1,002,341

PATENT SPECIFICATION

DRAWINGS ATTACHED

1,002,341

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Index at acceptance :—C2 C(1J1A1, 1J1A2, 1J1A3, 1J1B, 1J1C3)
Int. Cl.:—C 07 d

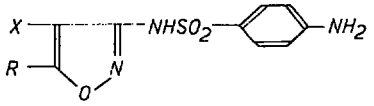
COMPLETE SPECIFICATION

Isoxazole Derivatives of Sulfanilamide and their preparation

We, SHIONOGI & CO. LTD., a Japanese Body Corporate, of 12, 3-chome, Dosho-machi, Higashi-ku, Osaka, Japan, 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: —

The present invention relates to isoxazole derivatives of sulfanilamide. More particularly, it relates to 3 - sulfanilamido - 4 - halogeno - 5 - alkylisoxazoles.

The isoxazole derivatives of sulfanilamide are represented by the formula:

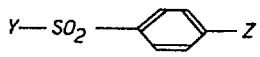


(I)

wherein R is an alkyl group having 1 to 5 carbon atoms (e.g. methyl, ethyl, propyl or butyl) and X is a halogen (e.g. chlorine, bromine or iodine).

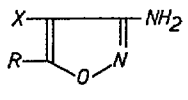
In living bodies these isoxazole derivatives of sulfanilamide of formula (I) show high antibacterial activity with low toxicity. They also show a high and prolonged sulfonamide level in the blood of living bodies.

According to the invention there is provided a process for preparing 3 - sulfanilamido - 4 - halogeno - 5 - alkylisoxazole which comprises condensing 3 - amino - 4-halogeno - 5 - alkylisoxazole with a *p*-substituted benzene-sulfonic acid derivative represented by the formula: —



wherein Y is a halogen atom, a hydroxyl group or an alkoxy, aryloxy or aralkoxy group and Z is a group convertible to amino by hydrolysis or reduction such as acyl-amino, nitro and azo, followed by the conversion of the *p*-substituent on the benzene ring of the resulting compound into an amino group.

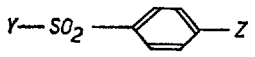
The 3 - sulfanilamido - 4 - halogeno - 5 - alkylisoxazole of formula (I) can be prepared by the interaction of 3 - amino - 4 - halogeno - 5 - alkylisoxazole represented by the formula:



(II)

[*Price 4s. 6d.*]

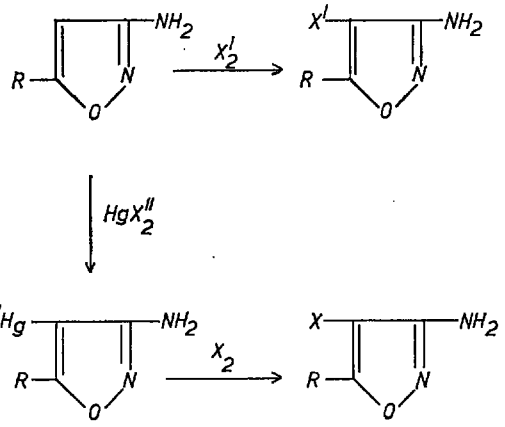
wherein R and X each have the same significance as designated above; with a *p*-substituted benzene-sulfonic acid derivative represented by the formula:



(III)

wherein Y and Z each have the same significance as designated above.

The starting materials of the present invention 3 - amino - 4 - halogeno - 5-alkylisoxazole of formula (II), which are described and claimed in our co-pending British Patent Application No. 26091/64 Serial No. (1002342) can be prepared by the treatment of 3-amino-5-alkylisoxazole with a halogenating agent as shown in the following scheme



