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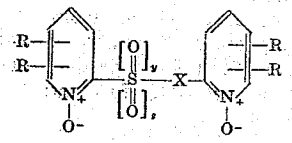
DERIVATIVES OF 2-MERCAPTOPYRIDINE 1-OXIDE

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5 Claims. (Cl. 260—294.8)

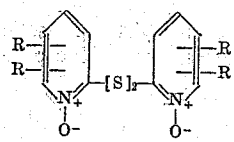
This invention relates to, and has for its object the provision of: (A) compounds of the general formula



wherein each R is a member of the class consisting of hydrogen, lower alkyl, (lower alkyl)-oxy and halogen, X is a member of the class consisting of —S—, and



groups, and y and z are each one of the numbers 0 or 1; and (B) methods of preparing the same. Defined otherwise, the compounds of this invention are members of the group consisting of compounds of the general formula:



and the sulfone and sulfoxide derivatives of these compounds, each R having the meaning given hereinbefore. Preferably one R is hydrogen or a lower alkyl group.

The compounds of this invention are useful as intermediates and as antibacterial agents. The compounds of this invention are especially active against a wide group of microorganisms, as indicated by the following in vitro spectra of representative compounds.

TABLE 1

Antibacterial activity

Compound	MIC μg/ml.		
	Staph. 209-P	K Pneum.	BCG
2,2'-dithiodipyridine 1,1'-dioxide	0.08	2	0.008
2,2'-dithio-bis-(4-methylpyridine)1,1'-dioxide	0.2	4	0.01
2,2'-dithiodipyridine 1,1',S-trioxide	0.3	2	0.015
2,2' disulfinyldipyridine 1,1'-dioxide	0.3	8	0.02

TABLE 2

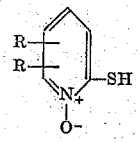
Antifungal activity

Microorganism	MIC μg/ml.				
	Control [1]	Derivative [2]			
		(a)	(b)	(c)	(d)
Aspergillus fumigatus	12.5	0.4	0.8	0.4	<0.4
Aspergillus niger	4.2	0.4	3.1	0.8	1.6
Candida albicans	50	0.4	1.6	3.1	3.1
Microsporum audouini	3.1	<0.4	0.8	0.4	0.4
Penicillin notatum	12.5	0.4	3.1	0.4	0.8
Rhodotorula glutinis	3.1	0.3	0.8	0.8	<0.4
Saccharomyces cerevisiae	1.6	0.3	0.8	0.4	<0.4
Trichophyton mentagrophytes	3.1	0.3	0.8	0.4	<0.4
Fusarium bulbigenum	50	0.4	6.3	0.8	1.6
Ceratostomella ulmi	3.1	0.3	0.8	0.4	<0.4

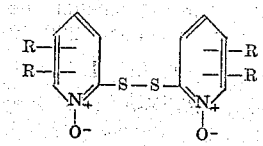
[1] 8-hydroxyquinoline.
[2] (a) 2,2'-dithiodipyridine 1,1'-dioxide;
(b) 2,2'-dithio-bis-(4-methylpyridine)1,1'-dioxide;
(c) 2,2'-dithiodipyridine 1,1',S-trioxide;
(d) 2,2'-disulfinyldipyridine 1,1'-dioxide.

Since the compounds of this invention possess such broad antibacterial and antifungal spectra, they are also utilizable in agriculture to combat plant diseases (for example against Peronospora growing on grapevine), and may be incorporated into plastics and fabrics in the conventional manner to increase their resistance to mildew or other fungus attack.

The 2,2'-dithiodipyridine 1,1'-dioxides of this invention may be prepared by the method comprising reacting compound (I), a 2-mercaptopyridine 1-oxide,



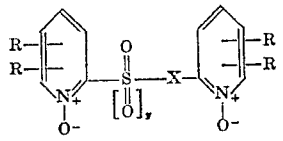
with an oxidizing agent of the peroxide type, such as peracids (peracetic, performic, perbenzoic, perphthalic) and (especially) hydrogen peroxide in water, preferably at room temperature, and recovering the reaction product, namely



