This print embodies the corrections allowed by the Decision of the Superintending Examiner, acting for the Comptroller-General, dated the ninth day of October, 1944, under Section 70, of the Patents and Designs Acts, 1907 to 1942.

PATENT SPECIFICATION



Convention Date (United States of America): July 31, 1941. **562,763**

Application Date (in United Kingdom): July 14, 1942. *No. 9799/42.*

Complete Specification Accepted: July 14, 1944.

(Under Section 6 (1) (a) of the Patents &c. (Emergency) Act, 1939, the proviso to Section 91 (4) of the Patents and Designs Acts, 1907 to 1942, became operative on June 3, 1944.)

(Sample has been furnished in this case under Section 2, sub-section 5, of the Patents and Designs Acts, 1907 to 1942).

COMPLETE SPECIFICATION

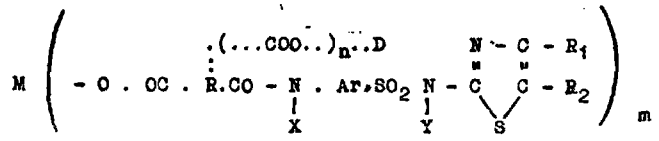
Amino-Substituents of Sulphanilamide Derivatives

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 nature of this invention and in what manner the same is to be performed, to be particularly described and ascertained in and by the following statement:—

This invention relates to N⁴-carboxyacyl-aminoarylsulphonamidothiazoles, in which the carboxyacyl group is the radical remaining when the hydroxyl group is removed from only one of the two or more carboxyl groups of a polycarboxylic acid, and the invention covers such products containing the remaining carboxyl group or groups unaltered as well as with the hydrogen in any of such remaining carboxyl groups replaced by a carboxylate-forming element or radical.

Such products are useful as intestinal antiseptics for combatting and reducing the concentration of organisms causing intestinal infection.

The products of this invention may be represented by the general formula:



in which M may be hydrogen as well as any radical capable of combining with a carboxyl radical to form a carboxylate, e.g. a metal an alkyl radical, a nitrogen base e.g. ammonium and corresponding radicals of alkylamines and alkanolamines; and R is the residue of a polycarboxylic acid, aliphatic as well as aromatic, stripped of its carboxyl groups: and D may be hydrogen as well as any of the radicals represented by M and when M is polyvalent D may represent some or all of the valences of M not satisfied by the single carboxyl group to which M is illustrated as being attached: and n may be zero as well as any whole number up to four, whereby the grouping . . . (. . . COO . .)$_n$ . . D represents the carboxyl and the carboxylate groups over two from any polycarboxylic acid having more than two carboxyl groups, and m is a small number equal to the valence of M when n is zero and also when each occurrence of radical D is either hydrogen or any other monovalent radical and also when each occurrence of the radical D (whether mono- or polyvalent) is different from the radical M; and since M and D may be separately polyvalent, m may be one when all of the carboxyl groups in the carboxyacyl radical satisfy all of the valences of such polyvalent radicals M and D: and X may be hydrogen as well as an alkyl radical having, for example, from one to about eight or more carbon atoms as well as an aryl radical such as phenyl and substituted-phenyl; and Ar is an aryl radical

(having, as shown in the general formula, a valance linked to nitrogen and a valence linked to sulphur) such as phenyl or naphthyl (unsubstituted or substituted); and Y may be hydrogen as well as an alkyl radical, saturated or unsaturated. for example, methyl and its higher homologues as well as an aralkyl radical, e.g. benzyl, as well as an aryl radical e.g. phenyl or naphthyl (unsubstituted as well as substituted); and R_1 and R_2 may be separately hydrogen as well as alkyl, aralkyl and aryl (including diphenyl) each of these types generally as described for Y above, and a nitrogen-containing radical as nitro and amino (unsubstituted and substituted as acyl- and alkyl-), and an oxygenated radical, for example, hydroxy or alkoxy, and carbalkoxy such as carbmethoxy, carboxyl, and haloalkyl as chlorethyl and halogen, for example, chlorine and bromine.

