

1

3,478,049

NITROFURYL SUBSTITUTED OXADIAZOLES

Anne Mary Von Esch, North Chicago, and Aldo J. Croveti, Lake Forest, Ill., assignors to Abbott Laboratories, North Chicago, Ill., a corporation of Illinois

No Drawing. Continuation-in-part of applications Ser. No. 314,863 and Ser. No. 314,891, Oct. 9, 1963. This application Mar. 28, 1966, Ser. No. 537,707

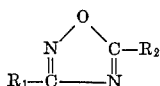
Int. Cl. C07d 85/06; A01n 9/22

U.S. Cl. 260—307

10 Claims

ABSTRACT OF THE DISCLOSURE

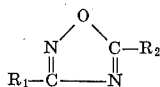
Compounds of the formula:



wherein when one of R_1 and R_2 is 5-nitro-2-furyl, the other represents hydrogen, alkyl, haloalkyl, halophenyl, loweralkylphenyl, haloloweralkylphenyl, aryloxyloweralkyl, hydroxyphenyl, aminophenyl, nitrophenyl, loweralkoxyphenyl, mercaptophenyl, acetylthiomethyl, loweralkylthiophenyl, halosulfonamidophenyl, sulfonamidophenyl, aralkyl, haloaralkyl, alkoxyaralkyl, pyridyl, pyridyloweralkyl, halopyridyl, carboxamido, carboalkoxy, carboalkoxyloweralkyl, carboalkoxyvinyl, loweralkenyl, furyl, furylalkenyl, thienyl, thienylalkenyl, pyridylalkenyl, pyrimidyl, halopyrimidyl, halofuryl, halothienyl, furylloweralkyl, thienyloweralkyl, oxazyl, isoxazyl, quinolyl, isoquinolyl, pyrazyl, imidazyl, pyrazinyl, or thiazyl, which are useful as antibacterial and antifungal agents.

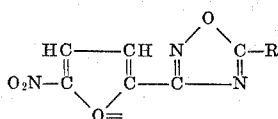
The present application is a continuation-in-part of co-pending applications Ser. Nos. 314,863 and 314,891, both filed October 9, 1963 and now abandoned.

This invention relates to compounds of the formula

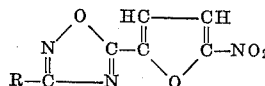


In this formula, when R_1 is 5-nitro-2-furyl, R_2 represents hydrogen, alkyl, haloalkyl, halophenyl, loweralkylphenyl, haloloweralkylphenyl, aryloxyloweralkyl, hydroxyphenyl, aminophenyl, nitrophenyl, loweralkoxyphenyl, mercaptophenyl, acetylthiomethyl, loweralkylthiophenyl, halosulfonamidophenyl, sulfonamidophenyl, aralkyl, haloaralkyl, alkoxyaralkyl, pyridyl, pyridyloweralkyl, halopyridyl, carboxamido, carboalkoxy, carboalkoxyloweralkyl, carboalkoxyvinyl, loweralkenyl, furyl, furylalkenyl, thienyl, thienylalkenyl, pyridylalkenyl, pyrimidyl, halopyrimidyl, halofuryl, halothienyl, furylloweralkyl, thienyloweralkyl, oxazyl, isoxazyl, quinolyl, isoquinolyl, pyrazyl, imidazyl, pyrazinyl, or thiazyl. Likewise, when R_2 is 5-nitro-2-furyl, R_1 may be any of the enumerated radicals except 5-nitro-2-furyl. The terms "loweralkyl" and "alkoxy" include the straight and branched alkyl and alkoxy radicals containing from one to five carbon atoms, inclusive, while "alkyl" includes radicals containing up to 17 carbon atoms.

More particularly, the compounds of the present invention have the formulae



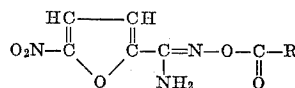
and



wherein R in these and succeeding formulae may be any of the previously enumerated radicals except 5-nitro-2-furyl.

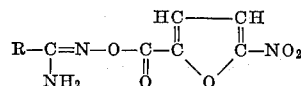
These compounds are useful as antibacterial and antifungal agents and can be employed as active, toxic constituents of disinfectant compositions for the control of a vast array of microorganisms such as *Salmonella typhimurium*, *Escherichia coli*, *Chaetomium globosum*, *Fusarium oxysporum*, *Proteus mirabilis*, *Proteus vulgaris*, and Alternario species. In such use, the compounds are dispersed on an inert solid or in a liquid such as water and applied as a dust or spray. In a typical application, the compound wherein R of Formula B was bromomethyl completely inhibited the growth of the above-named organisms when employed as an aqueous composition in a concentration of 25 parts per million. Additionally, these novel compounds are useful as anthelmintic agents when administered orally to animals at a dosage of 250 mg. daily. Likewise, the new compounds are effective against *Trichomonas vaginalis* in concentrations of 50 parts per million or less when applied topically. In another typical application, the compound wherein R of formula C was chloromethyl completely inhibited the growth of the above-named organisms when employed as an aqueous composition in a concentration of 25 parts per million.