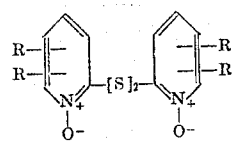
Utilizable reactants I include, inter alia: 2-mercaptopyridine 1-oxide, 3-methoxy-2-mercaptopyridine 1-oxide, 3-ethoxy-2-mercaptopyridine 1-oxide, 5-bromo-2-mercaptopyridine 1-oxide, 4-methyl-2-mercaptopyridine 1-oxide, 4,6-dimethyl-2-mercaptopyridine 1-oxide, 3-ethyl-6-methyl-2-mercaptopyridine 1-oxide, 3-methyl-2-mercaptopyridine 1-oxide, 2-mercapto-5-methylpyridine 1-oxide, 2-mercapto-6-methylpyridine 1-oxide, 2-mercapto-6-propylpyridine 1-oxide, 4-ethyl-2-mercaptopyridine 1-oxide (see, for example, J. A. C. S. 72: 4362, and U. S. application Serial No. 330,576, filed January 9, 1953 (now Patent No. 2,686,786, issued August 17, 1954), for the preparation of substituted 2-mercaptopyridine 1-oxides).

These 2,2'-dithiopyridine 1,1'-dioxides are utilized in preparing the sulfone and sulfoxide derivatives of this

invention. Thus, derivatives of the following general formula:

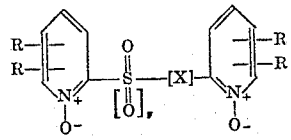


(wherein R, X and y have the meaning given hereinbefore) may be prepared by interacting a compound of the general formula (II):



with an oxidizing agent, such as peracids (peracetic, performic, perbenzoic, perphthalic acids) and peroxides (especially hydrogen peroxide) in acid solution. Utilizable compounds II (prepared as indicated hereinbefore) include, inter alia: 2,2'-dithiodipyridine, 1,1'-dioxide; 2,2'-dithio-bis-[3(4, 5 or 6)methylpyridine] 1,1'-dioxide; 2,2'-dithio-bis-(3-chloropyridine) 1,1'-dioxide; 2,2'-dithio-bis-(3-methoxypyridine) 1,1'-dioxide; 2,2'-dithio-bis-(4,6-dimethylpyridine) 1,1'-dioxide; 2,2'-dithio-bis-(3-ethyl-6-methylpyridine) 1,1'-dioxide.

Alternatively, the sulfones and sulfoxides of the general formula



wherein X and y have, and each R has the meaning given hereinbefore, may also be prepared directly by reacting a 2-mercaptopyridine 1-oxide (I) with an oxidizing agent of the peroxide type, and recovering the reaction product.

The following examples are illustrative, but by no means limitative, of the invention.

EXAMPLE 1

Preparation of 2,2'-dithiodipyridine 1,1'-dioxide

70 cc. 30% hydrogen peroxide solution diluted to 250 cc. with water is added slowly to the suspension of 42.3 g. 2-mercaptopyridine 1-oxide in 350 cc. water. The temperature rises to 45° C., and the appearance of the suspended solid changes (although a clear solution does not form at any time). The reaction mixture is stirred for one hour, and the solid then filtered off. The product, 2,2'-dithiodipyridine 1,1'-dioxide, weighs about 29 g., and melts at about 195–196° C. (dec). After crystallization from one liter of alcohol, the product weighs about 18.5 g. and melts at about 200–201° C. (dec).

EXAMPLE 2

Preparation of 2,2'-dithio-bis-(4-methylpyridine) 1,1'-dioxide

3 g. 2-mercapto-4-methylpyridine 1-oxide is suspended in 100 cc. water and 10 cc. 30% H_2O_2 diluted to 50 cc. is added thereto dropwise (gradually, a clear solution forms). The solution is stirred at room temperature for three hours, allowed to stand for 12–16 hours, and then concentrated to 20 cc. under reduced pressure. On cooling, crystals form, and are filtered off. The product, 2,2'-dithio-bis-(4-methylpyridine) 1,1'-dioxide, weighs about 800 mg. and melts at about 165–175° C. (dec.). After recrystallization from 40 cc. alcohol-ether (1:1), the product weighs about 500 mg. and melts at about 195–196° C. (dec.).