The carboxyacyl group (remaining group when the hydroxyl group is removed from only one of the at least two carboxyl groups of a polycarboxylic acid) may be derived from any desirable polycarboxylic acid, for example, aliphatic and aromatic, such as the aliphatic polycarboxylic acids as the saturated aliphatic polycarboxylic acids such as the dicarboxylic acids, oxalic and malonic acids and their methylene - non-substituted homologues, succinic, glutaric, adipic, pimelic, suberic, azelaic and sebacic acid and the like and derivatives thereof exemplified by malonic acid and its homologues, in any of which at least one of the hydrogens of at least one of the available chain methylene groups is replaced by any desirable substituent, for example, alkyl (saturated as well as unsaturated). hydroxy, amino, carboxyl, and the like. Of such derivatives, the saturated-alkyl-substituted-methylene type is shown by the monoalkyl examples as ethyl-malonic, butyl-malonic, iso-succinic (pyrotartaric or methyl-succinic) and ethyl-succinic acids, and the saturated-dialkyls by dimethyl - malonic and diethyl - malonic acids, and the unsaturated-alkyl by allyl - malonic acid. The hydroxy-substituted-methylene type are exemplified by tartronic (hydroxy-malonic) and malic (hydroxy-succinic, in the three isomeric forms) acids and the polyhydroxy-substituted by the dihydroxy type shown by tartaric (dihydroxy-succinic) acid and the tetrahydroxy example in talomucic acid. The amino-substituted-methylene type is demonstrated by aspartic (amino-succinic) and glutamic acids. The mixed-substituted-methylene type is shown by citramalic (2-hydroxy-2-methyl butane-dioic) and citric acids, the latter serving also to point out the carboxylic-substituted-methylene type.

Unsaturated aliphatic dicarboxylic acids from which the carboxyacyl radical is derived correspond to any of the above mentioned saturated examples having at least four carbon atoms and further particularized by maleic and citraconic (methylmaleic) acids and their respective isomers, fumaric and mesaconic (methyl-fumaric) acids.

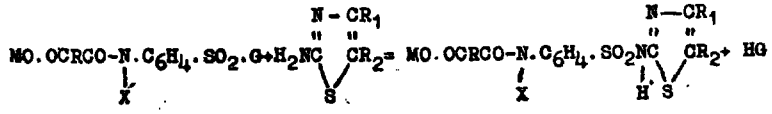
Other aliphatic polycarboxylic acids from which the carboxyacyl radical may be derived are the tribasic, saturated as well as unsaturated, acids exemplified respectively by tricarballylic and aconitic acids and derivatives thereof as those in which any of the methylene or chain hydrogens is replaced by any desirable substituent (as pointed out in relation to the dicarboxylic acids) illustrated by citric acid.

The aromatic (aryl) polycarboxylic acids from which the carboxyacyl radical may be derived may be an aryl dicarboxylic acid as well as one containing up to six carboxyl groups, as mellitic acid. and those having replaceable hydrogen atoms may or may not have other substituents on the aromatic nucleus. Those having no substituents on the aromatic nucleus are illustrated by the isomeric phthalic acids, phthalic (ortho). isophthalic (meta) and terephthalic (para). In those having other substituents on the nucleus, such substituents may be illustrated by alkyl (mono- and di-), alkoxy. hydroxy, halo, nitro and other common groups. for example, xylidic (or uvitic, 5-methyl-1, 3-dicarboxylicbenzene), cumidic, (dimethyl-phthalic), hemipic (dimethoxy-phthalic), and coccinic (hydroxy-methyl-phthalic) acids.

The invention also includes the preparation of these carboxacylaminobenzensulphonamidothiazoles, which are made by heating the desired polycarboxylic acid, its anhydride, or an ester, such as an alkyl ester, or a monohalide, such as the monochloride or a monochloride of the ester, thereof with the desired aminobenzenesulphonamidothiazole, either merely together or in an inert reaction medium such as an inert solvent, and as in the latter case separating the desired end product or, as in the case of the use of the ester, liberating the end product by hydrolysis, and in any case, where necessary, subjecting it to purification as by recrystallization. Thus, for example, with the aliphatic dicarboxylic acids having less than four carbon atoms in the chain, the alkyl diester of the dicarboxylic acid is reacted with the sulphanilamidothiazole selected.