The new compounds of Formula B can be readily prepared by heating at or above the melting point a compound of the formula



in the absence or presence of a solvent to liberate water and effect ring closure. The preparation of compounds of Formula D will hereinafter be described in detail and is fully described in co-pending application Ser. No. 314,875, filed October 9, 1963, now U.S. Patent 3,272,833. The compound thus formed is then crystallized from a suitable solvent such as ethanol, nitromethane or acetonitrile. If desired, equimolar amounts of 5-nitro-2-furylamidoxime and a compound of the Formula RCOX wherein X is a halogen, preferably chlorine or bromine, may be refluxed in an inert solvent such as toluene, xylene, dimethylformamide, or benzene in the presence of a hydrohalide acceptor such as pyridine, potassium carbonate, or triethylamine or in acetic acid without acid acceptor to form the intermediate compound designated in Formula D above in situ and without actually isolating said intermediate continuing the reaction at reflux temperature to close the ring. The reaction mixture is then concentrated and the residue recrystallized to obtain the desired oxadiazole as a crystalline solid. Alternatively, an excess of the compound RCOX can be employed as the solvent.

The new compounds of Formula C can likewise be readily prepared by heating at or above the melting point a compound of the formula



in the absence or presence of a solvent to liberate water and effect ring closure. The preparation of compounds of Formula E will hereinafter be described in detail and is fully described in co-pending application Serial No. 314,849, now U.S. Patent 3,272,828, filed October 9, 1963. The compound thus formed, if a solid, is then

crystallized from a suitable solvent such as ethanol nitromethane, or acetonitrile. If the compound is a liquid, it is isolated by distillation under reduced pressure. If desired, equimolar amounts of an R-substituted amidoxime and 5-nitro-2-furoyl chloride or bromide can be refluxed in an inert solvent such as acetone, toluene, xylene, dimethylformamide, or benzene in the presence of a hydrohalide acceptor such as pyridine, potassium carbonate, or triethylamine or in acetic acid without acid acceptor to form the intermediate compound designated in Formula E above in situ and without actually isolating said intermediate continuing the reaction at reflux temperature to close the ring. The reaction mixture is then concentrated and the residue recrystallized or distilled to obtain the desired oxadiazole.

The examples which follow are presented as illustrations rather than limitations of the invention.

EXAMPLE 1

O-nicotinoyl-5-nitro-2-furylamidoxime

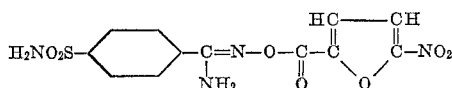
To 15 grams (0.08 mole) of 5-nitro-2-furylamidoxime, 6.05 grams (0.04 mole) of potassium carbonate in 175 ml. of acetone was added slowly with stirring and cooling a solution of 12.4 grams (0.08 mole) of nicotinoyl chloride (B.P.=90° C. at 15 mm. pressure) in 50 ml. of acetone. The mixture was then stirred at room temperature for 5 hours. The solid which formed was filtered off and crystallized from a dimethylformamide-water mixture to obtain the desired product which melted at 211° C.

Analysis.—Calculated: C=47.83%; H=2.92%; N=20.32%. Found: C=48.09%; H=2.90%; N=20.75%.

A 2.5 gram portion of the above product was heated with 1.3 grams of methyl iodide in nitromethane on a steam bath for 2.5 hours. The methiodide salt which formed was separated by filtration and after crystallization from a dimethylformamide-alcohol mixture was found to melt at 200° C.

EXAMPLE 2

O-(5-nitro-2-furoyl)-p-sulfonamidobenzamidoxime



To 4 grams (0.02 mole) of p-sulfonamidobenzamidoxime melting at 210° C. was added 1.28 grams (0.01 mole) of anhydrous potassium carbonate and 100 ml. of anhydrous acetone. The mixture was cooled to 0° C. and 3.26 grams (0.02 mole) of 5-nitro-2-furoyl chloride melting at 40° C. dissolved in 25 ml. of anhydrous acetone was added with stirring over a period of 15 minutes. The mixture was then stirred at room temperature for an additional 7 hours. The solid which formed was removed by filtration, washed successively with water and ethanol, and recrystallized from a dimethylformamide-water mixture at 100° C. to obtain the desired product as a crystalline yellow solid melting at 230° C. (sealed capillary) with decomposition.

Analysis.—Calculated: C=40.68%; H=2.84%; N=15.82%. Found: C=40.84%; H=2.86%; N=15.99%.

EXAMPLE 3

3-(5-nitro-2-furyl)-5-methyl-1,2,4-oxadiazole

R=methyl in Formula B

O-acetyl-5-nitro-2-furylamidoxime (5.3 grams, 0.025 mole) melting at 165° C. was heated at 170° C. for 15 minutes. Upon cooling, a brown oil formed which was crystallized from ethanol to obtain the desired oxadiazole. M.P.=105° C.

Analysis.—Calculated: C=43.08%; H=2.58%; N=21.54%. Found C=43.30%; H=2.67%; N=21.66%.