Use of a molar equivalent of 2-mercapto-3-ethoxypyridine 1-oxide or 2-mercapto-5-bromopyridine 1-oxide in place of 2-mercapto-4-methylpyridine 1-oxide in Example 2 yields 2,2'-dithio-bis-(3-ethoxypyridine) 1,1'-dioxide and 2,2'-dithio-bis-(5-bromopyridine) 1,1'-dioxide, respectively.

EXAMPLE 3

Preparation of 2,2'-dithiodipyridine 1,1'-S-trioxide

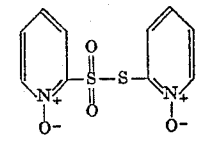
A mixture of 10.08 g. 2,2'-dithiodipyridine 1,1'-dioxide (cf. Example 1), 100 cc. acetic acid, and 4.4 g. 30% H_2O_2 is allowed to stand at room temperature for three days, and then concentrated to dryness under reduced pressure at 60° C. (bath). The residue is triturated with absolute alcohol to yield about 10.5 g. of a solid, 2,2'-dithiodipyridine 1,1',S-trioxide, melting at about 178–180° C. After recrystallization from 200 cc. alcohol, and then from 200 cc. acetonitrile, the product weighs about 3.5 g. and melts at about 185–186° C. (dec.).

Use of a molar equivalent of 2,2'-dithio-bis-(4-methylpyridine) 1,1'-dioxide (cf. Example 2) in place of 2,2'-dithiodipyridine 1,1'-dioxide in Example 3 yields 2,2'-dithio-bis-(4-methylpyridine) 1,1',S-trioxide.

EXAMPLE 4

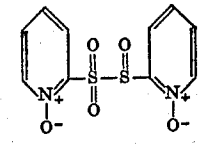
Preparation of 2,2'-disulfinyldipyridine 1,1'-dioxide

Proceeding as in Example 3, but employing 22 g. instead of 4.4 g. 30% H_2O_2 yields about 9 g. of 2,2'-disulfinyldipyridine 1,1'-dioxide, melting at about 179–180° C. (dec.). After recrystallization from 125 cc. absolute alcohol, the product, 2,2'-disulfinyldipyridine 1,1'-dioxide, weighs about 5 g. and melts at about 185–186° C. (dec.). It is possible this "disulfinyl" product may actually be a compound of the following formula:



Use of a molar equivalent of 2,2'-dithio-bis-(6-methylpyridine) 1,1'-dioxide (prepared in the same manner as the 4-methyl compound in Example 2) in place of 2,2'-dithiodipyridine 1,1'-dioxide in Example 4 yields 2,2'-disulfinyl-bis-(6-methylpyridine) 1,1'-dioxide.

To a solution of 12.6 g. of 2,2'-dithiodipyridine 1,1'-dioxide in 200 cc. acetic acid is added 34 g. 30% H_2O_2 and the resulting solution heated at 60–70° C. for 24 hours. The reaction mixture is concentrated to dryness under reduced pressure, yielding a solid which is crystallized from absolute alcohol. The product is



EXAMPLE 5

Preparation of 2,2'-dithio-bis-(4,6-dimethylpyridine) 1,1'-dioxide

(a) 2-BROMO-4,6-DIMETHYLPYRIDINE

To a solution of 91.5 g. 2-amino-4,6-dimethylpyridine in 850 cc. of 48% HBr is added dropwise 115 cc. bromine at 0–5° C. with vigorous stirring. A thick orange solid forms. After complete addition of the bromine the reaction mixture is diazotized with a solution of 130 g. sodium nitrite in 200 cc. water at 0° C. The reaction is then allowed to come to room temperature, made strongly alkaline by the addition of approximately one liter 50% NaOH at 10–15° C. and decolorized by the addition of 100 g. sodium sulfite in 500 cc. H_2O. The reaction mixture is steam distilled and the distillate extracted with 3×500 cc. ether. The ether is dried over $MgSO_4$ and removed. The residue is fractionated to yield about 64 g. of product, boiling at 92–94° C./7 mm.