(II)

wherein R and X each have the same significance as designated above, X^1 is chlorine or bromine and X^{11} is a halogen (e.g. chlorine, bromine, iodine). Thus, 3-amino-5-alkylisoxazole may be reacted with chlorine or bromine, preferably in an inert organic solvent (e.g. methanol, ethanol, acetic acid, chloroform, carbon tetrachloride, or trichloroethane), while cooling with water or ice to give 3-amino-4-chloro or bromo-5-alkylisoxazole. Alternatively, 3-amino-5-alkylisoxazole may be reacted with a mercuric halide (e.g. mercuric chloride, mercuric bromide or mercuric iodide) in a hydrous medium (e.g. water, water-methanol, water-ethanol or water acetic acid), preferably while refluxing, followed by the treatment of the resulting 3 - amino - 4 - halogeno-mercuri - 5 - alkyl - isoxazole with a mixture of a halogen (e.g. chlorine, bromine or iodine) and its alkali metal salt (e.g. potassium chloride, potassium bromide or potassium iodide) in a hydrous medium (e.g. water, water-methanol, water-ethanol or water-acetic acid) at room temperature or while heating to give 3 - amino - 4 - halogeno - 5-alkylisoxazole. These fundamental procedures may be also carried out with the previous and/or subsequent treatments which are obvious to those skilled in the art. In the former procedure, for instance, 3-amino-5-alkylisoxazole may be previously acylated and then subjected to halogenation, followed by deacylation of the acylamino group at the 3-position of the resulting intermediate whereby 3 - amino - 4 - halogeno - 5-alkylisoxazole is produced. As specific examples of 3 - amino - 4 - halogeno - 5 - alkylisoxazole, there may be included 3 - amino - 4 - chloro - 5 - methylisoxazole, 3-amino-4 - bromo - 5 - methylisoxazole, 3 - amino - 4 - iodo - 5 - methylisoxazole, 3-amino-4 - chloro - 5 - ethylisoxazole, 3 - amino - 4 - iodo - 5 - ethylisoxazole, 3 - amino - 4-chloro - 5 - *n* - propylisoxazole, 3 - amino - 4 - bromo - 5 - *n* - propylisoxazole, 3-amino - 4 - ~~ido~~ iodo - 5 - *iso* - propylisoxazole, 3 - amino - 4 - chloro - 5 - *n* - butylisoxasole and the like.

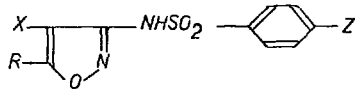
Another starting material of the present invention is a *p*-substituted benzenesulfonic acid derivative of formula (III), which is usually employed in the preparation

of sulfonamides. Examples of this derivative are *p*-acylaminobenzenesulfonic acid, *p*-nitrobenzenesulfonic acid, azobenzene - *p*,*p*¹ - disulfonic acid, *p* - acylaminobenzenesulfonic ester, *p* - nitrobenzenesulfonic ester, azobenzene - *p*,*p*¹ - disulfonic ester, *p*-acylaminobenzenesulfonyl halide, *p* - nitrobenzenesulfonyl halide, azobenzene - *p*,*p*¹-disulfonyl halide and the like. The acyl group includes not only alkanoyl (e.g. acetyl, propionyl or butyryl), aryloyl (e.g. benzoyl, toluoyl or xyloyl) and aralkanoyl (e.g. phenylacetyl or phenylpropionyl) groups but also alkoxycarbonyl (e.g. ethoxycarbonyl or propoxycarbonyl), aryloxycarbonyl (e.g. phenoxycarbonyl or tolyloxycarbonyl) and aralkoxycarbonyl (e.g. benzyloxycarbonyl or phenethyloxycarbonyl) groups, although the latter three are usually not included in the category of "acyl". Further, the ester includes the alkyl ester (e.g. methyl ester, ethyl ester or propyl ester), aryl ester (e.g. phenyl ester) and aralkyl ester (e.g. benzyl ester or phenethyl ester).