By heating O-formyl-5-nitro-2-furylamidoxime, O-propionyl-5-nitro-2-furylamidoxime, O-butyl-5-nitro-2-furylamidoxime or O-valeryl-5-nitro-2-furylamidoxime above their melting point, there is obtained the corresponding oxadiazoles wherein R of Formula B is hydrogen, ethyl, propyl, or butyl, respectively. The compound wherein R is ethyl melted at 98° C. and contained 20.28% nitrogen compared to the calculated value of 20.09% nitrogen.

EXAMPLE 4

3-(5-nitro-2-furyl)-5-phenyl-1,2,4-oxadiazole

R=phenyl in Formula B

O-benzoyl-5-nitro-2-furylamidoxime (8 grams, 0.029 mole) melting at 210° C. was heated at 215° C. on an oil bath for about 30 minutes. The residue resulting was crystallized from boiling ethanol to yield the desired oxadiazole as a cream-colored solid melting at 200° C.

Analysis.—Calculated: C=56.03%; H=2.74%; N=16.34%. Found: C=55.93%; H=2.65%; N=16.13%.

By heating O-(3-chlorobenzoyl)-5-nitro-2-furylamidoxime (M.P.=162° C.), O-(4-chlorobenzoyl)-5-nitro-2-furylamidoxime (M.P.=194° C.) or O-(2,5-dichlorobenzoyl)-5-nitro-2-furylamidoxime (M.P.=185° C.) slightly above their melting point for about 5 minutes, there is obtained the following oxadiazoles respectively wherein R in Formula B is as shown below:

R=3-chlorophenyl; M.P.=150° C.

R=4-chlorophenyl; M.P.=194° C.

R=2,5-dichlorophenyl; M.P.=152° C.

In like manner, other O-(halobenzoyl)-5-nitro-2-furylamidoximes such as O-(2-fluorobenzoyl)-5-nitro-2-furylamidoxime, O-(2,4-dibromobenzoyl)-5-nitro-2-furylamidoxime, O-(3,5-difluorobenzoyl)-5-nitro-2-furylamidoxime, or O-(2-chloro-4-bromobenzoyl)-5-nitro-2-furylamidoxime can be heated at or above their melting points to produce the corresponding 3-,5-nitro-2-furyl)-5-halo-phenyl-1,2,4-oxadiazoles.

EXAMPLE 5

3-(5-nitro-2-furyl)-5-chloromethyl-1,2,4-oxadiazole

R=chloromethyl in Formula B

O-chloroacetyl-5-nitro-2-furylamidoxime (1.10 grams, 0.004 mole) was heated at 185° C. for 5 minutes. Water was liberated and the resulting brown oil was cooled to 120° C. at which temperature a solid formed. Upon crystallization from ethanol, the desired oxadiazole was obtained as a cream-colored, crystalline solid which melted at 110° C. and contained 18.25% nitrogen compared to the calculated value of 18.31% nitrogen.

Similarly, by heating at or slightly above their melting points such compounds as O-bromoacetyl-5-nitro-2-furylamidoxime, O-iodoacetyl-5-nitro-2-furylamidoxime, O-dichloroacetyl-5-nitro-2-furylamidoxime, O-α-bromopropionyl-5-nitro-2-furylamidoxime or O-γ-chlorobutyryl-5-nitro-2-furylamidoxime, there is readily obtained the following oxadiazoles respectively wherein R in formula B is as indicated:

R=bromomethyl; M.P.=131° C.

R=idomethyl; M.P.=129° C.

R=dichloromethyl; M.P.=40° C.

R=α-bromoethyl; M.P.=79° C.

R=γ-chloropropyl; M.P.=68° C.

If desired, other O-haloloweralkanoyl-5-nitro-2-furylamidoximes can be heated at or above their melting points to liberate water and produce the corresponding 3-(5-nitro-2-furyl)-5-haloloweralkyl-1,2,4-oxadiazoles wherein R of Formula A is trifluoromethyl; α,α,γ-trichloropropyl; α,α-dibromobutyl; α-γ-diiodobutyl; α-chloro-β-bromovaleryl trichloromethyl, or α-bromovaleryl and similar haloloweralkyl radicals.

EXAMPLE 6

3-(5-nitro-2-furyl)-5-(3'-pyridyl)-1,2,4-oxadiazole
R=3-pyridyl in Formula B

O-nicotinoyl-5-nitro-2-furylamidoxime (8 grams) was heated at its melting point of 210° C. for 30 minutes.

obtained which melted at 107° C. Upon analysis, the product was found to contain 15.69% nitrogen compared to the calculated value of 15.73% nitrogen.

Using methods exemplified in the foregoing examples, the following compounds, wherein R refers to substitutions in Formula B, were made.