With the aliphatic acids having four and five carbon atoms in the chain and with the aromatic polycarboxylic acids having two carboxyl groups ortho to each other, the desired anhydride is taken as the starting material, while with the aliphatic acids having over five carbon atoms in the chain and with the aromatic acids having no carboxyl group in ortho position to another carboxyl group, the free acid may be heated directly with the selected sulphanilamidothiazole. If desired, the monohalide of the ester of any of the acids may be used as the starting material.

The invention relating to the preparation of these carboxyacylaminobenzenesulphonamidothiazoles also includes the preparation of them by starting, for example with a suitable carboxyacylaminobenzenesulphonyl halide, such as the chloride or bromide, and containing the desired carboxyacyl radical to be found in the final product, and reacting such carboxyacylaminobenzenesulphonyl halide with the desired 2-aminothiazole, preferably in a basic reaction medium, for example, containing a base which may be a solvent for the reaction starting materials, such as pyridine, although the reaction medium may instead be rendered alkaline by the addition of a suitable water-soluble alkaline substance, for example, sodium carbonate. The reaction may be illustrated by, but not restricted to, the following equation:



in which M, R, X, R_1 and R_2 have the same definition as given for the same elements in the general formula in the opening part of this specification and in which G may represent a halogen, for example, chlorine or bromine and the like, or may indicate an anhydride starting material suitably when two of the same main radicals are attached to G, in which event the reaction product in which G is an element might, for example, be H_2O.

The invention may be illustrated by, but not restricted to, the following examples:

Example I.

2-N⁴-oxalylsulphanilamidothiazole.

Five grams of sulphathiazole was mixed with 5.7 grams of ethyl oxalate and heated on a hot plate at 130—150° C. for two hours, with occasional stirring. At the end of this time, the reaction mixture was washed thoroughly with dilute hydrochloric acid and water. The ethyl ester of 2-N⁴-oxalylsulphanilamidothiazole was obtained in a yield of 86% and after three recrystallizations from dilute alcohol, it melted at 231—232° C. (with decomposition). Then fourteen grams of the ethyl ester of 2-N⁴-oxalylsulphanilamidothiazole was placed in 150 cc. of a 2.5% solution of sodium hydroxide and heated on the hot plate for one-half hour at 95—100° C. The solution was then decolorized with charcoal (Registered Trade Mark "Darco") and made slightly acid by the addition of concentrated hydrochloric acid. The 2-N⁴-oxalylsulphanilamidothiazole thus formed was purified by crystallization from dilute alcohol. Yield 71%, melting (with decomposition) at 203—205° C.

Example II.

2-N⁴-malonylsulphanilamidothiazole.

Using sulphathiazole and ethyl malonate and following the procedure of example I, the ethyl ester of 2-N⁴-malonylsulphanilamidothiazole, melting at 193—194.5° C°., was obtained in a similar manner and by like steps converted to 2-N⁴-malonylsulphanilamidothiazole which, after similar purification, decomposes between 240 and 250° C.

Example III

2-N⁴-succinylsulphanilamidothiazole.

3.92 grams of succinic anhydride was added to a boiling suspension of 10 grams of 2-sulphanilamidothiazole in 100 cc. of alcohol. The mixture was then refluxed for five minutes after the addition was complete at which time all of the solids were in solution. The solution was then cooled and diluted with an equal volume of water. The white solid precipitate which formed was filtered and recrystallized from dilute alcohol, yielding 2-N⁴-succinylsulphanilamidothiazole, melting at 184—186° C.

Example IV.

2-N⁴-phthalylsulphanilamidothiazole.

Five grams of phthalic anhydride was added to a boiling suspension of ten grams of sulphathiazole in 100 cc. of alcohol. The reaction product was worked up as in example 3, yielding 2-N⁴-phthalylsulphanilamidothiazole, which decomposes above 260° C.

EXAMPLE V.

2-N⁴-MALEYLSULPHANILAMIDOTHIAZOLE.

By replacing the succinic anhydride in example 3 by the equivalent amount of maleic anhydride, there is obtained 2-N⁴-maleylsulphanilamidothiazole melting at 213—215° C.

EXAMPLE VI.

2-N⁴-ADIPYLSULPHANILAMIDOTHIAZOLE.

A mixture of 10 grams of 2-sulphanilamidothiazole and 5.6 grams of adipic acid was heated at 140—150° C. for one hour. The product was treated with 60 cc. of 10% sodium carbonate to separate the insoluble, undesired by-products and the filtrate neutralized with dilute hydrochloric acid. The 2-N⁴-adipylsulphanilamidothiazole thus obtained was purified by redissolving in dilute ammonia and slowly precipitating with dilute hydrochloric acid. It melted at 196—197° C. after crystallization from water.

