

UNITED STATES PATENT OFFICE

2,430,094

ISOXAZOLE DERIVATIVES OF SULFANILAMIDE

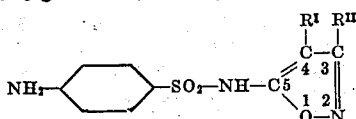
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Our invention relates to new isoxazole derivatives, and to processes for manufacturing them. These derivatives are the 5-sulfanilamido-isoxazoles of the general formula



wherein R^I and R^{II} are lower alkyl and/or lower alkoxy alkyl groups.

As is well known, hundreds of sulfanilamides have been synthesized, investigated and described in the literature. Only a few of them have their well established place in therapy and all hitherto known sulfa drugs have marked disadvantages.

One disadvantage of these known sulfanilamides is that they are weak acids and form sodium salts which in aqueous solution react strongly alkaline, having pH ranges from 9-11 (New and Nonofficial Remedies 1943, p. 187; Feinstein et al., C. A. 1941 1509; Ellingson, J. A. C. S. 1941, 2524). The strongly alkaline solutions cannot be sterilized by boiling or autoclaving as they are unstable under such conditions (see N. N. R. 1943, p. 187/189). They can only be injected intravenously and not intramuscularly, as they are highly irritating to the tissues; even on intravenous injection they tend to produce thrombosis of the veins.

Another disadvantage of the sulfa drugs is their insolubility or very slight solubility in aqueous solutions at the pH of the body fluids, especially of urine with pH 5.5-7. Their precipitation in the kidneys in form of crystals (consisting of the sulfa drugs themselves or their N⁴-acetyl derivatives) causes much trouble and can lead to the most severe consequences; the medical literature quotes many cases of renal calculus formation, impairment of urinary excretion, fatal toxemia and uremia.

With the object in view of overcoming these serious disadvantages of known sulfa compounds, we have made the surprising discovery that the compounds illustrated by the general formula shown above in which a disubstituted isoxazole ring is attached to the N¹-position of sulfanilamide possess relatively high acidity which is strong enough to enable these compounds to form water-soluble salts with bases, which salts possess neutral or nearly neutral reaction. Owing to this outstanding physico-chemical property and in contrast to all known sulfa compounds, the salts are therapeutical agents of greatly improved

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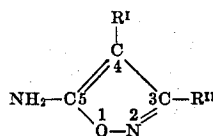
characteristics and can be injected without irritation, as we shall demonstrate further below.

Sulfanilamide derivatives with the isoxazole ring attached in N¹-position of the sulfanilamide molecule have already been described in literature. These compounds are different from those of the present invention, as they are substituted by the sulfanilamide radical in 4-position of the isoxazole ring; nothing has been reported on their chemotherapeutic properties or their therapeutic value. (Carlo Musante, Gazz. Chim. Ital. 71, 565, 1941.)

Also, one sulfanilyl derivative of 5-amino-isoxazole is known, namely, 5-sulfanilamido-3-methyl-isoxazole. This compound was first described by Backer and de Jonge (Rec. Trav. Chim. 61, 465, 1942) without any details on its chemotherapeutic activity. Later, Anderson, Faith, Marson, Winnek and Roblin (J. A. C. S. 64, 2903, 1942) synthesized the same compound and found some degree of bacteriostatic activity, but very little effect on experimental animal infections. Experiments made in our laboratories have confirmed these negative results.

We have discovered that the picture changes completely when both the 3- and 4- positions of the isoxazole ring of these sulfanilamide derivatives are replaced by an alkyl and/or corresponding alkoxy alkyl radical so that compounds of the above mentioned structural formula are obtained. These disubstituted derivatives have exhibited a high activity against experimental animal infections. Broad series of experiments have shown that their curative effect on mice infected with hemolytic streptococci, pneumococci type 1, 2 and 3, meningococci and staphylococci is comparable to the best sulfa drugs and surpasses them in some cases, especially with respect to meningococci and pneumococci. Their acute and chronic toxicity is very low; daily injections in rabbits with 1.0 g./kg. for four weeks and chronic feeding of rats with normal diet containing 2% of 5-sulfanilamido-3, 4-dimethyl-isoxazole for 8 weeks caused no significant change in blood picture, kidneys, liver and gastric mucosa, whereas the animals continued to gain weight.

The new compounds can be prepared by the condensation of a 5-amino-isoxazole derivative of the general formula



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wherein R^I and R^{II} stand for a lower alkyl group, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl and tert. butyl, and/or an alkoxy-substituted lower alkyl group such as methoxy-, ethoxy-, propoxy-, methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tertiary butyl radical with p-acetyl-amino-benzene-sulfonylchloride and splitting off the acetyl group from the thus obtained acetamino-benzene-sulfonylamino-isoxazole derivative, by a saponification process.

