# PATENT SPECIFICATION

814,276

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**Index at acceptance:—Class 2(3),** C2A(3:6), C2D43(B:D:H:S4), C2R15.
**International Classification:—C07d.**

COMPLETE SPECIFICATION

## 3-Sulphanilamido-5-Methylisoxazole and a process for its preparation

We, SHIONOGI & CO. LTD., of 12 3-chome, Doshomachi, Osaka, Japan, a Japanese Body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a new sulphonamide compound, i.e. 3 - sulphanilamido - 5-methylisoxazole and to the method for its preparation.

5 - sulphanilamido isoxazoles and methods for the preparation thereof are known (c.f. British Patent Specification No. 595,775). However, the synthesis of 3 - sulphanilamido isoxazoles in which the sulphanilamido residue is bonded to the third position at the nucleus of isoxazole has not to our knowledge heretofore been reported in any literature.

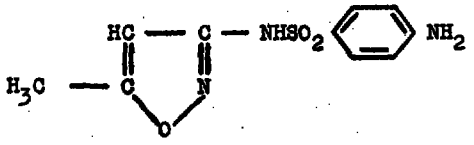
The object of the present invention is to obtain one of these new 3 - sulphanilamido isoxazoles, namely, 3 - sulphanilamido - 5-methylisoxazole, and to provide it for medicinal use as a new sulpha drug.

During a systematic search for the synthesis of new sulphonamide compounds structurally related to sulphisoxazole and to the evaluation of their anti-bacterial activity, we succeeded in synthesizing 3 - sulphanilamido - 5 - methylisoxazole and found that this new compound showed a high activity in both the *in vitro* and *in vivo* tests. That is, the anti-bacterial activity of the compound *in vitro* is similar to that of sulphisoxazole, but the anti-tuberculous activity *in vitro* of the new compound is higher than sulphisoxazole. The *in vitro* data compared with sulphisoxazole is as follows:

| Test organisms | 3-sulphanilamido 5-methylisoxazole (mol) | sulphisoxazole (mol) |
|---|---|---|
| Shigella dysenteriae (Shiga) | 1:500,000 | 1:500,000 |
| „ flexneri Variant Y | „ | „ |
| „ „ 2, 2a | „ | „ |
| „ „ 3, 3a | „ | „ |
| „ sonnei | 1:200,000 | 1:200,000 |
| „ flexneri 4, 4a | 1:500,000 | 1:500,000 |
| S. parathyphi A | 1:200,000 | 1:200,000 |
| „ B | „ | „ |
| „ C | „ | „ |
| S. typhi murium | „ | „ |
| Esch. coli communis | 1:200,000 | 1:200,000 |
| Pseudomonas aeruginosa | > 10,000 | × 10,000 |
| Kleb. pneumoniae | 1:200,000 | 1:100,000 |
| B. subtilis, PCI 219 | 1:200,000 | 1,100,000 |
| Staphylococcus aureus 209P | 1: 50,000 | 1:100,000 |
| „ „ Terashima | 1: 20,000 | 1: 20,000 |
| Mycobac, tuberculosis H37RV | 1: 10,000 | 1: 2,000 |

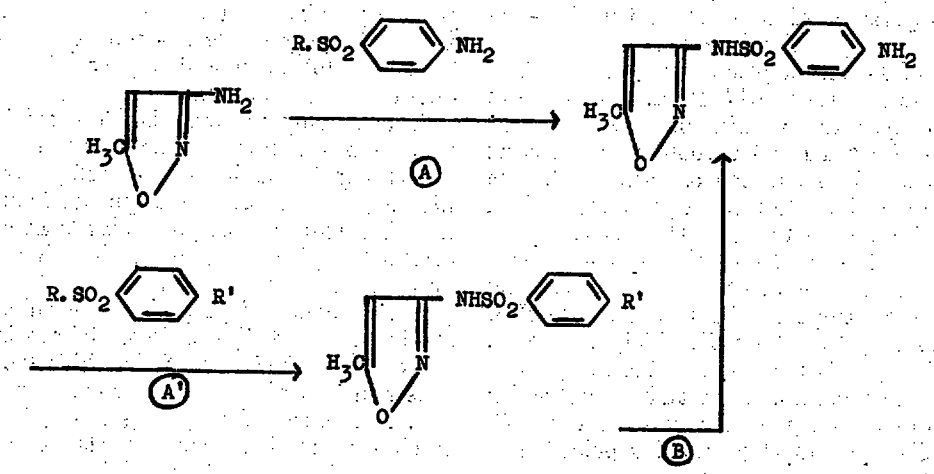
However, *in vivo* test, a clear difference could be seen with both compounds. Namely, by administering orally the compound of the invention to groups consisting of ten mice weighing each 17 to 18 g. at 2, 24, 48, 72 and 96 hours respectively after intraperitoneal injection of 100 MLD of Diplococcus pneumoniae, type 1, 80 and 10 survival percentages by the dose of 1 and 0.5 mg. per gram of body weight were observed, while the known sulphisoxazole only gave 50 and 0 per cent by the dose of 2 and 1 mg. in analogous experiments. The infections were fatal to all untreated animals, the ST 100 being two days. In this experiment, by oral administration the compound of the invention was shown to be more than twice as effective as sulphisoxazole.

