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CERTAIN NITROFURYL, THIADIAZOLYL AMINES

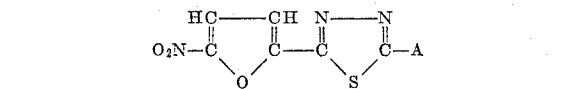
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6 Claims. (Cl. 260—306.8)

This invention relates to a new group of compounds possessing valuable properties as chemo-therapeutics. More particularly this invention relates to amino-nitro-furyl-thiadiazoles which may be represented by the following general formula:

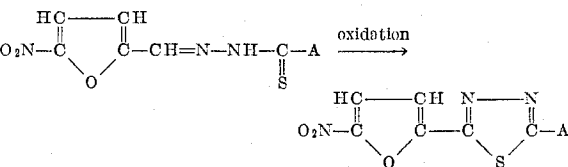


wherein A is selected from the group consisting of NH₂ and substituted NH₂-groups containing substituents having from 1 to 8 carbon atoms, for example alkyl radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl or allyl, a substituted alkyl such as carboxy methyl, aryl radicals such as phenyl, aralkyl radicals such as benzyl or phenethyl, alicyclic groups such as cyclohexyl, heterocyclic groups such as pyridyl. Thus, for example, the amino group may consist of a secondary amino group having such a substituent.

The novel compounds according to the invention have proved to possess surprisingly strong antibacterial activity and at the same time a remarkably low toxicity.

The invention also includes a process for producing the described compounds, which comprises treating 5-nitro-furfuralthiosemicarbazones with oxidizing agents causing an oxidative ring closure of the semicarbazone with formation of the corresponding thiadiazole compounds.

The reaction taking place may be illustrated by the following reaction formula:



wherein A has the significance indicated above.

As examples of a suitable oxidizing agents for this process may be mentioned salts of metals which occur in several oxidation stages, especially ferric salts, such as ferric chloride, ferric ammonium sulfate, potassium ferric sulfate, potassium ferric cyanide, sodium ferric cyanide, potassium ferric oxalate, sodium ferric oxalate, ferric ammonium citrate, ferric nitrate, ferric phosphate, ferric formate, ferric acetate and ferric benzoate.

The oxidizing reaction is preferably carried out by treating the compound to be oxidized in aqueous suspension with the oxidizing agent, suitably at elevated temperature, for example 60–90° C. The oxidation can also be carried out electrolytically.

As already stated above, the novel compounds according to the invention possess very strong antibacterial activity and it has been found that said activity in certain cases is practically independent of the kind of the substituents attached to the nitrogen atom in the amino group A. This is shown more in detail in the tables below.

In the Table I are stated those concentrations of the compound 5-amino-2-(5-nitrofuryl)-1,3,4-thiadiazole with unsubstituted amino group, wherein consequently

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A=NH₂, which cause total inhibition of growth of a number of different micro organisms. In the Table II are stated the lowest concentrations of compounds having different amino groups, which cause total inhibition of the growth of Staph. aureus.

TABLE I

Bacteriostatic Effect of the Compound 5-Amino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole Wherein A=NH₂.

Micro organism	Without serum	With 20-serum
Staph. aureus.....	1/160,000	1/160,000
E. coli.....	1/640,000	1/640,000
S. paratyphi Newport.....	1/1,280,000	1/2,560,000
S. typhimurium.....	1/1,280,000	1/1,280,000
S. cholerae suis.....	1/640,000	1/320,000
S. typhi.....	1/1,280,000	1/2,560,000
Str. dysgalactiae.....	1/40,000	1/20,000
M. tuberculosis.....	1/40,000	1/40,000

TABLE II

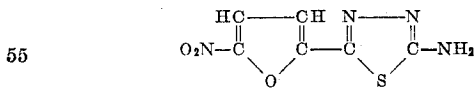
Bacteriostatic Effect on Staph. Aureus of the Compound 5-Amino-2-(Nitrofuryl)-1,3,4-Thiadiazole With Different Substituents in the Amino Group.