Example	R	Melting Point	Analyses	
			Calculated	Found
10.....	1-bromo-2-methyl propyl	(B.P.) 158° C./0.15 mm.	C, 38.00; H, 3.20; N, 13.30	C, 38.29; H, 3.50; N, 13.58.
11.....	1-bromo-1-methyl ethyl	104°-106°	C, 35.78; H, 2.67; N, 13.92	C, 35.52; H, 2.65; N, 14.01.
12.....	1-bromo-n-butyl	(B.P.) 160°/0.2 mm.	C, 38.00; H, 3.20; N, 13.30	C, 39.34; H, 3.47; N, 13.67.
13.....	1-bromo-n-pentyl	39°-41°	C, 40.01; H, 3.67; N, 12.73	C, 41.40; H, 3.68; N, 12.94.
14.....	1-bromo-n-undecyl	40°-51°	C, 49.28; H, 5.84; N, 10.14	C, 49.22; H, 5.87; N, 10.00.
15.....	1-bromo-n-pentadecyl	55°-57°	C, 53.61; H, 6.86; N, 8.93	C, 53.56; H, 6.70; N, 9.09.
16.....	5-bromo-2-furyl	195°-196°	C, 36.83; H, 1.23; N, 12.89	C, 36.95; H, 1.41; N, 12.74.
17.....	1-bromo-n-heptadecyl	60°-62°	C, 55.42; H, 7.28; N, 8.43	C, 55.60; H, 7.29; N, 8.70.
18.....	2,6-dichlorophenyl	176°-178°	C, 44.20; H, 1.55; N, 12.89	C, 44.46; H, 1.53; N, 12.74.
19.....	2,6-dimethoxy phenyl	159°-161°	C, 53.00; H, 3.50; N, 13.25	C, 53.06; H, 3.36; N, 13.10.
20.....	2,6-dichloro-4-pyridyl	204°-206°	C, 40.39; H, 1.23; N, 17.13	C, 40.67; H, 1.10; N, 16.95.
21.....	2-chloro-4-pyridyl	194°-196°	C, 45.14; H, 1.72; N, 19.15	C, 45.19; H, 1.78; N, 19.24.
22.....	2-quinolyl	292°-294°	C, 58.44; H, 2.62; N, 18.18	C, 58.48; H, 2.68; N, 18.55.
23.....	6-quinolyl	278°-280°	C, 58.44; H, 2.62; N, 18.18	C, 58.47; H, 2.59; N, 18.19.
24.....	Pyrazinyl	234°-236°	C, 46.34; H, 1.94; N, 27.02	C, 46.06; H, 1.98; N, 27.22.
25.....	2-(2-furyl)-ethenyl	199°-201°	C, 52.75; H, 2.58; N, 15.38	C, 52.68; H, 2.69; N, 15.58.
26.....	2,6-dichloro-4-pyrimidinyl	167°-169°	C, 36.61; H, 0.92; N, 21.35	C, 37.34; H, 1.60; N, 20.24.
27.....	1-chloropropyl	(B.P.) 164°/0.6 mm.	C, 35.78; H, 2.67; N, 13.92	C, 36.02; H, 2.55; N, 14.04.
28.....	2-furyl	188°-189°	C, 48.59; H, 2.04; N, 17.00	C, 48.86; H, 2.16; N, 17.19.
29.....	2,4-diketo-6-pyrimidinyl	321°-322°	C, 41.25; H, 1.73; N, 24.05	C, 41.14; H, 1.90; N, 24.15.
30.....	2-thienyl	201°-202°	C, 45.64; H, 1.92; N, 15.97	C, 45.39; H, 1.88; N, 15.76.
31.....	2-carboxyethyl	167°	C, 42.69; H, 2.79; N, 16.60	C, 42.92; H, 2.68; N, 16.40.
32.....	2-hydroxyphenyl	251°-252°	C, 52.75; H, 2.58; N, 15.38	C, 53.04; H, 2.76; N, 15.21.
33.....	Hydrogen	115.5°-116.5°	C, 39.79; H, 1.67; N, 23.20	C, 40.07; H, 1.68; N, 23.03.
34.....	Carboethoxy	143°	C, 42.69; H, 2.79; N, 16.60	C, 42.69; H, 3.04; N, 16.49.
35.....	5-chloro-2-thienyl	163°-164°	C, 40.35; H, 1.36; N, 14.12	C, 40.21; H, 1.28; N, 14.26.
36.....	4,5-dibromo-2-thienyl	214°-215°	C, 28.53; H, 0.72; N, 9.98	C, 28.67; H, 0.87; N, 10.02.
37.....	3,4,5-trichlorofuryl	164°-165°	C, 34.26; H, 0.29; N, 11.99	C, 34.17; H, 0.56; N, 11.96.
38.....	2,4-dichlorophenyl	137°-138°	C, 44.19; H, 1.54; N, 14.63	C, 44.16; H, 1.48; N, 12.52.
39.....	Phenoxyethyl	168°-169°	C, 54.36; H, 3.16; N, 14.63	C, 54.44; H, 2.30; N, 13.82.
40.....	4-methoxyphenyl	188°-189°	C, 54.36; H, 3.16; N, 14.63	C, 54.46; H, 3.11; N, 14.53.
41.....	4-ethoxyphenyl	185°-186°	C, 55.81; H, 3.68; N, 13.95	C, 56.12; H, 3.68; N, 13.54.
42.....	4-n-butoxyphenyl	131°-133°	C, 58.35; H, 4.59; N, 12.76	C, 58.46; H, 4.78; N, 12.76.
43.....	3-n-propoxyphenyl	123°-125°	C, 57.14; H, 4.16; N, 13.33	C, 56.99; H, 4.36; N, 13.33.
44.....	4-n-propoxyphenyl	164°-165°	C, 57.14; H, 4.16; N, 13.33	C, 56.98; H, 4.26; N, 13.09.

