthiazole and 70 cc. dry pyridine that was maintained by chilling to a temperature below 30° C. The flask was stoppered and allowed to stand overnight. The pyridine was removed under reduced pressure and the syrupy mixture poured into 400 cc. cold dilute HCl. After chilling, the product was removed, 21.17 g., 62.5% yield. A small sample was purified by crystallization from anhydrous alcohol after treating with charcoal; M. P. 195–6°, corr.

Example 34.—2-phenylmethanesulfonamido-4-methyl-5-carboxymethylthiazole.—20.17 g. (0.057 mole) of 2 - phenylmethanesulfonamido - 4 - methyl-5-methylcarbethoxythiazole was dissolved in 100 cc. 10% sodium hydroxide and the solution allowed to stand one hour. The solution was treated with charcoal and the product precipitated with hydrochloric acid, 17.14 g., 92% yield. It was purified by recrystallization from 50% alcohol after treating with charcoal; M. P. 252–3°, dec., corr.

Example 35.—Ethyl p-phenylmethanesulfonamidohippurate.—Nine grams (0.09 mole) of the ethyl ester of glycine dissolved in 75 cc. of dry pyridine was treated with 30 g. (0.1 mole) of p - phenylmethanesulfonamidobenzoyl chloride. After standing overnight about one-half the solvent was removed in vacuo on the steam-bath. The residue was added to cracked ice (100 g.) and acidified with excess concentrated hydrochloric acid. This precipitated a gum from which the solution was decanted. The gum was dissolved in 100 cc. of alcohol and 400 cc. of water added to precipitate the product which soon solidified. The yield was 25 g., M. P. 155–160°. This product was incompletely soluble in alkali and could not be reprecipitated as the ester. Recrystallization from alcohol raised the melting point to 170–172° but some alkali insoluble material remained. Recrystallization from benzene gave a pure product; M. P. 172–174°.

Example 36. — p-Phenylmethanesulfonamidohippuric acid.—Hydrolysis of some of the material containing an alkali insoluble portion which was filtered off, gave a free acid.

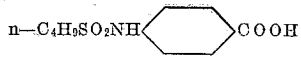
Among the compounds which are also included

in the invention and as part of the list contained on pages 10–12, are—

37. p-Carboxy-1-butanesulfonanilide.
38. p - Carboxy - 2-methyl-1-propanesulfonanilide.
39. p - Carboxy-3-methyl-1-butanesulfonanilide.
40. p-Carboxy-1-hexanesulfonanilide.
41. p - Carboxy-2-ethoxy-1-ethanesulfonanilide.

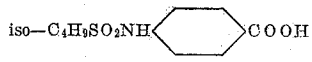
The preceding five compounds are prepared by replacing the 1-pentanesulfonyl bromide of Example 25 respectively by the corresponding sulfonyl halides, namely, (*a*) 1-butanesulfonyl chloride, (*b*) 2-methyl-1-propanesulfonyl chloride, (*c*) 3-methyl-1-butanesulfonyl chloride, (*d*) 1-hexanesulfonyl chloride, and (*e*) 2-ethoxy-1-ethanesulfonyl chloride, and by otherwise following the procedure of Example 25 obtaining the corresponding p-carbethoxy-1-alkanesulfonanilide, and then hydrolyzing the respective p-carbethoxy-1-alkane-sulfonanilide in accordance with the procedure of Example 26, thereby obtaining each of the respectively indicated end products which individually have the respective properties following:

Example 37. — p-Carboxy-1-butanesulfonanilide or



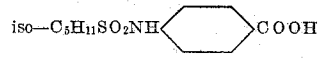
melting at 184–186° C.

Example 38.—p - Carboxy - 2 - methyl - 1-propanesulfonanilide or



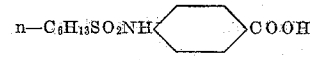
melting at 193–194° C.

Example 39.—p - Carboxy-3-methyl-1-butanesulfonanilide or



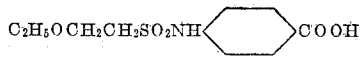
melting at 195–197° C.

Example 40.—p - Carboxy-1-hexanesulfonanilide or



melting at 192–194° C.

Example 41.—p - Carboxy-2-ethoxy-1-ethanesulfonanilide or



melting at 144–146° C., resolidifying and then remelting at 157–159° C.