Instead of p-acetylamino-benzene-sulfonylchloride, p-nitrobenzene-sulfonylchloride can be used for the condensation; in this case the resulting nitro compounds have to be reduced to the corresponding amino compounds in the usual way.

The water-soluble salts of our new compounds to which we have referred above and which have a neutral or nearly neutral reaction are those selected from the group consisting of the alkali metal, alkaline-earth metal and strong organic base salts. Sodium hydroxide, carbonate or bicarbonate can be used to form the sodium salt, and the free compounds can be titrated as monobasic acids with n-alkali in 50% alcohol. Ampul solutions for injections can easily be obtained from the alkali metal salts of our new compounds having a pH from 7.2-7.4; these solutions are stable and can be sterilized by boiling or autoclaving without decomposition. They do not show any irritation when given subcutaneously or intradermally (back and ear of the rabbit) even in concentrations of 10% and higher.

Renal complications due to precipitation of sulfa drugs or their acetyl derivatives depend on the solubility in urine at different pH. Gilligan and Plummer have shown these solubilities for 3 sulfa drugs with the pyrimidine nucleus (sulfadiazine, sulfamerazine and sulfamethazine, Proc. Soc. Exp. Biol. Med. 53, 142, 1943). It is obvious that only the solubilities at pH under 7 are relevant as urine is in most cases acid. We have determined the solubility of a characteristic member of our new compounds at various pH and compared with the curves of Gilligan and Plummer. The superiority of 5-sulfanilamido-3,4-dimethyl-isoxazole over the pyrimidine compounds is exhibited in a very drastic manner: the solubility at pH 5-7 is so high that neither the compound itself nor its acetyl derivative will be deposited in the kidneys.

The following examples illustrate our invention:

Example 1

112 parts of 3,4-dimethyl-5-amino-isoxazole were dissolved in a mixture of 100 vol. parts of pyridine and 100 vol. parts of acetone. The mixture is cooled with cold water and 240 parts p-acetamino-benzene sulfonic acid chloride are added in small portions under stirring at temperatures of below 30°. The mixture is left standing overnight at 20-30° and then the 5-acetamino-benzene-sulfonylamino-3,4-dimethyl-isoxazole is precipitated by the addition of water. Recrystallized from acetic acid or alcohol it forms small prisms of the melting point 210°.

$C_{13}H_{15}N_3O_4S$; calc.: C=50.5, H=4.85, N=13.6, equ. w.=309; found: C=50.33, H=4.87, N=13.22, equ. w.=309.

100 parts of the 5-acetamino-benzene-sulfonylamino-3,4-dimethyl-isoxazole are boiled under reflux with 500 vol. parts 15-20% aqueous hydrochloric acid for 30-45 minutes until all is dissolved. 500 parts crystallized sodium acetate are added

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and the liquid left cooling for crystallization. The sulfanilamido-3,4-dimethyl-isoxazole is sucked off, washed with water and dried. In the pure state it forms white prisms with the melting point of 193°.

Analysis: Calcd. for $C_{11}H_{13}N_3O_3S$: C=49.4, H=4.90, N=15.7, equiv. w.=267; found: C=49.54, H=5.00, N=15.72, equiv. w.=267.

Also, instead of the hydrochloric acid alkaline saponifying reagents can be used. 100 parts of acetamino-benzene-sulfonylamino-3,4-dimethyl-isoxazole are heated with 500 vol. parts 3N-sodium hydroxide solution on a steam bath for one hour. The solution furnished the 5-sulfanilamido-3,4-dimethyl-isoxazole when acidified with acetic acid in very good yield.

The 3,4-dimethyl-5-amino-isoxazole used as a starting material is prepared by reacting aceto-propionitrile with a hydroxylamine salt under simultaneous neutralization of the acid, liberated during the reaction in hot aqueous, not too diluted, solution. It crystallizes in beautiful white prisms from water and shows a M. P. of 125°.

Example 2

224 parts 5-amino-3,4-dimethyl-isoxazole are dissolved in a mixture of 160 vol. parts pyridine plus 160 vol. parts acetone and 370 parts p-nitrobenzene-5-sulfonylchloride are gradually added under cooling. After having stood at room temperature for 10 hours water is added. An oil is precipitated which soon solidifies by crystallization. The crystals are sucked off and washed with water. The crude p-nitrobenzene-5-sulfonylamino-3,4-dimethyl isoxazole contains some bis-p-nitrobenzene-sulfonylamino-dimethyl isoxazole (M. P. 207°) and can be separated from the latter by its solubility in alkali. The pure p-nitrobenzene-sulfonylamino-dimethyl isoxazole can be crystallized from diluted alcohol and melts at 164°.