Water was formed and the residue recrystallized from acetonitrile to obtain the desired oxadiazole as a white solid which melted at 192° C.

Analysis.—Calculated: C, 51.17%; H, 2.34%; N, 21.70%. Found: C, 51.32%; H, 2.28%; N, 21.71%.

In like manner, by heating at or above the melting point a compound of Formula D wherein R is phenoxyethyl, o-hydroxyphenyl, p-aminophenyl, p-nitrophenyl, p-methoxyphenyl, o-methylthiophenyl, p-sulfonamidophenyl, 4-chloro-3-sulfonamidophenyl, furyl, thienyl, pyrimidyl, bromofuryl, chlorothiophenyl, oxazyl, isoxazyl, quinolyl, isoquinolyl, pyrazyl, carboethoxy, carbomethoxyvinyl, furylmethyl, thienylmethyl, pyrazinyl, thiazyl, or imidazyl, the corresponding R-substituted oxadiazoles of Formula A are obtained.

EXAMPLE 7

3-(5-nitro-2-furyl)-5-benzyl-1,2,4-oxadiazole
R=propenyl in Formula B

A quantity of O-phenylacetyl-5-nitro-2-furylamidoxime is heated at its melting point for 15 minutes to liberate water and obtain the above-named oxadiazole having a molecular weight of 273.

EXAMPLE 8

3-(5-nitro-2-furyl)-5-propenyl-1,2,4-oxadiazole
R=propenyl in Formula B

This compound was prepared by heating O-crotonyl-5-nitrofurylamidoxime melting at 184° C. to a temperature of 190° C. for 10 minutes. After recrystallization from ethanol, the product melted at 145° C. Identity was confirmed by elemental analysis.

EXAMPLE 9

3-(5-nitro-2-furyl)-5-carbomethoxyethyl-1,2,4-oxadiazole
R=carbomethoxyethyl in Formula B

Three grams of O-carbomethoxypropionyl-5-nitrofurylamidoxime melting at 145° C. was heated at 190° C. to liberate water and close the ring. The brown liquid formed solidified upon the addition of ethanol and after recrystallization from boiling ethanol the desired oxadiazole was

The O-substituted 5-nitro-2-furylamidoximes employed as starting materials are known compounds or can be prepared by known methods. Thus, 5-nitro-2-furylamidoxime may be refluxed with an equimolar amount of an R-substituted acid chloride of the formula RCOCl in benzene and in the presence of an HCl acceptor. When the reaction is complete, the reaction mixture is cooled and concentrated to precipitate the desired product which can then be recrystallized from a suitable solvent.

The compound wherein R is carboxamido was likewise made by the methods previously described and found to have a melting point of 220°-221° C. Alternatively, this compound can be made by ammonolysis of the compound of Example 34.

Suitable solvents which may be used in the preparation of any of the enumerated compounds are benzene, chlorobenzene, toluene, xylene, or dimethylformamide.

If desired, other O-acyl-5-nitro-2-furylamidoximes can be heated at or above their melting points, in the absence or presence of a suitable solvent, to liberate water and effect ring closure to obtain the corresponding oxadiazoles wherein R of Formula B of o-mercaptophenyl, pyridylethenyl, thienylalkenyl, loweralkylthiophenyl, furylloweralkyl, aminophenyl, nitrophenyl, halosulfonamidophenyl, sulfonamidophenyl, carboloweralkoxyvinyl, isoxazyl, isoquinolyl, imidazyl, or thiazyl.

EXAMPLE 45

5-(5-nitro-2-furyl)-3-chloromethyl-1,2,4-oxadiazole
R=chloromethyl in Formula C

A solution of 10.26 grams of O-(5-nitro-2-furoyl)-chloroacetamidoxime in 175 ml. of n-butanol was heated under reflux for 2 hours. The reaction mixture was then concentrated and distilled under reduced pressure to obtain the desired oxadiazole which boiled at 149° C. at 0.25 mm. pressure and had a refractive index n_D^{25} of 1.6038. Upon analysis, the product was found to contain 18.35% nitrogen compared to the calculated value of 18.30% nitrogen.

Similarly, by heating at or slightly above their melting points in the presence or absence of a solvent such

compounds as O-(5-nitro-2-furoyl)-bromoacetamidoxime, O-(5-nitro-2-furoyl)-iodoacetamidoxime, O-(5-nitro-2-furoyl)-dichloroacetamidoxime, or O-(5-nitro-2-furoyl)- γ -chlorobutyramidoxime, there is readily obtained the following oxadiazoles, respectively, wherein R in Formula C is bromomethyl, iodomethyl, dichloromethyl, or γ -chloropropyl.