Amino group:	Without serum
NH ₂	1/160,000
NHCH ₃	1/80,000
NHC ₂ H ₅	1/80,000
NHCH ₂ CH=CH ₂	1/40,000
NHC ₆ H ₁₁	1/80,000
NHCH ₂ C ₆ H ₅	1/320,000
NHCH ₂ CO ₂ C ₂ H ₅	1/80,000

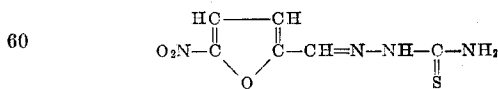
As examples of other micro organisms on which the compounds in question have proved to possess a strong growth inhibiting effect may be mentioned strains of the geni Salmonella and Shigella, bacteria of coli- and streptococcus types, Haemophilus influenzae, Trichomonas vaginalis and Trichophyton.

It is well known that many compounds containing the nitrofuran nucleus possess antibacterial properties. The surprisingly strong antibacterial activity of the novel compounds according to the invention is due to the combination of the nitrofuryl group with the thiadiazole group in such a way that both these radicals are contained in the molecule which is a condition for the characteristic antibacterial spectrum obtained by the compounds of the invention. This will be apparent by a comparison between the following substances:

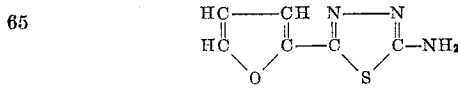
(1) 5-(2-nitrofuryl)-2-amino-thiadiazole-1,3,4-, according to the invention.



(2) 5-nitrofurfurylidenthiosemicarbazide.



(3) 5-furyl-2-aminothiadiazole-1,3,4.



In Table III are stated the lowest concentrations of these three compounds which cause total inhibition of the growth of a number of micro organisms in a milieu containing 20% bovine serum.

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TABLE III

Micro organism	Substance No. 1	Substance No. 2	Substance No. 3
<i>S. typhi murium</i> (Breslau).....	1/1, 280, 000	1/40, 000	>1/5, 000
<i>S. Newport</i>	1/2, 560, 000	1/80, 000	>1/5, 000
<i>S. cholera suis</i>	1/320, 000	1/80, 000	>1/5, 000
<i>Typhus</i>	1/2, 560, 000	1/160, 000	>1/5, 000

As will be seen from the table, the substance No. 1, i.e. the compound according to the invention, has a bacteriostatic effect of a very much higher order of magnitude than the substances Nos. 2 and 3.

Especially valuable among the nitrofurylthiadiazole compounds according to the invention are 5-amino-2-(5-nitrofuryl)-1,3,4-thiadiazole, 5-methylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole, 5-ethylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole, 5-allylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole, 5-benzylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole, and further also 5-cyclohexylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole and 5-phenylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole.

The process of the invention may be explained in greater detail by reference to the following specific examples which represent practical embodiments of our process.

Example 1.—5-Amino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

164 g. of 5-nitro-2-furfuralthiosemicarbazone is suspended in 511 ml. water and 765 ml. of 50% ferric chloride solution is added thereto. The mixture is heated to 60–90° C. for 45 minutes while stirring. The raw reaction product so obtained is recrystallized twice from diluted dimethylformamide. On cooling the solution, yellow crystals crystallize out which melt at 270–271° C. with decomposition, yield 94 g. (57%).

Example 2.—5-Amino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

In an electrolysis vessel holding about 500 ml. is inserted a porous clay cell having a volume of about 200 ml. In this cell is poured a suspension of 21.4 g. of 5-nitro-2-furfuralthiosemicarbazone in about 125 ml. 15% potassium ferric sulfate solution. The suspension is stirred effectively by the aid of a rotating perforated platine anode with a surface of about 5×4 cm.=20 cm.². In the cathode space outside the clay cell diluted sulphuric acid is introduced and a cylinder-shaped cathode made from a sheet of copper, for example, is inserted therein.

After the cathode liquid has been heated to about 70° C. electrolysis is carried out with a current of about 2 amp. for 4 hours. The current is then opened and the content of the anodic cell is filtered. The raw reaction product is washed 5 times with hot water and then recrystallized from diluted dimethyl formamide. Melting point 270–272° C. (decomposition). Yield 14 g. (65%).

Example 3.—5-Methylamino-2-(5-Nitro-2-Furyl)-1,3,4-Thiadiazole

16.4 g. of 1-(5-nitro-2-furfural)-4-methylthiosemicarbazone is suspended in 50 ml. water and 70 g. of 50% FeCl₃-solution is added thereto. The mixture is heated while stirring for 45 minutes. After cooling the crystals are filtered off and washed with hot water. The raw reaction product so obtained is recrystallized from a mixture of ethanol and dioxane. Melting point 219–221° C. (decomposition). Yield 10.4 g. (63%).