40 parts of the p-nitrobenzene-sulfonylamino-dimethyl isoxazole are suspended in 200 vol. parts alcohol and 150 vol. parts concentrated hydrochloric acid and heated to 60-70°. 40 parts zinc dust are gradually added under stirring. When the vigorous reaction has ceased the mixture is still kept boiling under reflux for 30 minutes and then filtered from some undissolved zinc dust. 200 vol. parts water and 100 parts crystallized sodium acetate are added. The p-amino benzenesulfonyl-5-amino-3,4-dimethyl isoxazole soon crystallizes and can be sucked off. It is identical with the product obtained in Example 1.

Example 3

126 parts of 3-ethyl-4-methyl-5-amino-isoxazole (J. Pract. Chem. 47, 128 (1893)) are converted to 5-p-acetamino-benzene-sulfonylamino-3-ethyl-4-methyl isoxazole in analogy to Example 1. The compound forms white prisms of the M. P. 169°.

Analysis: Calcd. for $C_{14}H_{17}N_3O_4S$: C=52.0, H=5.3, N=13.0; found: C=52.19, H=5.45.

The saponification may be carried out with 18% hydrochloric acid or 3 N-sodiumhydroxide solution in analogy to Example 1. It furnishes the 5-sulfanilamido-3-ethyl-4-methyl-isoxazole which melts at 127°.

Analysis: Calcd. for $C_{12}H_{15}N_3O_3S$: C=51.2, H=5.43, N=14.95; found: C=51.28, H=5.42.

Example 4

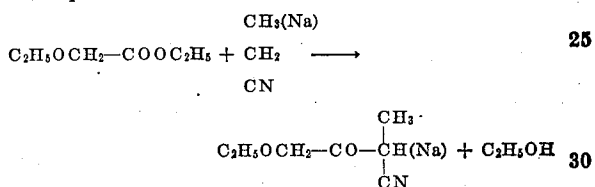
156 parts 3-ethoxymethyl-4-methyl-5-amino-isoxazole are converted to the corresponding

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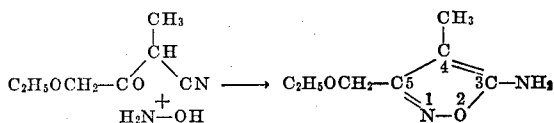
acetyl-sulfanilamid with 240 parts p-acetaminobenzene-sulfonic acid chloride in pyridine, acetone and the latter is saponified in analogy to Example 1. The 5-sulfanilamido-3-ethoxymethyl-4-methyl-isoxazole thus obtained has a M. P. of 127°.

Analysis: Calcd. for $C_{13}H_{17}O_4N_3S$: C=50.2, H=5.46, N=13.5; found: C=49.95, H=5.27.

The 3-ethoxymethyl-4-methyl-5-amino isoxazole can be prepared in the following way: A mixture of 70 parts ethoxyethylacetate and 35 parts propionitrile are gradually added to a suspension of 11 parts sodium in 100 vol. parts benzene or ether. The sodium gradually goes in solution under evolution of hydrogen. The vessel is cooled with ice-water from the outside and a reflux condenser is used on the top of the vessel. The reaction is usually terminated after 5-6 hours when all sodium has dissolved. Water is carefully added, shaken, and the aqueous layer removed. It contains the sodium compound of ethoxyacetyl-propionitrile formed according to the equation:



The solution is acidified with acetic acid, the oil which separates is taken up in ether, the ether layer is washed with water and the ether is then distilled off, finally in a vacuum. The residue forms a slight brown oil and is pure enough for the formation of the 3-ethoxy-methyl-4-methyl-5-amino-isoxazole according to the equation:



30 parts of the crude ethoxyacetyl-propionitrile are heated with 18 parts hydroxylamine-hydrochloride in a mixture of 20 vol. parts alcohol and 5 vol. parts water under addition of 25 parts potassium acetate for 30 minutes at 80° under reflux. The reaction mixture is left to cool off and then extracted with ethyl acetate. The extract is dried over sodium sulfate and the ethylacetate distilled off. The residue crystallizes after cooling and can be recrystallized from water. The 3-ethoxymethyl-4-methyl-5-amino-isoxazole thus obtained forms white prisms or plates and melts at 69-70°.