EXAMPLE VII.

2-N⁴-MALYLSULPHANILAMIDO-4-METHYL-THIAZOLE.

A mixture of 20 grams of 2-sulphanilamido-4-methyl-thiazole and 7 grams of malic acid monochloride reacted and processed as in Example VI (omitting the heating), yields 2-N⁴-malylsulphanilamido-4-methyl-thiazole.

By replacing the ethyl malonate in Example II by an equivalent amount of a suitable dialkyl ester of any of the alkyl (saturated as well as unsaturated) derivatives of malonic acid by the same procedure there will be obtained the corresponding 2-N⁴-alkylmalonylsulphanilamidothiazoles. Similarly, the ethyl malonate in Example II may be replaced by the equivalent quantity of a similar ester of tartronic acid.

By replacing the succinic anhydride in Example III by the equivalent quantity of the possible inner anhydrides of other succinic acid derivatives, corresponding carboxyacylsulphanilamidothiazoles are obtained, for example 2-N⁴-glutaryl sulphanilamidothiazole (m.p. 196° to 197° C.). The corresponding carboxyacylsulphanilamidothiazoles derived from the trans-form succinic acid derivatives may be obtained by replacing the ethyl malonate in Example II by an equivalent quantity of a corresponding monochloride-ester of such succinic acid derivative or unsaturated isomer and with little or no heating, for example with the equivalent quantity of the monochloride of the ethyl ester of for example fumaric or mesaconic acid.

By replacing the adipic acid of Example VI by a corresponding equivalent quantity of sebacic acid 2-N⁴-sebacylsulphanilamidothiazole (m.p. 171—172° C.) is obtained.

Furthermore, by replacing the 2-sulphanilamidothiazole in any of the Examples by any thiazole-nuclearly substituted 2-sulphanilamidothiazole having any of the substituents of the type represented by R_1 and R_2 in the general formula for the products of this invention, there are obtained the corresponding carboxyacylsulphanilamidothiazoles in which there are nuclear substituents on the thiazole ring at the 4- and 5-positions. Among such compounds as well as among all of the various products of the invention, it has been found that those in which the carboxyacylamino radical is para in position to the sulphonamido radical possess particularly desirable properties especially in so far as intestinal antisepsis is concerned. Thus, by varying the sulphanilamidothiazole starting material by employing corresponding materials in which the thiazole nucleus is substituted a variety of substances can be obtained.

To obtain the compounds of the invention in which Y of the structural formula is a positive radical of the type hereinabove disclosed for Y, the sulphanilamidothiazole starting material employed to produce the thiazole nuclearly substituted compounds of the invention as shown above is alkylated or aralkylated or arylated by reaction with the necessary suitable alkylating, aralkylating or arylating agent to attach to the sulphonamido nitrogen the desired positive radical. Alkylating agents such as an alkyl halide, as methyl chloride or ethyl chloride or bromide, or an alkyl sulphate as an alkyl sulphonate, may be employed to replace the hydrogen represented by Y by the desired alkyl radical, and by using the corresponding aralkylating or arylating agent, by the desired aralkyl or aryl radical. By reacting the thus obtained aminobenzene-sulphonalkyl-, aralkyl-, or aryl-amido thiazole with the desired polycarboxylic acid, there is obtained any desired product of the invention having a positive radical other than hydrogen for the element Y in the general formula.

By replacing the succinyl, the carboxyacyl group, in any of the above thiazole-nuclearly substituted, as well as in the N¹-substituted, compounds of the invention, by the carboxyacyl radical derived from any other polycarboxylic acid of the type hereinabove disclosed, the corresponding compound of the invention with the corresponding different carboxyacyl radical is obtained.

From the various exemplifications of the compounds of the invention, there is

seen that they may be generally referred to as carboxylacylaminoarylsulphonyl derivatives of aminothiazoles, in which the thiazole portion, as indicated by the thiazole nucleus and the elements R_1 and R_2 in the general formula, is referred to generally as "thiazoles" to embrace not only those compounds in which the thiazole radical is derived from thiazole itself, but also those in which the thiazole portion is derived from thiazole nuclearly substituted, and in which derivatives, the amino radical through which the thiazole portion is attached to the sulphur, is either unsubstituted or substituted by a positive radical.