(b) 2-BROMO-4,6-DIMETHYLPYRIDINE 1-OXIDE HYDROCHLORIDE

64 g. 2-bromo-4,6-dimethylpyridine is dissolved in 200 cc. acetic acid and 100 g. 40% peracetic acid is added keeping the temperature below 15° C. After complete addition, the reaction is allowed to come to room temperature and then heated at 45° C. for 12 hours. The acetic acid is removed under reduced pressure and the residue poured onto cracked ice and made strongly alkaline with 40% KOH. The oil which precipitates is extracted with 3×200 cc. chloroform. The chloroform is dried over $MgSO_4$ and then dry HCl gas added until acid to Congo. This solution is concentrated to 250 cc. under reduced pressure to yield about 62 g. product, which melts at about 157–158° C. (dec.). After recrystallization from absolute alcohol, the product melts at about 157–158° C. (dec.).

(c) 2-MERCAPTO-4,6-DIMETHYLPYRIDINE 1-OXIDE

A solution of 2.38 g. 2-bromo-4,6-dimethylpyridine 1-oxide HCl in 20 cc. absolute alcohol is added to a solution of 0.76 g. thiourea in 20 cc. absolute alcohol. The solution is refluxed for 15 minutes and then concentrated under reduced pressure. The resulting oil is dissolved in 100 cc. H_2O and solid Na_2CO_3 added until the solution is alkaline. After standing 15 minutes, the solution is filtered and acidified with 10% HCl. The crystalline solid is filtered and melts at 105–107° C. After recrystallization from 25 cc. aqueous alcohol, the compound melts at about 108–109° C.

Alternatively, 2-bromo-4,6-dimethylpyridine 1-hydrochloride in water is neturalized with sodium hydroxide solution; and to this solution is added a solution of sodium hydrosulfide in water and the procedure continues as in Example 2*b* of Patent No. 2,686,786 to yield 2-mercapto-4,6-dimethylpyridine 1-oxide.

(d) 2,2-DITHIO-BIS-(4,6-DIMETHYLPYRIDYL) 1,1'-DIOXIDE

To a suspension of 0.775 g. 2-mercapto-4,6-dimethylpyridine 1-oxide in 50 cc. H_2O is added 2.3 g. 30% H_2O_2 in 50 cc. H_2O at room temperature. The reaction is warmed on a steam bath for a few minutes to cause solution. After cooling, a crystalline solid precipitates and is filtered. The product weighs about 310 mg. and melts at about 192–194° C. After recrystallization from aqueous alcohol, the product melts at about 228–229° C.

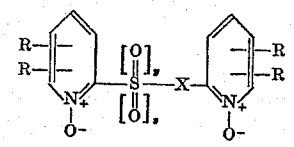
Use of a molar equivalent of 2-amino-3-ethyl-6-methylpyridine in place of 2-amino-4,6-dimethylpyridine in Example 5 yields 2,2'-dithio-bis-(3-ethyl-6-methylpyridine) 1,1'-dioxide.

Use of a molar equivalent of 2,2'-dithio-bis-(4,6-dimethylpyridine) 1,1'-dioxide or 2,2'-dithio-bis-(3-ethyl-6-methylpyridine) 1,1'-dioxide in place of 2,2'-dithiopyridine 1,1'-dioxide in Example 4 yields 2,2'-disulfinyl-bis-(4,6-dimethylpyridine) 1,1'-dioxide and 2,2'-disulfinyl-bis-(3-ethyl-6-methylpyridine) 1,1'-dioxide, respectively.

The invention may be variously otherwise embodied within the scope of the appended claims.

We claim:

1. Compounds of the general formula:

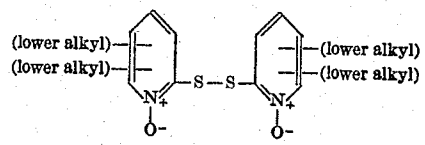


wherein each R is a member of the class consisting of hydrogen, lower alkyl, (lower alkyl)-oxy, and halogen, X is a member of the class consisting of —S— and



groups, and *y* and *z* are each one of the numbers 0 and 1.

2. Compounds of the general formula:



3. 2,2'-dithiopyridine 1,1'-dioxide.
4. 2,2'-dithiopyridine 1,1', S-trioxide.
5. 2,2'-disulfinyldipyridine 1,1'-dioxide.

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