The following are examples of *p*-substituted benzenesulfonic acid derivatives. *p*-acetylaminobenzenesulfonic acid, *p* - propionylaminobenzenesulfonic acid, *p* - benzoylaminobenzenesulfonic acid, *p* - ethoxycarbonylaminobenzenesulfonic acid, *p* - benzyloxycarbonylamino - benzenesulfonic acid, *p* - nitrobenzenesulfonic acid, methyl *p*-acetylaminobenzenesulfonate, ethyl *p* - acetylaminobenzenesulfonate, benzyl *p* - acetylaminobenzenesulfonate, ethyl *p* - nitrobenzenesulfonate, ethyl azobenzene - *p*,*p*¹ - disulfonate, *p* - acetylaminobenzenesulfonyl chloride, *p* - acetylaminobenzenesulfonyl bromide, *p* - propionylaminobenzenesulfonyl chloride, *p* - benzoylaminobenzenesulfonyl chloride, *p* - ethoxycarbonylaminobenzenesulfonyl chloride, *p* - phenoxycarbonylaminobenzenesulfonyl bromide, *p* - benzyloxycarbonylaminobenzenesulfonyl chloride, *p*-nitrobenzenesulfonyl chloride, azobenzene - *p*,*p*¹ - disulfonyl chloride and azobenzene - *p*,*p*¹ - disulfonyl bromide. Of these *p* - substituted benzenesulfonic acid derivatives, *p* - alkanoylaminobenzenesulfonyl halide is the most reactive.

According to the process of the present invention, the said two starting materials are first subjected to condensation. The reaction can be executed by treating 3 - amino-4 - halogeno - 5 - alkylisoxazole of formula (II) with a *p*-substituted benzenesulfonic acid derivative of formula (III) in an inert solvent. The inert solvent should be able to dissolve at least one of the starting materials and may be generally selected from lower alkanols (e.g. methanol or ethanol), lower aliphatic ketones (e.g. acetone or methyl ethyl ketone), aromatic hydrocarbons (e.g. benzene or toluene), aliphatic esters (e.g. methyl acetate or ethyl acetate), ethers (e.g. ether), cyclic ethers (e.g. dioxane or tetrahydrofuran) or halogenoalkanes (e.g. chloroform, dichloroethane or carbon tetrachloride). When a *p*-substituted benzenesulfonyl halide is used as the starting material, the condensation is a kind of deacidation reaction, and the presence of a basic substance is preferred. Organic bases such as pyridine bases (e.g. pyridine, picoline, lutidine or collidine) and trialkylamines (e.g. triethylamine) or inorganic bases such as alkali metal carbonates (e.g. sodium carbonate or potassium carbonate), alkali metal bicarbonate (e.g. sodium bicarbonate or potassium bicarbonate) and alkaline earth metal carbonates (e.g. calcium carbonate or barium carbonate) may be used as the basic substance. These basic substances may be used in the form of a mixture, suspension or solution in the said inert organic solvent or, in the case of a liquid alone. The reaction temperature depends on the kind of starting materials and/or the reaction medium.

As the result of condensation, there is obtained 3 - (*p* - substituted benzenesulfonylamino) - 4 - halogeno - 5 - alkylisoxazole represented by the formula:

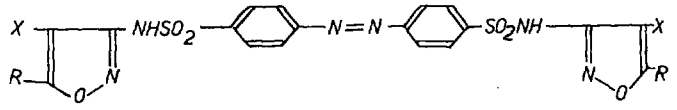


(IV)

wherein R, X and Z each have the same significance as designated above.

The 3 - (*p* - substituted benzenesulfonylamino) - 4 - halogeno - 5 - alkylisoxazole of formula (IV) thus-prepared is next subjected to conversion of the *p*-substituent on the benzene ring into an amino group. The conversion procedure to be applied depends on the *p*-substituent. When the *p*-substituent is an acylamino group, hydrolysis may be employed. The hydrolysis reaction may be carried out by a *per se* conventional manner *i.e.* heating with acid or alkali. When the *p*-substituent is a nitro group, a reduction procedure is adopted which is usually employed for the conversion of the nitro group on an aromatic ring into an amino group. For instance, the reduction using a reducing agent such as metal-acid, metal-alkanol and metal-liquid ammonia, catalytic reduction or electrolytic reduction may be used. The method wherein the reduction is carried out

using a combination of a metal (e.g. zinc or tin) with an acid (e.g. hydrochloric acid, acetic acid or glacial acetic acid containing hydrogen chloride) at room temperature or with heating is particularly preferred from the economical viewpoint. The catalytic reduction using nickel catalyst, palladium catalyst or platinum catalyst is also preferred for ease of operation and to lessen the risk of side-reaction. When the *p*-substituent is an azo group, the 3 - (*p* - substituted benzenesulfonylamino) - 4 - halogeno - 5 - alkylisoxazole of formula (IV) can be rewritten more clearly as follows:



(IV¹)

wherein R and X each have the same significance as designated above. In this case, the conversion may be accomplished by reduction. For instance, there may be employed the reduction using a reducing agent such as stannous chloride-hydrochloric acid and alkali metal dithionite, catalytic reduction and electrolytic reduction. The catalytic reduction using Raney nickel in an aqueous solution of alkali hydroxide or platinum oxide in dioxane is particularly preferred.

The product of the present invention is 3 - sulfanilamido - 4 - halogeno - 5 - alkylisoxazole of formula (I), which includes specifically the following compounds: 3-sulfanilamido - 4 - chloro - 5 - methyl - isoxazole, 3 - sulfanilamido - 4 - bromo - 5-methylisoxazole, 3 - sulfanilamido - 4 - iodo - 5 - methylisoxazole, 3 - sulfanilamido-4 - chloro - 5 - ethylisoxazole, 3 - sulfanilamido - 4 - bromo - 5 - ethylisoxazole, 3-sulfanilamido - 4 - iodo - 5 - ethylisoxazole, 3 - sulfanilamido - 4 - chloro - 5 - *n*-propylisoxazole, 3 - sulfanilamido - 4 - bromo - 5 - *iso* - propylisoxazole, 3 - sulfanilamido - 4 - iodo - 5 - *n* - propylisoxazole, 3 - sulfanilamido - 4 - bromo - 5 - *n* - butylisoxazole and 3 - sulfanilamido - 4 - iodo - 5 - *n* - butylisoxazole.

These 3 - sulfanilamido - 4 - halogeno - 5 - alkylisoxazoles of formula (I) are useful as antibacterial agents in combatting infections of pathogenic bacteria. 3 - sulfanilamido - 4 - iodo - 5 - methylisoxazole is especially useful in this respect and its animal and clinical test data are set forth below, compared with the closely related known sulfonamide, 3 - sulfanilamido - 5 - ~~methylisiloxazole~~ methylisoxazole (United Kingdom Patent Specification No. 814,276).

The in vitro antibacterial spectra of the sulfonamides were determined by an agar streak dilution method. Serial two-fold dilutions of the sulfonamide were prepared in synthetic medium and the surface of the agar was streaked with suitable dilution of young broth cultures. The lowest concentration of sulfonamide which prevented visible growth after 24 hours of incubation at 37°C. was designated as the minimal inhibitory concentration. The results are shown in Table I.

TABLE I. ANTIBACTERIAL SPECTRA (IN VITRO)

Test Organisms	Minimum Inhibitory Concentration (mcg per ml)	
	3-Sulfanilamido-4-iodo-5-methyl-isoxazole	3-Sulfanilamido 5-methyl-isoxazole
Shigella paradysenteriae, Komagome B_1	1.0	0.5
Shigella paradysenteriae, Kawase	1.0	0.5
Shigella paradysenteriae, Ohara	2.0	1.0
Salmonella paratyphi A	16.0	8.0
Salmonella paratyphi B	16.0	8.0
Salmonella paratyphi C	4.0	2.0
Salmonella typhi murium	8.0	4.0
Escherichia coli communis	16.0	8.0
Klebsiella pneumoniae	8.0	4.0
Bacillus subtilis, PCI—219	32.0	4.0

From this Table, it is seen that the invitro antibacterial spectrum of 3-sulfanilamido - 4 - iodo - 5 - methylisoxazole is quite identical with that of 3 - sulfanilamido-5 - methylisoxazole, although there is a slight difference in activity.