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

a. Compressed tablet.—10,000 grams of lactose and 100,000 grams of 4'-carboxy-phenylmethanesulfonanilide are uniformly mixed and wetted with sufficient water to permit its ready granulation in the usual way. 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 compound and lactose. The final mixture is then tableted (using ½ inch die standard curvature punches) yielding 200,000 tablets of 0.58 gram each, and each containing 0.5 gram of 4'-carboxy-phenylmethanesulfonanilide. By replacing the quantity of this compound by the same quantity of any other selected compound, for example, any of compounds of Examples 1 or 3 to 35 tablets of the same individual weight and same content of any of the other adjuvants are obtained.

b. Compressed tablet containing penicillin.—10,000 grams of lactose are mixed with 100,000 grams of p-carboxy-1-pentanesulfonanilide and granulated as in the preceding example. 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 and tableted with the same die as in the preceding example yielding 200,000 tablets weighing 0.6 gram and each containing 0.5 gram of p-carboxy-1-pentanesulfonanilide and 25,000 units penicillin (plus 10% excess). Any other selected compound, for example, any of the compounds of the examples above may be used in equal amount to obtain tablets of the same weight and same content of any of the other compounds of the invention.

c. Compressed tablet with penicillin.—100,000 grams of 4'-carboxy-phenylmethanesulfonanilide and 16,000 grams of lactose are mixed and granulated as shown above. 6749 grams of crystalline penicillin sodium (1630 units per mg.), 2651 grams of dried cornstarch,600 grams karaya gun powder, 2800 grams talc, and 1200 grams calcium stearate are mixed together under atmospheric conditions controlled as in the preceding example and under the same conditions mixed with the granulation and tableted with the same die, yielding 200,000 tablets of 0.65 gram each and each containing 50,000 units penicillin (plus 10% excess).

d. Compressed tablet with magnesium trisilicate.—100,000 grams of 4'-carboxy-β-phenethylsulfonanilide are uniformly mixed with 3000 grams of magnesium trisilicate and 7000 grams of lactose and wetted and granulated as in the preceding examples. 2000 grams of dried cornstarch, 500 grams of karaya gum powder, 2500 grams talc and 1000 grams of calcium stearate are mixed together and then mixed with the granulation and then tableted with the same type of die as before yielding 200,000 tablets of 0.58 gram each and each containing 0.5 gram of adjuvant 3.

e. Compressed tablet with penicillin and magnesium trisilicate.—100,000 grams of p-carboxy-1-heptane-sulfonanilide, 3000 grams magnesium trisilicate, and 7000 grams lactose are mixed and granulated as before described. Under atmosphere controlled as in the preceding example 3375 grams of the same crystalline penicillin sodium, 2625 grams of dried cornstarch, 500 grams karaya gum powder, 2500 grams talc, and 1000 grams calcium stearate are mixed and then mixed with the granulation, and this mixture tableted as before yielding 200,000 tablets of 0.6 gram each and each containing 0.5 gram of the compound and 25,000 units penicillin (plus 10% excess).

f. Compressed tablet with penicillin and magnesium trisilicate.—100,000 grams of p-carboxy-1-heptanesulfonanilide, 3000 grams magnesium trisilicate and 13,000 grams of lactose are mixed and granulated in the manner noted. Under atmosphere controlled as above 6749 grams of the same crystalline penicillin sodium, 2651 grams dried cornstarch, 600 grams karaya gum powder, 2800 grams talc, and 1200 grams calcium stearate

are intimately mixed and then mixed with the granulation and this mixture tableted as before, yielding 200,000 tablets of 0.65 gram each and each containing 0.5 gram of the compound and 50,000 units penicillin (plus 10% excess).

g. Dry filled capsule.—540 kilos of 4-nitro-4'-carboxy-phenylmethanesulfonanilide were filled into hard gelatin telescopic capsules size #00 (natural color) with 0.5 gram of adjuvant per capsule.

h. Dry filled capsule with penicillin.—Under atmosphere controlled as in the preceding examples of compositions containing penicillin, 25 kilos of 4'-carboxy-phenylmethanesulfonanilide, 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 compound and 25,000 units penicillin (plus 10% excess).

i. Dry filled capsules with penicillin.—As in the preceding example, 25 kilos of N-methyl-4'-carboxy-phenylmethanesulfonanilide, 1690 grams of the same crystalline penicillin sodium, and 310 grams of dried cornstarch are intimately and uniformly mixed and encapsulated in the same type and size of capsule, yielding 50,000 capsules, each holding 0.54 gram of mixture containing 0.5 gram of compound and 50,000 units penicillin (plus 10% excess).