Example 4.—5-Amino-2-(5-Nitrofuryl)-1,3,4-thiadiazole

6.5 g. of 5-nitro-2-furfuralthiosemicarbazone and 30 g. of ferric ammonium sulfate are mixed with 100 ml. water and heated on water bath for about 1 hour while stirring. The precipitate which is thus formed is filtered off and dried. Weight 5.1 g. After recrystallization from dimethyl sulfoxide 4.0 g. of 5-amino-2-(5-nitrofuryl)-

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1,3,4-thiadiazole is obtained which corresponds to a yield of 63%. M.P. 270–272° C. with decomposition.

Example 5.—5-Amino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

4.2 g. of 5-nitro-2-furfuralthiosemicarbazone and 20 g. of potassium ferric cyanide in 100 ml. water are heated on water bath for about 1 hour. The raw product so obtained is filtered off and dried and leaked with concentrated cold formic acid and filtered. The filtrate is diluted with water and hereby yellow crystals of 5-amino-2-(5-nitrofuryl)-1,3,4-thiadiazole are formed which after drying weigh 2.4 g., corresponding to a yield of 57%. The compound is decomposed at 270–272° C.

Example 6.—5-Ethylamino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

24.2 g. of 1-(5-nitrofurfural)-4-ethylthiosemicarbazone are treated with 100 ml. of 50% ferric chloride solution and 100 ml. water as described in Example 3. After recrystallization from ethanol-dioxane 13.7 g. (57%) of 5-ethylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole are obtained in the form of yellowish brown needles, M.P. 219–221.5° C.

Example 7.—5-n-Propylamino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

25.6 g. of 1-(5-nitrofurfural)-4-n-propylthiosemicarbazone are treated with 100 ml. of 50% FeCl₃-solution and 100 ml. water in the manner described in Example 3. After recrystallization from ethanol 16.3 g. (64%) of 5-n-propylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole are obtained in the form of yellow needles, M.P. 190–191° C.

Example 8.—5-Isopropylamino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

18.8 g. of 1-(5-nitrofurfural)-4-isopropylthiosemicarbazone are treated with 70 ml. of 50% FeCl₃-solution and 70 ml. water as described in Example 3. After recrystallization from ethanol-dioxane 12 g. (65%) of 5-isopropylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole in the form of brilliant yellow scales, M.P. 213–215° C. are obtained.

Example 9.—5-N-Butylamino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

27 g. of 1-(5-nitrofurfural)-4-n-butylthiosemicarbazide are treated with 100 ml. of 50% FeCl₃-solution and 100 ml. water as described in Example 3. After recrystallization from ethanol-dioxane 15.7 g. (58%) of 5-n-butylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole in the form of yellow needles are obtained, M.P. 186–187° C.

Example 10.—5-Isobutylamino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

13.5 g. of 1-(5-nitrofurfural)-4-isobutylthiosemicarbazone are treated with 50 ml. of FeCl₃-solution and 50 ml. water as described in Example 3. After recrystallization from ethanol 8.8 g. (65%) of 5-isobutylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole are obtained in the form of yellow scales. M.P. 183.5–184.5° C.

Example 11.—5-N-Hexylamino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

11.9 g. of 1-(5-nitrofurfural)-4-n-hexylthiosemicarbazone are heated with 40 ml. of 50% FeCl₃-solution and 40 ml. water in the manner described in Example 3. After recrystallization from ethanol 5.8 g. (49%) of 5-n-hexylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole in the form of yellow crystals are obtained. M.P. 162.5–163.5° C.

Example 12.—5-Allylamino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

25.4 g. of 1-(5-nitrofurfural)-4-allylthiosemicarbazone are reacted with ferric chloride and water as described in Example 3. After recrystallization from ethanol 18.3 g. (72%) of 5-allylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole are obtained in the form of a mixture of brownish yellow

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needles and yellow scales, which latter on heating are converted to the former kind of crystals which melt at 172.5–175.5° C.

Example 13.—5-Carboxymethylamino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

2.5 g. of 1-(5-nitrofurfural)-4-carbethoxymethylthiosemicarbazone are treated with 10 ml. of 50% FeCl₃-solution and 10 ml. water in the manner described in Example 3. After recrystallization from ethanol 2.0 g. of 5-carbethoxymethylamino-2-nitrofuryl-1,3,4-thiadiazole in the form of yellow scales, M.P. 172.5–174° C. are obtained.