To determine the in vivo activity of the sulfonamides against Diplococcus pneumoniae and Klebsiella pneumoniae in mice, the experimental infections were produced in a group of 10 mice by intraperitoneal injections of the bacteria using 100 MLD (minimum lethal dose) of the bacterial cultures. The mice were treated 3, 24, 48, 72 and 96 hours after infection. The sulfonamide, emulsified with gum arabic, was administered orally to the group of mice, and survival of infected mice was recorded up to 10 days after infection, at which time the tests were terminated. The percentage deaths were plotted against logarithmic dose on logarithmic probability scale paper and the dose of sulfonamide (mg/kg) giving protection to 50% of the mice was read off from the graph. The results are shown in Table II.

TABLE II. ANTIBACTERIAL ACTIVITY (IN VIVO)
a) DIPLOCOCCUS PNEUMONIAE, TYPE 1

Sulfonamides	Dosage (mg/kg/day)	No. Alive/No. Tested	Percent Effect	Median Effective Dose (ED_{50}) (mg/kg)
3-Sulfanilamido 4-iodo-5-methyl isoxazole	500	3/10	30	780
	750	4/10	40	
	1000	7/10	70	
3-Sulfanilamido 5-methyl-isoxazole	500	1/10	10	920
	750	3/10	30	
	1000	6/10	60	

TABLE II—cont.

b) KLEBSIELLA PNEUMONIAE

Sulfonamides	Dosage (mg/kg/day)	No. Alive/ No. Tested	Percent Effect	Median Effective Dose (ED_{50}) (mg/kg)
3-Sulfanilamido 4-iodo-5-methyl-isoxazole	250	1/10	10	540
	500	5/10	50	
	750	9/10	90	
	1000	10/10	100	
3-Sulfanilamido-5-methyl-isoxazole	250	0/10	0	650
	500	3/10	30	
	750	6/10	60	
	1000	9/10	90	

From the above Table, it can be seen that 3 - sulfanilamido - 4 - iodo - 5 - methylisoxazole is more effective than 3 -sulfanilamido - 5 - methylisoxazole against pneumococcal and Klebsiella infections.

In order to ascertain the absorption of the sulfonamides in human beings, the sulfonamides were orally administered to human subjects at a dose of 2 grams, and citrated venous samples of blood were obtained before and at various intervals after administration. The blood specimens were centrifuged within 30 minutes of drawing, and plasma harvested into sterile test tube. The plasma samples so obtained were analyzed for free sulfonamide by the Tsuda method (Yakugaku (Science of Drugs), Vol. 2, 12 (1948)). The averages of free values of both sulfonamides obtained at the various intervals are shown graphically in the accompanying drawing. The solid line represents average free 3 - sulfanilamido - 4 - iodo - 5 - methylisoxazole plasma level and the broken line shows average free 3 - sulfanilamido - 5 - methylisoxazole plasma level.

From the Figure, it can be seen that 3 - sulfanilamido - 4 - iodo - 5 - methylisoxazole and 3 - sulfanilamido - 5 -methylisoxazole are rapidly absorbed and reaches identical maximum plasma peaks, 4 hours after administration, but the former shows a higher maximum peak value with a slower drop in concentration than the latter. It is, therefore, obvious that 3 -sulfanilamido - 4 - iodo - 5 - methylisoxazole shows far better maintenance of plasma levels than does 3 - sulfanilamido - 5 - methylisoxazole.

To determine the acute toxicity, the sulfonamides were emulsified with gum arabic and administered orally to mice. The animals were observed for 7 days and deaths were recorded each day. The median lethal dose (LD_{50}) was determined graphically by plotting the dilution factor of the dose against the percentage deaths, using logarithmic probability scale paper. The results are shown in Table III.

TABLE III. ACUTE TOXICITY (PER OS, IN MICE)

Sulfonamides	Median Lethal Dose (LD_{50}) (mg/kg)
3-Sulfanilamido-4-iodo-5-methylisoxazole	4,500
3-Sulfanilamido-5-methyl-isoxazole	2,500

From this Table, it is obvious that 3 - sulfanilamido - 4 - iodo - 5 - methylisoxazole is remarkably less toxic than 3 - sulfanilamido - 5 - methylisoxazole.