If desired, other O-(5-nitro-2-furoyl)-haloloweralkylamidoximes can be heated at or above their melting points to liberate water and produce the corresponding 5-(5-nitro-2-furyl)-3-haloloweralkyl-1,2,4-oxadiazoles wherein R of Formula C is trifluoromethyl, α,α,γ -trichloropropyl, α,α -dibromobutyl, α,γ -diiodobutyl, α -chloro- β -bromovaleryl, trichloromethyl, or α -bromovaleryl and similar haloloweralkyl radicals.

EXAMPLE 46

5-(5-nitro-2-furyl)-3-(4-sulfonamidophenyl)-1,2,4-oxadiazole

R=sulfonamidophenyl in Formula C

To 11 grams (0.05 mole) of p-sulfonamidobenzamidoxime and 3.53 grams (0.025 mole) of potassium carbonate in 150 ml. of acetone was added with stirring 8.96 grams (0.05 mole) of 5-nitro-2-furoyl chloride in 25 ml. of acetone. The mixture was refluxed for 4 hours, and the solid which formed upon cooling was separated by filtration and recrystallized from a dimethylformamide-water mixture to obtain the desired oxadiazole which melted at 247° C.

Analysis.—Calculated: C, 42.84%; H, 2.40%; N, 16.66%. Found: C, 42.93%; H, 2.44%; N, 16.61%.

In like manner, the reaction of 5-nitro-2-furoyl chloride with an R-substituted amidoxime wherein R is phenoxymethyl, hydroxyphenyl, methoxyphenyl, acylaminophenyl, methylthiophenyl, furyl, thienyl, pyrimidyl, oxazyl, bromofuryl, chlorothieryl, isoxazyl, quinolyl, isoquinolyl, pyrazyl, carbethoxy, pyrazinyl, thiazyl, carbomethoxyethyl, or carbazamidomethyl, the corresponding R-substituted oxadiazoles of Formula C are obtained.

EXAMPLE 47

5-(5-nitro-2-furyl)-3-methyl-1,2,4-oxadiazole

R=methyl in Formula C

O-(5-nitro-2-furoyl)-acetamidoxime is heated above its melting point for 15 minutes. The reaction mixture is then crystallized from ethanol to obtain the desired oxadiazole having a molecular weight of 195.

By heating O-(5-nitro-2-furoyl)-formamidoxime, O-(5-nitro-2-furoyl)-propionamidoxime, O-(5-nitro-2-furoyl)-butyramidoxime, or O-(5-nitro-2-furoyl)-valeramidoxime

EXAMPLE 48

5-(5-nitro-2-furyl)-3-halophenyl-1,2,4-oxadiazoles

R=halophenyl in Formula C

By heating O-(5-nitro-2-furoyl)-3-chlorobenzamidoxime, O-(5-nitro-2-furoyl)-4-chlorobenzamidoxime, or O-(5-nitro-2-furoyl)-2,5-dichlorobenzamidoxime slightly above their melting points for about 5 minutes there is obtained the following oxadiazoles, respectively, wherein R in Formula C is 3-chlorophenyl, 4-chlorophenyl, or 2,5-dichlorophenyl.

In like manner, other O-(5-nitro-2-furoyl)-halo benzamidoximes such as O-(5-nitro-2-furoyl)-fluoro benzamidoxime, O-(5-nitro-2-furoyl)-2,4-dibromobenzamidoxime, O-(5-nitro-2-furoyl)-3,5-difluorobenzamidoxime, O-(5-nitro-2-furoyl)-2-iodobenzamidoxime, or O-(5-nitro-2-furoyl)-2-chloro-4-bromobenzamidoxime can be heated at or above their melting points to produce the corresponding 5-(5-nitro-2-furyl)-3-halophenyl-1,2,4-oxadiazoles.

EXAMPLE 49

5-(5-nitro-2-furyl)-3-benzyl-1,2,4-oxadiazole

R=benzyl in Formula C

A quantity of O-(5-nitro-2-furoyl)-benzacetamidoxime is heated at its melting point for 15 minutes to liberate water and obtain the above-named oxadiazole having a molecular weight of 273.

EXAMPLE 50

5-(5-nitro-2-furyl)-3-(p-nitrophenyl)-1,2,4-oxadiazole

R=nitrophenyl in Formula C

O-(5-nitro-2-furoyl)-p-nitrobenzamidoxime (5.56 g., 0.017 mole) was heated at 230° C. under reduced pressure for 5 minutes. The resulting product was crystallized from nitromethane and melted at 212° C.

Analysis.—Calculated: C, 47.69%; H, 2.00%; N, 18.54%. Found: C, 47.65%; H, 2.26%; N, 18.72%.

EXAMPLE 51

By heating O-(5-nitro-2-furoyl)-picolinamidoxime above its melting point of 217° C. for 5 minutes, water was liberated and the desired 5-(5-nitro-2-furyl)-3-(2-pyridyl)-1,2,4-oxadiazole which formed was crystallized from nitromethane. M.P.=199° C.

Analysis.—Calculated: C, 51.17%; H, 2.34%; N, 21.70%. Found: C, 51.19%; H, 2.50%; N, 21.87%.