0.9 g. of the carboxymethyl derivative is heated for 3 hours with 20 ml. of 5 normal sulfuric acid. The resulting substance is filtered off, washed and dried. After recrystallization from dioxane-ethanol 0.8 g. of 5-carboxymethylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole in the form of light yellow crystals are obtained. M.P. 246–248° C.

Example 14.—5-(2-Methoxyethylamino)-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

4.1 g. of 1-(5-nitrofurfural)-4-(2-methoxyethyl)-thiosemicarbazone are heated with 15 ml. of 50% FeCl₃-solution and 50 ml. water as described in Example 3. After recrystallization from ethanol 3.0 g. (74%) of 5-(2-methoxyethylamino)-2-(5-nitrofuryl)-1,3,4-thiadiazole in the form of yellow needles are obtained. M.P. 169–171° C.

Example 15.—5-Benzylamino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

15.2 g. of 1-(5-nitrofurfural)-4-benzylthiosemicarbazone are heated with 50 ml. of 50% FeCl₃-solution and 50 ml. water in the manner described in Example 3. After recrystallization from ethanol-dioxane 7.4 g. (49%) of 5-benzylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole in the form of yellowish brown crystals, M.P. 190.5–191.5° C., are obtained.

Example 16.—5-(2-Phenylethylamino)-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

2.5 g. of 1-(5-nitrofurfural)-4-(2-phenylethyl)-thiosemicarbazone are heated with 10 ml. of 50% FeCl₃-solution and 10 ml. water in the manner described in Example 3. After recrystallization from ethanol 1.9 g. (76%) of 5-(2-phenylethylamino)-2-(5-nitrofuryl)-1,3,4-thiadiazole are obtained in the form of brilliant yellow crystals, which due to polymorphy melt at 160–169° C.

Example 17.—5-Phenylamino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

8.1 g. of 1-(5-nitrofurfural)-4-phenylthiosemicarbazone

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are heated with 30 ml. of 50% FeCl₃-solution and 30 ml. water as described in Example 3. After recrystallization from ethanol-dioxane 5.1 g. (59%) of 5-phenylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole are obtained in the form of light yellow crystals which are decomposed at 253–254.5° C.

Example 18.—5-(2-Pyridylamino)-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

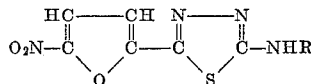
2.9 g. of 1-(5-nitrofurfural)-4-(2-pyridyl)-thiosemicarbazone are heated with 10 ml. of 50% FeCl₃-solution and 10 ml. water in the manner described in Example 3. After recrystallization from dimethylformamide 1.7 g. (59%) of 5-(2-pyridylamino)-2-(5-nitrofuryl)-1,3,4-thiadiazole are obtained in the form of brilliant filthy needles, which are decomposed at 330–340° C.

Example 19.—5-Cyclohexylamino-2-(5-Nitrofuryl)-1,3,4-Thiadiazole

29.6 g. of 1-(5-nitrofurfural)-4-cyclohexylthiosemicarbazide are carefully pulverized and heated with FeCl₃-solution and water as described in Example 3. The raw product so obtained consisting of brown balls are washed, dried and recrystallized from ethanol. Hereby a mixture of brown scales and yellow filthy crystals is obtained, both kinds of which are decomposed at 175–178° C. Yield 21.8 g. (73%).

What we claim is:

1. A compound of the formula:



wherein R is a member of the group consisting of hydrogen, lower alkyl, allyl, lower carboxy alkyl, methoxy ethyl, phenyl, benzyl, phenethyl, cyclohexyl and pyridyl.

2. 5-methylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole.

3. 5-ethylamino-2-(5-nitrofuryl)-1,3,4-thiadiazole.

4. A compound according to claim 1 wherein R is n-propyl.

5. A compound according to claim 1 wherein R is isopropyl.

6. A compound according to claim 1 wherein R is n-butyl.

References Cited in the file of this patent

- Collonna et al.: Chem. Abstracts, vol. 44, column 128 (1950).
Bambas: "Chem. of Heterocyclic Comp'ds," vol. 4, pages 106, 112–113 (1952).