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## BASIC ESTERS OF CERTAIN SUBSTITUTED ISOXAZOLE-4-CARBOXYLIC ACIDS

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14 Claims

### ABSTRACT OF THE DISCLOSURE

This invention relates to the provision of a new class of compounds. It relates further to new compositions of matter which are useful in the control of trichomoniasis. It relates further to the use of such compositions in the treatment of trichomoniasis. More specifically, it relates to the provision of esters of 3-(or 5)-(5'-nitrofur-2'-yl)-5-(or 3)-(lower)alkyl-isoxazol-4-yl carboxylates characterized by trichomonocidal activity.

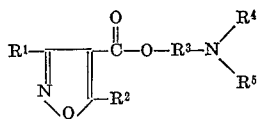
### BACKGROUND OF THE INVENTION

Trichomoniasis is a disease caused by trichomonads in both humans and animals. The disease in the human female is characterized by a persistent vaginal discharge. The trichomonad also sometimes invades the male urethra and bladder. In animals, trichomoniasis is a venereal disease accompanied by abortion, sterility and pyometra. Because of the seriousness of the disease, various attempts have been made to develop effective trichomonocidal agents. These attempts have been successful in part, but an agent which is effective against one species of trichomonad may not be as effective against another species, and it is not uncommon to find that a trichomonocide which is generally non-toxic to one species of host may be toxic to specific members of that species. Thus, there is a continuing need for the development of new trichomonocidal composition for the medical armamentarium so that treatment of a particular individual can be adjusted to that individual by choice of the trichomonocidal compound which best suits the immediate situation.

It is thus an object of the present invention to provide a new class of chemical compounds. It is another object of this invention to provide new trichomonocidal compositions of matter. It is a further object of the present invention to provide a method of treating trichomoniasis which involves administering the new trichomonocidal compositions of this invention in a suitable dosage unit form. Other objects of this invention will be apparent from the ensuing description.

### SUMMARY OF THE INVENTION

The present invention is based upon the discovery of new compounds and of good trichomonocidal activity therein. These compounds are (lower)alkyl esters of 3-(or 5)-(5'-nitrofur-2'-yl)-5-(or 3)-(lower)alkyl-isoxazol-4-yl carboxylates which may be characterized by the following general formula I:

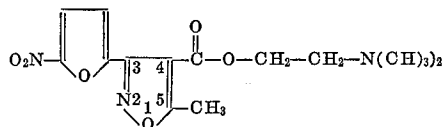


wherein one of R<sup>1</sup> and R<sup>2</sup> is 5'-nitro-2'-furyl and the other is a (lower)alkyl; R<sup>3</sup> is a (lower)alkylene or (lower)alkylidene; R<sup>4</sup> and R<sup>5</sup> may be each a (lower)alkyl or together may form a ring system of up to ten atoms which may contain an additional heteroatom, such as oxygen or

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sulfur. The term "(lower)alkyl" as used herein means straight, cyclic and branched chain alkyl groups having from one to six carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, amyl, cyclohexyl, hexyl, etc. The terms "(lower)alkylene" and "(lower)alkylidene" as used herein mean straight and branched chain hydrocarbon residues, respectively, having from one to ten carbon atoms, such as methylene, ethylene, propylene, ethylidene, etc.

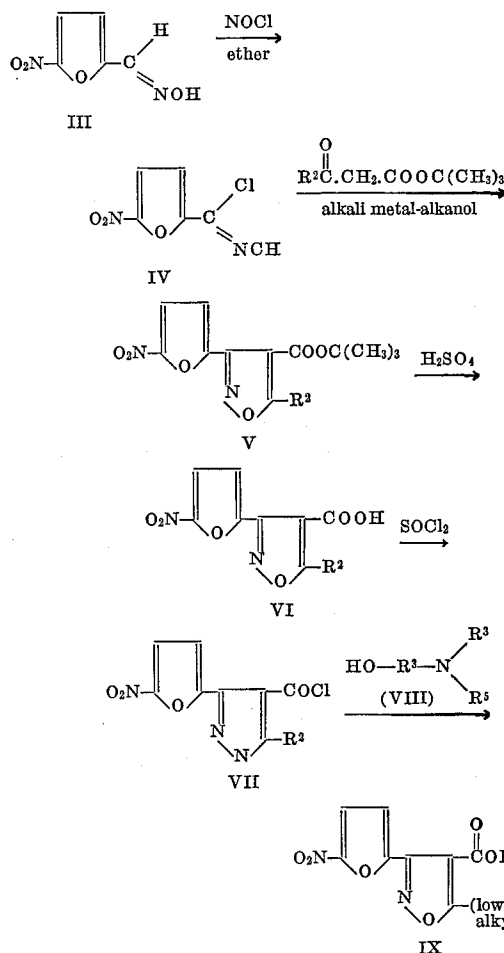
The preferred embodiments of the present invention are the dialkylaminoalkyl esters an example of which is the compound of the Formula II:



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and is named, for example, di-N-methylaminoethyl 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate.

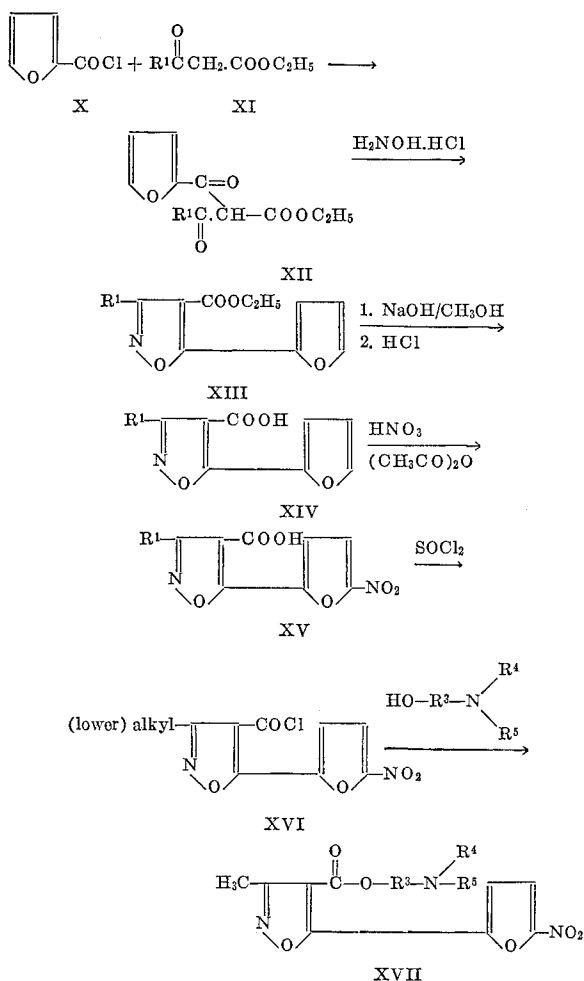
The 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate esters are prepared from 5-nitrofur-2-aldoxime according to the following scheme in which R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> have the meaning set forth above.



The 3-(lower)alkyl-5-(5'-nitro-2'-furyl)isoxazol-4-carboxylate esters were prepared according to the following

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scheme in which R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> have the meaning set forth above.



In the foregoing reaction scheme, 5-nitrofur-2-aldoxime (III) (M.P. 114–116°), which was formed from 5-nitrofurfural on treatment with hydroxylamine hydrochloride, was chlorinated with nitrosyl chloride in ether [following the general procedure of Reinholdt et al., Ann. 451, 161 (1926)] giving the chloraldoxime (IV), M.P. 104–107°. Compound IV was condensed with a tert-butyl alkanoylacetate (e.g., the acetoacetate) in the presence of an alkali metal alkoxide in an alkanol (e.g., sodium methoxide in methanol [following the procedure of Doyle et al., J. Chem. Soc. 5845 (1963)]) to give tert-butyl 5-(lower)alkyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate (V). Hydrolysis of the latter with concentrated sulfuric acid for two hours at 60° gives 5-(lower)alkyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylic acid (VI). Heating Compound VI with thionyl chloride under reflux for five hours gives 5-(lower)alkyl-3-(5'-nitro-2'-furyl)isoxazol-4-carbonyl chloride (VII). By condensation of Compound VII with various amino alcohols (VIII), compounds of Formula IX are obtained. Condensation with amino alcohols of Formula VIII is normally conducted at reduced temperature (e.g., on an ice bath) in a water-miscible organic solvent such as acetone. There may be present in the reaction mixture an organic base such as triethylamine or pyridine. The condensation is a mildly exothermic reaction and yields a solid material which can be washed up by extraction and recrystallization techniques to give the desired product of Formula IX.