Making a summary of the above results, it can be said that 3 - sulfanilamido - 4-

iodo - 5 - methylisoxazole is useful as a long-acting sulfonamide which exhibits a high antibacterial activity especially in living bodies. It may be also said that the sulfonamide is employed for producing a high and prolonged sulfonamide level in blood in view of its excellent absorption and low toxicity. The other 3 - sulfanilamido - 4 - halogeno - 5 - alkylisoxazoles of formula (I) also have similar properties.

The 3 - sulfanilamido - 4 - halogeno - 5 - alkylisoxazoles of the present invention can be prepared and administered to living bodies such as animals and human beings in a wide variety of oral and parenteral dosage forms, singly or in a mixture with other coacting compounds. They can be associated with a carrier which can be a solid material or liquid, in which the sulfonamides are dissolved, dispersed or suspended. The solid composition can take the form of tablets, powders, capsules or the like, preferably in unit dosage forms for simple administration or precise dosages. Prior to the preparation, some changes may be made to the sulfonamides, the changes being obvious to those skilled in the art. In a *per se* conventional manner, for instance, the sulfonamides may be converted to the alkali metal salts thereof, which are suitable for liquid preparations such as those used for injection. However, the administration of these derivatives to living bodies for the production of high and prolonged sulfonamide level in blood should be within the scope of the present invention, because it is substantially equivalent to the administration of the sulfonamides *per se*.

The following examples represent specific embodiments of the present invention. The abbreviations used in these examples are intended to have the following means: g, gram(s); ml, millilitre(s); and °C., degrees centigrade.

EXAMPLE 1.

3 - Sulfanilamido - 4 - chloro - 5 - methylisoxazole.:— To a solution of 3-amino - 4 - chloro - 5 - methylisoxazole (6 g) in a mixture of pyridine (4 ml) and benzene (20 ml), there is added *p*-acetylaminobenzenesulfonyl chloride (11 g), and the resultant mixture is stirred for 2 hours at 50°C. After cooling, the benzene layer is removed by decantation. To the residue, there is added water and stirred to gradually precipitate crystals. The crystals are collected by filtration and heated with 10% sodium hydroxide solution (40 ml) on a water bath for 1 hour. After cooling, the reaction mixture is acidified with hydrochloric acid. The precipitated crystals are collected by filtration and recrystallized from ethanol to give 3 - sulfanilamido - 4 - chloro - 5-methylisoxazole (4.4 g) as colorless prisms melting at 182 to 184°C. By repetition of the recrystallization, there are obtained pure crystals melting at 187 to 188°C.

Anal. Calcd. for $C_{10}H_{10}O_3N_3SCl$: C, 41.81; H, 3.49; N, 14.63; Found: C, 42.02; H, 3.57; N, 14.60.

EXAMPLE 2.

3 - Sulfanilamido - 4 - bromo - 5 - methylisoxazole.:— To a solution of 3-amino - 4 - bromo - 5 - methylisoxazole (20 g) in a mixture of pyridine (15 ml) and benzene (100 ml), there is added *p*-acetylaminobenzenesulfonyl chloride (25 g), and the resultant mixture is stirred for 2 hours at 50°C. The precipitated crystals are collected by filtration and hydrolysed with 10% sodium hydroxide solution (100 ml) while heating on a water bath. The precipitated crystals are collected by filtration and recrystallized from ethanol to give 3 - sulfanilamido - 4 - bromo - 5 - methylisoxazole (9.5 g) as colorless needles melting at 183°C. to 184°C.

Anal. Calcd. for $C_{10}H_{10}O_3N_3SBr$: C, 36.11; H, 3.00; N, 12.34. Found: C, 36.37; H, 2.92; N, 12.38.

EXAMPLE 3.

3 - Sulfanilamido - 4 - iodo - 5 - methylisoxazole.:— To a solution of 3-amino - 4 - iodo - 5 - methylisoxazole (2.2 g) in a mixture of pyridine (1.5 ml) and benzene (20 ml), there is added *p*-acetylaminobenzenesulfonyl chloride (2.5 g), and the resultant mixture is stirred for 2 hours at 50°C. The precipitated crystals are collected by filtration and hydrolyzed with 10% sodium hydroxide solution (10 ml) while heating on a water bath. The precipitated crystals are collected by filtration and recrystallized from ethanol to give 3 - sulfanilamido - 4 - iodo - 5 - methylisoxazole (1 g) as colorless needles melting at 201°C. to 202°C. (decomp.). By repetition of the recrystallization, there are obtained pure crystals melting at 209°C. to 210°C. (decomp.).