The products of the invention, in which M and D of the general formula are hydrogen are generally practicably water soluble, are usually neutral compounds, become very substantially soluble in water when the free carboxyl group or groups in the product is converted to the carboxylate form by the use of the equivalent amount of alkali or ammonium hydroxide or amine or alkanolamine. Thus, the compounds in which M and D are hydrogen may exhibit a solubility in water within about five or up to about ten per cent., whereas the carboxylate form of the same compound may have a solubility up to about fifty per cent. and even higher.

The carboxylate form of any of the compounds of the invention may be prepared, for example, by adding to a small amount of water an excess of the compound over its solubility in water and dissolving the excess by stirring in a sufficient quantity of, for example, anhydrous sodium carbonate. The solution is preferably filtered and from the filtrate the highly soluble sodium salt can be isolated, for example, by adding an equal volume of alcohol and pouring the resulting solution into about 10 volumes of acetone. The substance thrown out of solution is permitted to settle and the supernatant liquid withdrawn and the residue preferably treated several times with fresh acetone. After decanting the acetone from the last treatment, the resulting desired sodium salt may be dried preferably under vacuum.

Other metal carboxylate salts of the compounds such as the copper, gold, iron and bismuth salts and the like may be obtained by reacting the alkali metal salt, preferably in aqueous solution, with a suitable soluble salt of the metal, the carboxylate salt of which is desired. The desired carboxylate salt is obtained by resulting double decomposition.

The applicability of the compounds of the invention in intestinal antisepsis, for example, against the coliform type of bacteria, is particularly exemplified by 2 - N^4 - succinylsulphanilamidothiazole which has been found to give a prompt drop from one hundred million to as low as only sixty per cent. cubic centimeter in the intestinal flora in dogs.

In general, the carboxyacylsulphanilyl derivatives of the aminothiazoles, in which the carboxyacyl radical is aliphatic and contains four carbon atoms in the aliphatic chain are especially effective as such intestinal antiseptics for it is possible to build up a high concentration of them in the intestinal tract and without a simultaneously high blood level and yet with substantially no noticeable indication of toxic symptoms. Among these particularly effective compounds are not only those in which the aliphatic chain is saturated, such as those in which the carboxyacyl radical is derived from succinic, malic (the three isomeric forms), aspartic, citramaleic, pyrotartaric, ethyl succinic, tartaric and ketosuccinic acids and their substituted derivatives, but also those in which the aliphatic chain is unsaturated, such as those in which the carboxyacyl radical is obtained from maleic, citraconic, fumaric and mesaconic acids and their substituted derivatives. The N^4-carboxyacyl products of the invention show distinctive activity.

These compounds, applicable as intestinal antiseptics, exhibit such activity by the attachment to the various nuclear portions of the compound, of substituents the introduction of which into the basic nuclei leaves the compound substantially non-toxic. Similarly, the metallic element in the compounds used as intestinal antiseptics are such that their inclusion in the compound introduces no toxic characteristic.

The various compounds, used as intestinal antiseptics, are administered orally, either in the form of tablets, capsules or powders of the solid material or as solutions of any desired concentration, exceeding, if desired, 50%.

In the specification and claims the carboxyacyl radical, as hereinabove defined, derived from specific polycarboxylic acids herein named, is designated by replacing the terminal "-ic" in the name of the acid by the ending "-yl" as, for example, the succinyl, oxalyl, malonyl, phthalyl, maleyl, adipyl, glutaryl, aspartyl, tartaryl, fumaryl, mesaconyl, and citryl carboxyacyl radicals and the like derived respectively from succinic, oxalic, malonic, phthalic, maleic, adipic, glutaric, aspartic, tartaric, fumaric, mesaconic, and citric acids and the like.

The term "benzene" as used in the

claims, for example, in the expression " carboxyacylaminobenzenesulphonamidothiazoles " covers the divalent residue —C_6H_4—, to one free valence of which the carboxyacylamino group is linked and to the other free valance of which the sulfur of the sulfonyl group is attached so that there are only those two substituents on the benzene ring. On the other hand, the term " phenyl " as used in the claims, for example, " carboxyacylaminophenylsulphonamidothiazoles " is generic to the divalent residue —C_6H_4— as just hereinabove defined with respect to the term " benzene ", or otherwise referred to as non-substituted-phenyl, and to the substituted-phenyl nucleus in which one or more of the remaining four hydrogen atoms are replaced by additional substituents on the ring.