The 3-(lower)alkyl-5-(5'-nitro-2'-furyl)isoxazol-4-carboxylate esters are prepared from 2-furoyl chloride (X) by condensation with an alkali metal salt of an alkyl alkanoylacetate (e.g. sodio ethyl acetoacetate) in the pres-

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ence of an inert solvent (e.g. benzene) to give Compound XII which is treated with hydroxylamine hydrochloride, giving Compound XIII, ethyl 3-R<sup>1</sup>-5-(2'-furyl)-isoxazol-4-carboxylate. The latter is hydrolyzed with an alcoholic base or acid to Compound XIV, 3-R<sup>1</sup>-5-(2'-furyl)-isoxazol-4-carboxylic acid. The acid is nitrated with concentrated nitric acid in acetic anhydride to give Compound XV, 3-R<sup>1</sup>-5-(5'-nitro-2'-furyl)isoxazol-4-carboxylic acid. Compound XV may be converted to the 4-carbonyl chloride (Compound XVI) by heating under reflux for about two–three hours with thionyl chloride. Condensation of Compound XVI with an aminoalcohol of Formula VIII as described above, gives the desired compounds of Formula XVII.

Among the aminoalcohols of Formula VIII which are useful for the above-described reactions with Compounds VII or XVI are di-N-methylethanolamine, di-N-methyl-γ-aminopropanol, di-N-cyclohexylethanolamine, 3-azabicyclo[3.2.2]nonane-3-ethanol, N-methylol-pyrrolidone, N-methylol-morpholine, N-methylol-thiamorpholine, and the like.

The compounds of Formula I are anti-bacterial agents which exhibit significant in vitro and in vivo inhibitory activity against *Trichomonas foetus* and *Trichomonas vaginalis*. Trichomonocidal compositions can be formulated with the compounds of the present invention as the active component so as to be administered in the form of tablets, dragees, capsules, suppositories, injectable liquids or liquids to be administered in drops, emulsions, suspensions, syrups and the like. The formulation should contain the active trichomonocidal component and conventional pharmaceutical excipients. The trichomonocidal compositions should contain at least 0.1% of the active trichomonocidal component. The actual percentage of the active component in the composition may be varied and should conveniently be between about 2% and 60%, or more, of the weight of each dosage unit. The amount of active ingredient in a therapeutically useful composition or preparation should be such that a suitable dosage unit will be obtained. In general, the trichomonocidal compositions of the present invention should contain an amount of active ingredient such that the dosage schedule will result in the daily administration of between 10 and 500 mg./kg. of body weight of animal being treated.

The following examples are presented to further illustrate the present invention.

#### EXAMPLE 1

Di-N-methyl-β-aminoethyl 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate

5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carbonyl chloride (12.8 g., 0.05 mole) was dissolved in acetone (400 ml.) and this solution was cooled in an ice-salt bath. Di-N-methyl-ethanolamine (12.7 g. of a 70% aqueous solution; 0.1 mole) was added slowly to the stirred solution. There was a mild exothermic reaction and a solid separated. The reaction mixture was left at room temperature for three hours, the acetone then removed under reduced pressure, water (100 ml.) added, and the mixture extracted with ether (4 × 100 ml.). A small amount of insoluble material was discarded. The combined ether extracts were dried over magnesium sulfate, filtered and solvent removed when an oil was obtained. The oil was extracted with hot hexane and the insoluble material discarded. On cooling the hexane solution, di-N-methyl-β-aminoethyl 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate crystallized as yellow needles, M.P. 46–48°, weight 15.4 g. (62%). The infrared and n.m.r. spectra agree with the proposed structure.

#### EXAMPLE 2

Di-N-methyl-γ-aminopropyl 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate

Di-N-methyl-γ-aminopropanol (1.7 g., 16 mmole) dissolved in acetone (10 ml.), was added dropwise to a

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stirred ice-cold solution of 5-methyl-3-(5'-nitro-2'-furyl) isoxazol-4-carbonyl chloride (2.05 g., 8 mmole) in acetone (50 ml.). There was an immediate reaction as shown by the formation of a precipitate. After three hours at room temperature, the acetone was removed under reduced pressure, water (50 ml.) added, and the mixture extracted with ethyl acetate (3 × 50 ml.). The combined ethyl acetate layers were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The oil that was thus obtained crystallized on cooling with scratching. It was recrystallized from hexane, discarding a small amount of hexane insoluble material. The yield of 0.6 g. (24%) of di-N-methyl- $\gamma$ -aminopropyl 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate, M.P. 45–46°, was obtained. The infrared and n.m.r. spectra are in agreement with the assigned structure.