j. Dry filled capsule with magnesium trisilicate.—25 kilos of 2-phenylmethanesulfonamido-5-carboxymethyl-4-methylthiazole and 1 kilo of magnesium trisilicate were intimately and uniformly mixed and encapsulated in the same size and type of capsule as before, yielding 50,000 capsules, each holding 0.52 gram of mixture containing 0.5 gram of the compound.

k. Dry filled capsule with magnesium trisilicate and penicillin.—Under atmosphere controlled as in Example *b*, 25 kilos of 4'-carboxy-phenylmethanesulfonanilide, 850 grams of the same crystalline penicillin sodium, and 150 grams of magnesium trisilicate are intimately and uniformly mixed and encapsulated in the same size and type of capsule, yielding 50,000 capsules, each holding 0.52 gram of mixture and containing 0.5 gram of the compound and 25,000 units penicillin (plus 10% excess).

l. Dry filled capsule with magnesium trisilicate and penicillin.—Under atmosphere controlled as in Example *b*, 25 kilos of p-carboxy-β-phenylethanesulfonanilide 1.69 kilos of the same crystalline penicillin sodium, and 310 grams of magnesium trisilicate are intimately and uniformly mixed and encapsulated in the same size and type of capsule, yielding 50,000 capsules, each holding 0.54 gram of mixture and containing 0.5 gram of the compound and 50,000 units penicillin (plus 10% excess).

While each of the individual examples of dry filled capsules has been illustrated with the respectively disclosed compound, the latter in each of them may be replaced by any other suitable compound, for example, any of those of Examples 1 through 41.

m. Soft elastic capsule.—50 kilos of p-carboxy-1-propanesulfonanilide are homogeneously dispersed in 50 kilos of corn oil and the composition encapsulated in known manner in soft, elastic, sheet gelatin, hermetically sealed capsules to yield 100,000 capsules with the one gram of composition net content in each.

n. Soft elastic capsule with penicillin.—Under atmosphere controlled as in Example *b*, 1.69 kilos of the same crystalline penicillin sodium are homogeneously dispersed in 48.31 kilos of corn oil and 50 kilos of 4'-carboxy-phenylmethanesulfonanilide similarly dispersed in the oil, and the resulting composition encapsulated in known manner in soft gelatin capsules as in Example *m*, yielding 100,000 capsules, each holding one gram net of the composition and containing 0.5 gram of the compound with 25,000 units penicillin (plus 10% excess).

o. Soluble elastic capsule.—7.5 kilos of magnesium trisilicate and 50 kilos of 2-phenylmethanesulfonamido-4-carboxythiazole are intimately and uniformly mixed and the mixture homogeneously dispersed in 42.5 kilos of corn oil, and the resulting dispersion encapsulated in soluble elastic capsules as in the two preceding examples, yielding 100,000 capsules, each holding one gram net of the dispersion and containing 0.5 gram of the compound.

p. Soluble elastic capsule with penicillin and magnesium trisilicate.—Under atmosphere as controlled in Example *b*, 1687 grams of the same crystalline penicillin sodium, 7313 grams of magnesium trisilicate, and 50 kilos of 3-amino-4'-carboxyphenylmethanesulfonanilide are intimately and uniformly mixed and the mixture homogeneously dispersed in 41 kilos of corn oil, and the dispersion encapsulated in the same type of soluble elastic capsules as in the three preceding examples, yielding 100,000 capsules each holding one gram net of the dispersion and containing 0.5 gram of the compound with 25,000 units penicillin (plus 10% excess).

While in each of the preceding examples of soluble elastic capsules a respective individual compound of the invention was included, any other of the new compounds may be similarly included by substituting the same quantity of it in any of the particular examples. The same applies to the compressed tablets.

q. Ampul.—10 kilos of 4'-carboxy-phenylmethanesulfonanilide are suspended in very nearly 50 liters of pyrogen-free distilled water and 1452 grams of sodium hydroxide are added to help in its dissolution. 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 ampuls for 5 cc. liquid content each, which are then flame-sealed and autoclaved at 15 pounds pressure for 20 minutes. If larger ampuls, containing a multiple dose, are prepared, a preservative is advantageously included.

r. Ampul.—250 grams of hydrous chlorobutanol are dissolved in very nearly 50 liters of sterile, pyrogen-free, distilled water, 16.67 kilos of p - carboxy - 1 - pentane-sulfonanilide are stirred in and 2368 grams of sodium hydroxide are added to assist in the dissolution of the adjuvant, and 390 grams of monopotassium phosphate are added with water to make 50 liters of total solution. The solution is filtered and filled into ampuls for 5 cc. liquid content each, which are then flame-sealed and sterilized by autoclaving as in the preceding example.