Using methods exemplified in the foregoing examples, the following compounds, wherein R refers to substitutions in Formula C, were made.

Example	R	Melting Point	Analyses	
			Calculated	Found
52	CH ₂ Cl (chloromethyl)	56°-58°	C, 36.62; H, 1.77; N, 18.30	C, 36.68; H, 1.79; N, 18.35
53	2-pyridyl	198°-199°	C, 51.17; H, 2.34; N, 21.70	C, 51.19; H, 2.50; N, 21.87
54	4-pyridyl	152°-153°	C, 51.17; H, 2.34; N, 21.70	C, 51.48; H, 2.25; N, 21.70
55	4-pyridyl methiodide	187°-189°	C, 36.02; H, 2.27; N, 14.00	C, 36.27; H, 2.32; N, 14.03
56	p-Methoxyphenyl	177°-178°	C, 54.36; H, 3.16; N, 14.63	C, 54.60; H, 3.15; N, 14.42
57	3-pyridyl	166°-167°	C, 51.17; H, 2.34; N, 21.70	C, 51.13; H, 2.27; N, 21.64
58	3-pyridyl-N-oxide	256° dec.	C, 48.17; H, 2.21; N, 20.43	C, 48.27; H, 2.26; N, 20.54
59	3-pyridylmethiodide	206° dec.	C, 36.02; H, 2.27; N, 14.00	C, 35.94; H, 2.49; N, 14.01
60	3-pyridyl-N-oxide	208°-209° dec.	C, 48.17; H, 2.21; N, 20.43	C, 48.08; H, 2.18; N, 20.34
61	p-Sulfonamidophenyl	247° dec.	C, 42.85; H, 2.40; N, 16.66	C, 42.93; H, 2.44; N, 16.61
62	p-Nitrobenzyl	110°-111°	C, 49.40; H, 2.55; N, 17.72	C, 49.53; H, 2.47; N, 17.92
63	3,4-dimethoxybenzyl	112°-114°	C, 54.40; H, 3.96; N, 12.68	C, 54.23; H, 4.02; N, 12.80
64	3-chlorophenyl	149°-150°	C, 49.50; H, 2.06; N, 14.40	C, 49.53; H, 2.22; N, 14.27
65	4-chlorobenzyl	133°	C, 51.15; H, 2.63; N, 13.72	C, 51.47; H, 2.64; N, 13.60
66	4,4-dimethyl phenyl	163°-165°	C, 58.95; H, 3.89; N, 14.73	C, 58.99; H, 3.91; N, 14.82
67	p-Methyl phenyl	167°-168°	C, 57.56; H, 3.34; N, 15.50	C, 57.30; H, 3.29; N, 15.37
68	p-chlorophenyl	162°-164°	C, 49.42; H, 2.07; N, 14.41	C, 49.55; H, 2.31; N, 14.27
69	3-chloro-4-methylphenyl	149°-151°	C, 51.07; H, 2.64; N, 13.75	C, 51.17; H, 2.85; N, 13.79
70	2-furyl	193°-195° dec.	C, 48.59; H, 2.04; N, 17.00	C, 48.88; H, 2.14; N, 17.15
71	3-picolyl	104°-106°	C, 52.94; H, 2.96; N, 20.58	C, 52.87; H, 3.08; N, 20.70
72	1-isoquinolyl	197°-199°	C, 58.44; H, 2.62; N, 18.18	C, 58.60; H, 2.57; N, 18.13
73	2-quinolyl	245°-247°		

above their melting points, there is obtained the corresponding oxadiazoles wherein R of Formula C is hydrogen, ethyl, propyl, or butyl, respectively.

The R-substituted amidoximes employed as one of the starting materials are known compounds or can be prepared by refluxing equimolar amounts of an alkali metal

hydroxide, hydroxylamine hydrochloride, and a nitrile of the formula $R-C\equiv N$ in ethanol. The solution is filtered and the filtrate concentrated to recover the desired amidoxime as a residue which can be purified by recrystallization from a suitable solvent.

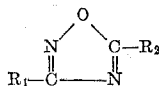
In like manner, other O-(5-nitro-2-furoyl) amidoximes can be heated at or above their melting points, in the absence or presence of a suitable solvent, to liberate water and effect ring closure to obtain the corresponding oxadiazoles wherein R of the Formula C is aryloxyloweralkyl, aminophenyl, mercaptophenyl, loweralkylthio-
phenyl, halosulfonamidophenyl, halopyridyl, carboxamido, carboalkoxy, carboalkoxyloweralkyl, carboalkoxyvinyl, loweralkenyl, furylalkenyl, thienylalkenyl, pyridylalkenyl, pyrimidyl, halopyrimidyl, halofuryl, halothieryl, furylloweralkyl, thienylloweralkyl, oxazolyl, imidazolyl, or pyrazinyl.

Referring to Formula B, the compound wherein R is acetylthiomethyl was made by methods herein disclosed and found to have a melting point of 112°–114° C. Upon analysis, the compound was found to contain 40.17% carbon, 2.72% hydrogen, 15.69% nitrogen, and 11.76% sulfur compared to the calculated values of 40.14% carbon, 2.62% hydrogen, 15.61% nitrogen, and 11.91% sulfur.