Anal. Calcd. for $C_{10}H_{10}O_3N_3SI$: C, 31.66; H, 2.64; N, 11.11. Found: C, 32.16; H, 2.72; N, 10.71.

While the foregoing examples are directed to simplest and presently-preferred specific embodiments, more complex embodiments wherein the moiety corresponding to

R is a lower alkyl higher than methyl may mutatis mutandis be similarly prepared and used.

WHAT WE CLAIM IS:—

1. 3 - Sulfanilamido - 4 - chloro - 5 - alkylisoxazole of which the alkyl group has 1 to 5 carbon atoms.

2. 3 - Sulfanilamido - 4 - bromo - 5 - alkylisoxazole of which the alkyl group has 1 to 5 carbon atoms.

3. 3 - Sulfanilamido - 4 - iodo - 5 - alkylisoxazole of which the alkyl group has 1 to 5 carbon atoms.

4. 3-Sulfanilamido-4-iodo-5-methylisoxazole.

5. 3-Sulfanilamido-4-chloro-5-methylisoxazole.

6. 3-Sulfanilamido-4-bromo-5-methylisoxazole.

7. 3-Sulfanilamido-4-chloro-5-ethylisoxazole.

8. 3-Sulfanilamido-4-bromo-5-ethylisoxazole.

9. 3-Sulfanilamido-4-iodo-5-ethylisoxazole.

10. 3-Sulfanilamido-4-chloro-5-*n*-propylisoxazole.

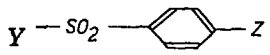
11. 3-Sulfanilamido-4-bromo-5-*iso*-propylisoxazole.

12. 3-Sulfanilamido-4-iodo-5-*n*-propylisoxazole.

13. 3-Sulfanilamido-4-bromo-5-*n*-butylisoxazole.

14. 3-Sulfanilamido-4-iodo-5-*n*-butylisoxazole.

15. A process for preparing an antibacterially active 3 - sulfanilamido - 4-halogeno - 5 - alkylisoxazole which comprises condensing 3 - amino - 4 - halogeno - 5-alkylisoxazole with a *p*-substituted benzenesulfonic acid derivative represented by the formula:



wherein Y is a chlorine, bromine or iodine atom, a hydroxyl group or an alkoxy, aryloxy or aralkoxy group and Z is a group convertible to amino by hydrolysis or reduction such as acylamino, nitro and azo, followed by the conversion of the *p*-substituent on the benzene ring of the resulting compound into an amino group.

16. A process as claimed in claim 15 for preparing 3 - sulfanilamido - 4 - chloro-5 - alkylisoxazole of which the alkyl group has from 1 to 5 carbon atoms, comprising condensing 3 - amino - 4 - chloro - 5 - alkylisoxazole.

17. A process as claimed in claim 15 for preparing 3 - sulfanilamido - 4 - bromo-5 - alkylisoxazole of which the alkyl group has from 1 to 5 carbon atoms, comprising condensing 3 - amino - 4 - bromo - 5 - alkylisoxazole.

18. A process as claimed in claim 15 for preparing 3 - sulfanilamido - 4 - iodo-5 - alkylisoxazole of which the alkyl group has from 1 to 5 carbon atoms, comprising condensing 3 - amino - 4 - iodo - 5 - alkylisoxazole.

19. A process as claimed in claim 15 for preparing 3 - sulfanilamido - 4 - iodo-5 - methylisoxazole comprising condensing 3 - amino - 4 - iodo - 5 - methylisoxazole.

20. A process for preparing 3 - sulfanilamido - 4 - halogeno - 5 - alkylisoxazoles, substantially as described herein, with reference to the foregoing Examples.

21. 3 - Sulfanilamido - 4 - halogeno - 5 - alkylisoxazoles when prepared by the process of any of claims 15 to 20.