Analysis: Calcd. for $C_7H_{12}O_2N_2$: C=53.8, H=7.7, N=17.95; found: C=53.98, H=7.61.

Example 5

267 parts 5-(p-amino-benzene-sulfonyl)-amino-3,4-dimethyl isoxazole (Examples 1 and 2) are heated with 330 vol. 3 N-sodiumhydroxide under stirring until all is dissolved. When chilled the sodium salt of the sulfanilamide crystallizes in beautiful inch-long prisms which contain 5 mol water of crystallization.

The solubility of the sodium compound in hot water is very high. At 37° it is 16%, at 25° it is 7.4%, calculated on the basis of water-free substance.

Example 6

In a similar way, the lithium salt of 5-(p-amino-benzene-sulfonyl)-amino-3,4-dimethyl-isoxazole

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can be prepared. It dissolves even at 0° to more than 20% in water. It crystallizes in large prisms which contain four mol water of crystallization and its solubility in water is over 20% at 0-5°.

Example 7

If the sodium salt of Example 5 is dissolved in water and the aqueous solution shaken with an excess of 5-sulfanilamido-3,4-dimethyl-isoxazole, the pH of the solution changes from a little above pH 8 to pH 7.2. The solution is filtered and can be sterilized at 100° without changing the properties.

In a similar way, a solution of the lithium salt of pH 7.2 to 7.4 can be prepared. Stable solutions which contain 20% or more of the sulfanilamide can also be prepared. Similar solutions with a pH varying from 7-7.5 can be obtained from the preparations of Examples 3 and 4.

Example 8

If an aqueous suspension of 5-sulfanilamido-3,4-dimethyl-isoxazole is heated with an excess of calcium carbonate and then filtered, a stable solution containing the calcium salt of the sulfanilamide is obtained. It has similar properties of Example 7 solutions. Instead of the calcium carbonate, magnesium carbonate gives a stable solution containing the magnesium salt of the sulfanilamide. Similar solutions are obtainable from the preparations of Examples 3 and 4.

Example 9

If an aqueous suspension of 5-sulfanilamido-3,4-dimethyl isoxazole is treated with diethanolamine to a pH of 7.2 to 7.4, the compound dissolves and furnishes a stable solution containing the diethanolamine salt of the sulfanilamide.

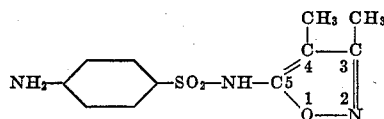
High concentrated stable solutions of the sulfanilamide showing a pH of 7.2 to 7.4 thus can be prepared. Similar solutions result if, instead of diethanolamine, other organic bases such as ethanolamine, ethylenediamine are used.

If instead of the 5-sulfanilamido-3,4-dimethyl isoxazole the sulfanilamides from Examples 3 and 4 are used, solutions of the respective sulfanilamides showing analogy to the properties of the 5-sulfanilamido-3,4-dimethyl isoxazole are obtained.

What we claim is:

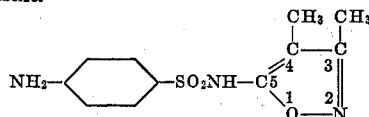
1. A compound selected from the group consisting of 5-sulfanilamido-3,4-dimethyl-isoxazole, 5-sulfanilamido-3-oxymethyl-4-methyl-isoxazole, and 5-sulfanilamido-3-ethyl-4-methyl-isoxazole, and alkali metal salts thereof.

2. A compound of the class consisting of 5-sulfanilamido-3,4-dimethyl-isoxazole of the formula



and alkali metal salts thereof.

3. 5-sulfanilamide-3,4-dimethyl isoxazole of the formula



4. The sodium salt of 5-sulfanilamido-3,4-dimethyl-isoxazole.

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5. The lithium salt of 5-sulfanilamido-3,4-dimethyl-isoxazole.

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MAX HOFFER.

REFERENCES CITED

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

UNITED STATES PATENTS

Number	Name	Date
2,324,013	Moore	July 13, 1943
2,361,624	Hamilton	Oct. 31, 1944

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Number	Name	Date
2,362,087	Newberry	Nov. 7, 1944
2,362,336	Anderson	Nov. 7, 1944

FOREIGN PATENTS

Number	Country	Date
111,230	Australia	Aug. 22, 1940
114,894	Australia	Apr. 2, 1942

OTHER REFERENCES

Chemical Reviews, Aug. 1940, pp. 105-109.
Journal Amer. Chem. Soc., vol. 64, pp. 2902-2905 (Dec. 1942).
Chem. Abstracts, vol. 38, page 2327.