Specification No. 544,215 (as open to public inspection under Section 91(4) of the Acts) discloses a process for preparing mono-amino-benzene-sulphamido-thiazole derivatives wherein 2-amino-thiazole or its derivatives substituted in the heterocyclic ring by alkyl, aryl or aralkyl radicals are treated with acylated 4-aminobenzene-sulphonyl halogenides in the presence of compounds containing a tertiary nitrogen atom in a heterocyclic ring, the reaction being effected in a ketonic solvent free from hydroxyl groups and the acyl group of the product being split off by known methods.

In Specification No. 533,495 a process is described for the manufacture of benzene-sulphamido-thiazole derivatives wherein a benzene sulphonic acid, the nucleus of which contains as a substituent at least one amino group or a group capable of conversion into an amino group or a derivative thereof is converted in the form of a reactive acid derivative for example a halide, and in known manner into a heterocyclic substituted benzene sulphamido compound. In one example of such process 2-aminothiazole is reacted with acetyl sulphanilic acid chloride.

Specification No. 517,272 describes a process for the preparation of 2-(*p*-aminobenzene-sulphonamido)-thiazole and -benzthiazole derivatives by the action of a benzene sulphonyl halide containing as a substituent in the *p*-position an acylamino group convertible to an amino group by hydrolysis on a thiazole or benzthiazole containing an amino group in the 2-position, which compounds may contain other substituents, and then, hydrolysing the acylamino group in the resulting compound to form an amino group.

In contradistinction to the use of simple substituted thiazoles in the above-mentioned specifications, the present invention involves the heating of the appropriate polycarboxylic acid or its derivatives with the appropriate aminobenzenesulphonamidothiazole.

Samples have been furnished under Section 2, sub-Section 5, of the Patents & Designs Acts, 1907 to 1942 as follows:—

SUCCINYLSULPHATHIAZOLE.

20 grams (0.2 mol) of 2-amino-thiazole was dissolved in 75 cc. of anhydrous pyridine and 27.4 grams (0.1 mol) of N^4-succinylaminobenzenesulphonyl chloride was added slowly with stirring. After the addition was completed, the solution was heated on the steam-bath for one-half hour and the pyridine was then removed by distillation under reduced pressure. The resulting residue was triturated with 50 cc. of cold water and the brown insoluble solid (4 grams) was filtered off, and the aqueous filtrate was acidified with the suitable amount of concentrated hydrochloric acid. After chilling for several days, 6.8 grams of succinylsulphathiazole was obtained. Nitrogen analysis 11.86% found; 11.83 calculated.

2-(*p*-SUCCINYLAMIDOBENZENESULPHONAMIDO)-4-METHYL-THIAZOLE.

1.5 grams (0.0055 mol) of 2-sulphanilamido-4-methylthiazole were suspended in 20 cc. of anhydrous alcohol and the mixture heated to boiling. Then 1.1 grams (0.0110 mol) of succinic anhydride were added in portions over a few minutes to the boiling suspension and the boiling of the mixture was continued for five minutes after the addition was completed. Solution of the reactants was then complete before precipitation of the reaction product began. When the precipitation of the reaction product appeared to have been completed the solution was permitted to cool and the reaction product filtered off and purified by solution in 25 cc. of saturated aqueous sodium carbonate solution and re-precipitation therefrom by the addition of dilute hydrochloric acid until the solution was acid to litmus. The thus far purified 2-(N^4-succinylsulphanilamido)-4-methyl-thiazole was then dissolved in sufficient hot 60% dioxane to take it completely in solution and sufficient " Darco " decolourising charcoal (about one-quarter of a gram) was added to decolourise the solution. After filtering off the decolourising charcoal, the 2-(N^4-succinylsulphanilamido)-4-methylthiazole was crystallised off from the filtrate. It melted at 257.5° to 258° C. (with decomposition).

Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

claims, for example, in the expression " carboxyacylaminobenzenesulphonamidothiazoles " covers the divalent residue —C_6H_4—, to one free valence of which the carboxyacylamino group is linked and to the other free valance of which the sulfur of the sulfonyl group is attached so that there are only those two substituents on the benzene ring. On the other hand, the term " phenyl " as used in the claims, for example, " carboxyacylaminophenylsulphonamidothiazoles " is generic to the divalent residue —C_6H_4— as just hereinabove defined with respect to the term " benzene ", or otherwise referred to as non-substituted-phenyl, and to the substituted-phenyl nucleus in which one or more of the remaining four hydrogen atoms are replaced by additional substituents on the ring.

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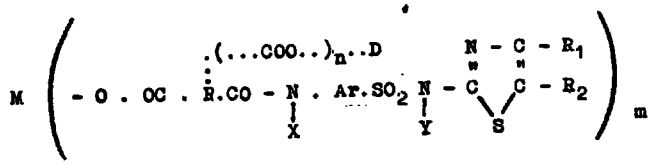
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Having now particularly described and ascertained the nature of our said invention and in what manner the same is to be performed, we declare that what we claim is:—

1. A process for the preparation of an N^4-carboxyacyl - aminoarylsulphonamidothiazole of the formula:



wherein M, *m*, Ar, X, Y, D, R, R_1 and R_2 have the meaning hereinbefore assigned to them, for example the preparation of a carboxylacylamino - benzenesulphonamidothiazole which comprises heating the appropriate polycarboxylic acid, its anhydride, or an ester, such as an alkyl ester or a monohalide, such as the monochloride or a monochloride of the ester with the appropriate aminobenzenesulphonamidothiazole or by reacting a carboxyacylaminobenzenesulphonyl halide with the appropriate 2-aminothiazole preferably in a basic reaction medium, and separating the desired end product.

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

3. A process as claimed in claim 1 wherein when an ester is used as a starting material the end product is liberated from the reaction mixture by hydrolysis.

4. A process as claimed in any one of the preceding claims, wherein when employing an aliphatic carboxyl acid having less than 4 carbon atoms in the chain the alkyl diester of the dicarboxylic acid is reacted with the sulphanilamidothiazole.

5. A process as claimed in any one of the preceding claims, wherein in the case of aliphatic acids having 4 or 5 carbon atoms in the chain and of aromatic polycarboxylic acids having two carboxyl groups ortho to each other, the anhydride is employed as the starting material.

6. A process as claimed in any one of claims 1 to 4 wherein when the aliphatic acid has more than five carbon atoms in the chain and when aromatic acids having no carboxyl group ortho to another carboxyl group are employed the free acid is heated directly with the sulphanilamidothiazole.

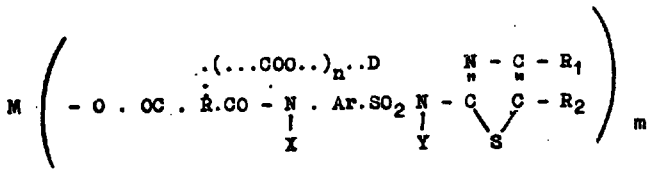
7. A process as claimed in any one of the preceding claims wherein the monohalide of the ester of any of the acids is used as the starting material.

8. A process as claimed in any one of claims 1 to 6 wherein the carboxyacylaminoarylsulphonamidothiazole is prepared by reacting carboxyacylaminobenzenesulphonyl halide and the appropriate 2-aminothiazole in a basic reaction medium which is a solvent for the starting materials.

9. A process as claimed in claim 8, wherein the solvent for the starting materials is pyridine or wherein the reaction medium is rendered alkaline by the addition of a water-soluble alkaline substance e.g. sodium carbonate.

10. A process for the production of a carboxyacyl - aminoarylsulphonamidothiazole substantially as described in any one of the Examples hereinbefore set forth.

11. An N^4-carboxyacyl-aminoarylsulphonamidothiazole having the general formula:



(wherein M, *m*, Ar X, Y, D, R, R_1 and R_2 have the meanings hereinbefore assigned to them) when prepared or produced by the process claimed in any one of the preceding claims.

12. Succinylsulphathiazole when prepared or produced by the process claimed in Claim 1.

13. Phthalylsulphathiazole when prepared or produced by the process claimed in Claim 1.

Dated this 14th day of July, 1942.

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H.A.