s. Flame-sealed ampul filled with penicillin.—12.5 kilos of 4'-carboxy-phenylmethanesulfonanilide are stirred into very nearly 30 liters of sterile, pyrogen-free distilled water and 1795 grams of sodium hydroxide are added to aid in its dissolution. Then 390 grams of monopotassium phosphate are added and, under atmos-

phere conditions as in Example *b*, 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 ampul-vials. The contents of the vials are then quickly frozen by rotating them in a bath of methyl "Cellosolve" chilled with "Dry-Ice" to —70° C., and desiccated under high vacuum for 48 hours by the method and apparatus as in United States Patent No. 2,353,985 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 ampul-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 compound. Of course, the product may be prepared in vials similar to those used for penicillin, i. e., rubber stoppered vials, or other containers, if desired.

t. Ampul 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 *b*, 10 kilos of p-carboxy-1-pentanesulfonanilide 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 the compound. It is put up in flame-sealed ampuls containing suitable volume of the suspension which is as stable as the ordinary penicillin in peanut oil preparation. Other types of containers, such as the ordinary ampul vials, or vials such as are used with penicillin, may be used.

While each of the preceding examples of particular ampul preparations contains its respective specific new compound, each of them may be prepared with any of the other compounds of the invention.

v. Elixir.—In very nearly 100 liters of distilled water are dissolved 25 kilos of the sodium salt of 4' - carboxyphenylmethanesulfonanilide. To this are added a solution of 100 grams of Synfleur artificial strawberry and 100 grams of amaranth (Food Drug & Cosmetic Red #2) dissolved in 17.9 liters of USP alcohol. To the resulting solution are added 10 kilos of sucrose and sufficient water to give a total volume of 100 liters. The resulting elixir contains 17% of alcohol and each teaspoonful of it contains one gram of the new compound. The particular compound used may be replaced by the same quantity of other compounds of the invention. The artificial strawberry flavoring may be replaced by any other suitable flavoring as may be the approved coloring amaranth.

w. Sterile isotonic solution.—0.5 kilos of hydrous chlorobutanol is dissolved in very nearly 100 liters of sterile, pyrogen-free, distilled water, and 5 kilos of the sodium salt of 4'-carboxyphenylmethanesulfonanilide are dissolved in the resulting solution and sufficient water is added to make a total volume of 100 liters. The finished, sterile, isotonic solution may be dispensed in 100 cc. containers.

In the various examples *a* through *w* where no particular specifications for individual ingredients are given, it is understood that there is used such quality of the various ingredients as is suitable for incorporation in pharmaceutical preparations.

Of particular importance, from the standpoint of combination of effectiveness in blocking the tubular excretion of penicillin, low toxicity, and adequate absorption from the gastrointestinal tract, are 4' - carboxy - phenylmethanesulfonanilide and its alkali metal salts, and p-carboxy-1-pentanesulfonanilide and its alkali metal salts.

I claim:

1. Compounds of the formula:

$$R_1CH_2SO_2NHR_2COOH$$

in which R_1 is selected from the class consisting of hydrocarbon and dialkyl ether radicals having a total of from 3 to 7 carbon atoms, phenyl, aminophenyl, nitrophenyl, halophenyl, and benzyl, and R_2 is selected from the class consisting of benzene and thiazole.

2. N-(benzylsulfonyl)-p-aminobenzoic acid.

JAMES M. SPRAGUE.

REFERENCES CITED

The following references are of record in the file of this patent:

Schroeter: Ber. Deut. Chem. Gessell, vol. 40, page 1615 (1907).

Salkowski: Ber. Deut. Chem. Gessell, vol. 49, pp. 1376–1382 (1916).

Certificate of Correction

Patent No. 2,531,367 November 21, 1950

JAMES M. SPRAGUE

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction as follows:

Column 10, line 9, for "phenylethane-" read *phenylethene-*; line 10, for "Phenyl-ethanesulfonyl" read *Phenyl-ethenesulfonyl*; column 13, line 2, for "on pages 10–12" read *in column 6*; column 14, line 32, for "gun" read *gum*; and that the said Letters Patent should be read as corrected above, so that the same may conform to the record of the case in the Patent Office.

Signed and sealed this 28th day of August, A. D. 1951.

[SEAL]

THOMAS F. MURPHY,
Assistant Commissioner of Patents.