3 - Sulphanilamido - 5 - methylisoxazole has the following formula:



This compound may be synthesized by condensing 3 - amino - 5 - methylisoxazole with a *p* - substituted benzene sulphonyl halide or ester in which the *p* - substituent is an amino group or a group convertible to an amino group by reduction or hydrolysis and changing, when the *p* - substituent is not an amino group, the *p* - substituent of the benzene sulphonamide derivatives thus produced into an amino group. These reactions are illustrated by the following equations:

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wherein

R = an alkoxy group or a halogen atom.

$R^1$ = a group changeable to an amino group.

In the above reaction, the condensation steps A and $A^1$ may be carried out without solvents, however, the employment of an inert solvent whereby the uniformity of reaction may be attained generally, gives a good result.

In the present process, the kind of solvent used is decided by the non-reactivity thereof, however, when *p*-substituted benzene sulphonyl halides are condensed with 3 - amino - 5-methylisoxazole, basic or basified solvents such as pyridine, picoline or acetone with sodium bicarbonate are preferably used. Also, as the easily reactive derivatives of p-substituted benzene sulphonic acids, *p* - substituted benzene sulphonyl halides, especially the chlorides, are ordinarily used. However, other functional derivatives of benzene sulphonic acids such as the ester may also be employed. Step B succeeds step $A^1$ in which 5 - methyl - 3 - benzene sulphonamido isoxazole, having a substituent changeable to an amino group at the fourth position of the benzene nucleus, is produced. It is meant to include a nitro, acylamino or carbalkoxyamino group as the substituent at the 4-position of the reactive benzene sulphonic acid derivatives. The type of reaction in step B is defined according to the kind of substituent $R^1$. Namely, when $R^1$ is an acylamino radical such as an acetamino group or a carbalkoxyamino radical such as a carbethoxy amino group, the intermediate should be saponified, while when $R^1$ is a nitro group, the intermediate should be reduced. Such reactions may be performed according to the usual chemical manner, such as for example, heating with aqueous sodium hydroxide solution for the hydrolysis or treating with zinc dust and hydrochloric acid for the reduction.

3 - Amino - 5 - methylisoxazole, the starting material in the present invention, is also a new compound. This compound is obtained by hydrolysis of ethyl 5 - methylisoxazole-3-carbamate succeeding to the Curtius' degradation of 5 - methylisoxazole - 3 - carboxylic acid according to Freri's method (c.f. C.A. *26*, 5953(1932)) and forms prismatic crystals melting at 61—2° C.

EXAMPLE.

(a) Preparation of 3 - amino - 5 - methylisoxazole.

1.7 g. of ethyl 5 - methylisoxazole - 3 - carbamate was heated on a boiling water-bath with 5 cc. of a 10% aqueous sodium hydroxide solution for 8 hours, then the reaction mixture was extracted several times with ether or benzene and the extract was cooled after the removal of the solvent and drying. The residue was solidified after a while and gave prismatic crystals, melting point 61 to 62° C., of 3 - amino - 5 - methylisoxazole by recrystallization from benzene.

Elemental analysis for empirical formula $C_4H_6ON_2$. Calculated: C, 48.97; H, 6.16; N, 28.57. Found: C, 49.42; H, 6.50; N, 28.28.

This substance is a new compound and is also obtained by a similar hydrolysis of benzyl 5 - methylisoxazole - 3 - carbamate, melting point 80—81° C.

(b) Preparation of 3 - acetylsulphanilamido-5 - methylisoxazole.

0.9 g. of 3 - amino - 5 - methylisoxazole in 5 cc. of pyridine was allowed to react with ~~2.00~~ 2.09 g. of acetylsulphanilyl chloride accompanied with the generation of heat. After about one hour, water was added to the reaction mixture and the crystal precipitated out was recrystallized from alcohol to give 2.5 g. of 3 - acetylsulphanilamido - 5 - methylisoxazole, melting point (decomposition) 220—221° C.

Elemental analysis for empirical formula $C_{12}H_{13}O_4N_3S$. Calculated: C, 48.81; H, 4.40; N, 14.33. Found: C, 49.08; H, 4.63; N, 14.05.