While the invention has been illustrated by the foregoing examples, it will be apparent that various equivalent changes and modifications may be resorted to without departing from the spirit thereof.

What is claimed is:

1. A compound of the formula



wherein when one of R_1 and R_2 is 5-nitro-2-furyl, the other is a member of the group consisting of hydrogen, alkyl, mono or di haloalkyl, mono or di halophenyl, mono or di methylphenyl, halomethylphenyl, phenoxyloweralkyl, hydroxyphenyl, aminophenyl, nitrophenyl, loweralkoxyphenyl, mercaptophenyl, acetylthiomethyl, loweralkylthiophenyl, halosulfonamidophenyl, sulfonamidophenyl, phenylalkyl, halophenylalkyl, alkoxyphenylalkyl, pyridyl, pyridylloweralkyl, halopyridyl, carboxamido, carbomethoxy, carbomethoxyloweralkyl, propenyl, furyl, thienyl, pyrimidyl, halopyrimidyl, halofuryl, halothieryl, furylloweralkyl, quinolyl, isoquinolyl, and pyrazinyl; the terms "loweralkyl" and "alkoxy" including the straight and branched alkyl and alkoxy radicals containing from one to five carbon atoms, inclusive, while "alkyl" includes radicals containing up to 17 carbon atoms.

2. A compound as claimed in claim 1 wherein R_1 is 5-nitro-2-furyl and R_2 is a member of the group consisting of hydrogen, alkyl, mono or di haloalkyl, mono or dihalophenyl, phenylalkyl, halophenylalkyl, alkoxyphenylalkyl, phenylalkyl, halophenylalkyl, alkoxyphenylalkyl, pyridyl, pyridylloweralkyl, halopyridyl, carboxamido, carbomethoxy, carbomethoxyloweralkyl, propenyl, furyl, thienyl, pyrimidyl, halopyrimidyl, halofuryl, halothieryl, furylloweralkyl, quinolyl, isoquinolyl, and pyrazinyl; the terms "loweralkyl" and "alkoxy" including the straight and branched alkyl and alkoxy radicals containing from one to five carbon atoms, inclusive, while "alkyl" includes radicals containing up to 17 carbon atoms.

thiomethyl, loweralkylthiophenyl, halosulfonamidophenyl, sulfonamidophenyl, phenylalkyl, halophenylalkyl, alkoxyphenylalkyl, pyridyl, pyridylloweralkyl, halopyridyl, carboxamido, carbomethoxy, carbomethoxyloweralkyl, propenyl, furyl, thienyl, pyrimidyl, halopyrimidyl, halofuryl, halothieryl, furylloweralkyl, quinolyl, isoquinolyl, and pyrazinyl; the terms "loweralkyl" and "alkoxy" including the straight and branched alkyl and alkoxy radicals containing from one to five carbon atoms, inclusive, while "alkyl" includes radicals containing up to 17 carbon atoms.

3. A compound as claimed in claim 2 wherein R_2 is mono or di haloalkyl.

4. A compound as claimed in claim 2 wherein R_2 is loweralkyl.

5. A compound as claimed in claim 2 wherein R_2 is a member of the group consisting of mono and di halophenyl.

6. A compound as claimed in claim 2 wherein R_2 is a member of the group consisting of mono and di loweralkoxyphenyl.

7. A compound as claimed in claim 1 wherein R_2 is 5-nitro-2-furyl and R_1 is a member of the group consisting of hydrogen, alkyl, mono or di haloalkyl, mono or dihalophenyl, mono or di methylphenyl, halomethylphenyl, phenoxyloweralkyl, hydroxyphenyl, aminophenyl, nitrophenyl, loweralkoxyphenyl, mercaptophenyl, acetylthiomethyl, loweralkylthiophenyl, halosulfonamidophenyl, sulfonamidophenyl, phenylalkyl, halophenylalkyl, alkoxyphenylalkyl, pyridyl, pyridylloweralkyl, halopyridyl, carboxamido, carbomethoxy, carbomethoxyloweralkyl, propenyl, furyl, thienyl, pyrimidyl, halopyrimidyl, halofuryl, halothieryl, furylloweralkyl, quinolyl, isoquinolyl, and pyrazinyl; the terms "loweralkyl" and "alkoxy" including the straight and branched alkyl and alkoxy radicals containing from one to five carbon atoms, inclusive, while "alkyl" includes radicals containing up to 17 carbon atoms.

8. A compound as claimed in claim 7 wherein R_1 is a member of the group consisting of mono or di haloloweralkyl.

9. A compound as claimed in claim 7 wherein R_1 is loweralkyl.

10. A compound as claimed in claim 7 wherein R_1 is a member of the group consisting of mono or di halophenyl.

References Cited

UNITED STATES PATENTS

3,337,541 8/1967 Haraoka et al. ----- 260—307

ALEX MAZEL, Primary Examiner

R. J. GALLAGHER, Assistant Examiner

U.S. Cl. X.R.

260—251, 256.4, 288, 296, 302; 424—250, 251, 258, 263, 270, 272