22. Antibacterially active compositions comprising a pharmaceutically acceptable carrier and one or more compounds as claimed in any of claims 1 to 14 or 21.

23. A process for producing a prolonged sulfonamide level in the blood of animals other than human beings comprising administering one or more of the compounds claimed in any one of claims 1 to 14 or 21.

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R is a lower alkyl higher than methyl may mutatis mutandis be similarly prepared and used.

WHAT WE CLAIM IS:—

1. 3 - Sulfanilamido - 4 - chloro - 5 - alkylisoxazole of which the alkyl group has 1 to 5 carbon atoms.

2. 3 - Sulfanilamido - 4 - bromo - 5 - alkylisoxazole of which the alkyl group has 1 to 5 carbon atoms.

3. 3 - Sulfanilamido - 4 - iodo - 5 - alkylisoxazole of which the alkyl group has 1 to 5 carbon atoms.

4. 3-Sulfanilamido-4-iodo-5-methylisoxazole.

5. 3-Sulfanilamido-4-chloro-5-methylisoxazole.

6. 3-Sulfanilamido-4-bromo-5-methylisoxazole.

7. 3-Sulfanilamido-4-chloro-5-ethylisoxazole.

8. 3-Sulfanilamido-4-bromo-5-ethylisoxazole.

9. 3-Sulfanilamido-4-iodo-5-ethylisoxazole.

10. 3-Sulfanilamido-4-chloro-5-*n*-propylisoxazole.

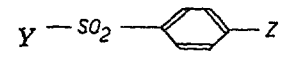
11. 3-Sulfanilamido-4-bromo-5-*iso*-propylisoxazole.

12. 3-Sulfanilamido-4-iodo-5-*n*-propylisoxazole.

13. 3-Sulfanilamido-4-bromo-5-*n*-butylisoxazole.

14. 3-Sulfanilamido-4-iodo-5-*n*-butylisoxazole.

15. A process for preparing an antibacterially active 3 - sulfanilamido - 4-halogeno - 5 - alkylisoxazole which comprises condensing 3 - amino - 4 - halogeno - 5-alkylisoxazole with a *p*-substituted benzenesulfonic acid derivative represented by the formula:



wherein Y is a chlorine, bromine or iodine atom, a hydroxyl group or an alkoxy, aryloxy or aralkoxy group and Z is a group convertible to amino by hydrolysis or reduction such as acylamino, nitro and azo, followed by the conversion of the *p*-substituent on the benzene ring of the resulting compound into an amino group.

16. A process as claimed in claim 15 for preparing 3 - sulfanilamido - 4 - chloro-5 - alkylisoxazole of which the alkyl group has from 1 to 5 carbon atoms, comprising condensing 3 - amino - 4 - chloro - 5 - alkylisoxazole.

17. A process as claimed in claim 15 for preparing 3 - sulfanilamido - 4 - bromo-5 - alkylisoxazole of which the alkyl group has from 1 to 5 carbon atoms, comprising condensing 3 - amino - 4 - bromo - 5 - alkylisoxazole.

18. A process as claimed in claim 15 for preparing 3 - sulfanilamido - 4 - iodo-5 - alkylisoxazole of which the alkyl group has from 1 to 5 carbon atoms, comprising condensing 3 - amino - 4 - iodo - 5 - alkylisoxazole.

19. A process as claimed in claim 15 for preparing 3 - sulfanilamido - 4 - iodo-5 - methylisoxazole comprising condensing 3 - amino - 4 - iodo - 5 - methylisoxazole.

20. A process for preparing 3 - sulfanilamido - 4 - halogeno - 5 - alkylisoxazoles, substantially as described herein, with reference to the foregoing Examples.

21. 3 - Sulfanilamido - 4 - halogeno - 5 - alkylisoxazoles when prepared by the process of any of claims 15 to 20.

22. Antibacterially active compositions comprising a pharmaceutically acceptable carrier and one or more compounds as claimed in any of claims 1 to 14 or 21.

23. A process for producing a prolonged sulfonamide level in the blood of animals other than human beings comprising administering one or more of the compounds claimed in any one of claims 1 to 14 or 21.

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