A similar result was obtained by the condensation in a sodium bicarbonate - acetone medium.

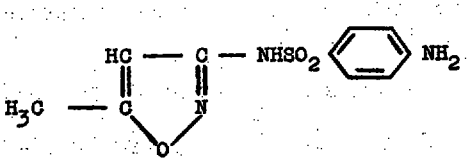
(c) Preparation of 3 - sulphanilamido - 5-methylisoxazole.

2 g. of 3 -acetylsulphanilamido - 5 - methylisoxazole was heated with 10 cc. of an aqueous sodium hydroxide solution on a water - bath for one hour and after cooling the reactant was acidified by addition of acetic acid. The precipitate thus formed was recrystallized from dilute alcohol to give 15 g. of colourless prisms of 3 - sulphanilamido - 5 - methylisoxazole, melting point 167° C. Elemental analysis for empirical formula $C_{10}H_{11}O_3N_3S$. Calculated: C, 47.43; H, 4.35; N, 16.60. Found: C, 47.96; H, 4.49; N, 16.52.

This compound is bitter and by acetylation in pyridine base gives the corresponding $N^1$, $N^4$ - diacetyl compound, melting point 209—210° C.

WHAT WE CLAIM IS:—

1. 3 - Sulphanilamido - 5 - methylisoxazole having the formula



2. A method of preparing 3 - sulphanilamido - 5 - methylisoxazole which comprises condensing 3 - amino - 5 - methylisoxazole with a *para* - amino - benzene sulphonyl halide or ester.

3. A method of preparing 3 - sulphanilamido - 5 - methylisoxazole which comprises condensing 3 - amino - 5 - methylisoxazole with a *para* - substituted benzene sulphonyl halide or ester in which the *para*-substituent is a group convertible to an amino group by reduction or hydrolysis and changing the *para*-substituent of the benzene sulphonamide derivative thus produced into an amino group.

4. A method of preparing 3 - sulphanilamido - 5 - methylisoxazole which comprises condensing 3 - amino - 5 - methylisoxazole with a *para* - substituted benzene sulphonyl halide or ester in which the *para*-substituent is an acylamino or a carbalkoxyamino group and saponifying the *para* - substituent of the benzene sulphonamide derivative thus produced to an amino group.

5. A method of preparing 3 - sulphanilamido - 5 - methylisoxazole which comprises condensing 3 - amino - 5 - methylisoxazole with a *para*-nitrobenzene sulphonyl halide or ester and reducing the *para*-substituent of the benzene sulphonamide derivative thus produced to an amino group.

6. A method of preparing 3 - sulphanilamido - 5 - methylisoxazole as claimed in any one of claims 2, 3, 4 or 5, in which the condensation is carried out in an inert solvent.

7. A method of preparing 3 - sulphanilamido - 5 - methylisoxazole as claimed in any one of claims 2, 3, 4 or 5 wherein a *para*-substituted benzene sulphonyl halide is condensed with 3 - amino - 5 - methylisoxazole.

8. A method of preparing 3 - sulphanilamido - 5 - methylisoxazole as claimed in claim 7, wherein the *para* - substituted benzene sulphonyl halide is a *para* - substituted benzene sulphonyl chloride.

9. A method of preparing 3 - sulphanilamido - 5 - methylisoxazole as claimed in any one of claims 2, 3, 4 or 5, wherein a *para*-substituted benzene sulphonyl ester is condensed with 3 - amino - 5 - methylisoxazole.

10. A method of preparing 3 - sulphanilamido - 5 - methylisoxazole according to any one of claims 2, 3, 4 or 5, in which the condensation is carried out in a solvent comprising pyridine, picoline or acetone with sodium bicarbonate.

11. A method of preparing 3 - sulphanilamido - 5 - methylisoxazole substantially as described with reference to the Example hereinbefore set forth.

12. 3 - Sulphanilamido - 5 - methylisoxazole whenever prepared by the method claimed in claim 11.

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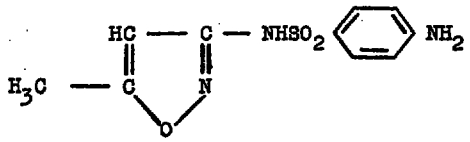
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9. A method of preparing 3 - sulphanilamido - 5 - methylisoxazole as claimed in any one of claims 2, 3, 4 or 5, wherein a *para*-substituted benzene sulphonyl ester is condensed with 3 - amino - 5 - methylisoxazole.

10. A method of preparing 3 - sulphanilamido - 5 - methylisoxazole according to any one of claims 2, 3, 4 or 5, in which the condensation is carried out in a solvent comprising pyridine, picoline or acetone with sodium bicarbonate.

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