## EXAMPLE 3

Preparation of di-N-methyl- $\gamma$ -aminopropyl 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate

A mixture of triethylamine (54.5 g., 0.54 mole) and di-N-methyl- $\gamma$ -aminopropanol (50.5 g., 0.49 mole) in anhydrous acetone (400 ml.) was added slowly to an ice-cold stirred solution of 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carbonyl chloride (115.4 g., 0.45 mole) in acetone (1900 ml.). The reaction mixture was left at room temperature for three hours and the insoluble material filtered. The insoluble material was discarded since it showed no carbonyl absorption in the infrared. The filtrate was concentrated under reduced pressure and the residue extracted with ethyl acetate (1 liter) and filtered. The solid was discarded. The ethyl acetate layer was extracted with brine and dried over magnesium sulfate, filtered and the ethyl acetate removed under reduced pressure. The residue was extracted with hot hexane (3 × 1 liter). The hexane solution, when cooled, deposited bright yellow crystals, weight 73.2 g. (50%), M.P. 46–48°. The infrared and n.m.r. spectra of this compound were identical with those obtained in Example 2.

## EXAMPLE 4

Di-N-ethyl- $\beta$ -aminoethyl 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate

Di-N-ethyl- $\beta$ -aminoethanol (0.468 g., 4 mmole) dissolved in anhydrous acetone (10 ml.) was added to a stirred ice-cold solution of 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carbonyl chloride (1.026 g., 4 mmole) in anhydrous acetone (40 ml.). The mixture was left at room temperature overnight and acetone removed under reduced pressure. The residue was shaken with 1 N aqueous sodium hydroxide (50 ml.) and ether (50 ml.). The ether layer was dried over magnesium sulfate, filtered and the ether removed under reduced pressure when an oil was obtained. The oil was extracted with hot hexane (4 × 50 ml.). On cooling the hexane solution 0.5 g. (83%) of di-N-ethyl- $\beta$ -aminoethyl 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate, M.P. 35–38°, was obtained. The infrared and n.m.r. spectra are in agreement with the assigned structure.

## EXAMPLE 5

Preparation of Di-N-ethyl- $\beta$ -aminoethyl 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate

A solution of di-N-ethyl- $\beta$ -aminoethanol (59.0 g., 0.5 mole) in anhydrous acetone (400 ml.) was added to a stirred ice-cold solution of 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carbonyl chloride (65.0 g., 0.25 mole) in acetone (2 liters). The reaction mixture was left at room temperature overnight and the acetone removed under reduced pressure. Ice water (1 liter) was added, and the mixture extracted with ethyl acetate (3 × 300 ml.). The ethyl acetate layer was dried over magnesium sulfate, filtered and ethyl acetate removed under reduced pressure when an oil was obtained. The oil was extracted with hot hexane (4 × 500 ml.). A yield of 73 g. (87%) of yellow

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crystals, M.P. 36–41° was obtained on cooling the hexane solution. The infrared and n.m.r. spectra of this compound were identical with those obtained from the compound in Example 4.

## EXAMPLE 6

Di-N-ethyl- $\beta$ -aminoethyl 3-methyl-5-(5'-nitro-2'-furyl)isoxazol-4-carboxylate

A solution of di-N-ethyl- $\beta$ -aminoethanol (3.5 g., 0.03 mole) in acetone (10 ml.) was added to a stirred ice-cold solution of 3-methyl-5-(5'-nitro-2'-furyl)isoxazol-4-carbonyl chloride (3.9 g., 0.015 mole) in acetone (90 ml.). The reaction mixture was left at room temperature overnight and the acetone removed under reduced pressure. Water (50 ml.) was added to the residue and the mixture extracted with ethyl acetate (3 × 50 ml.). The combined ethyl acetate extracts were extracted with brine (2 × 25 ml.), dried over magnesium sulfate, filtered and solvent removed under reduced pressure. The resulting solid was recrystallized from hexane (discarding the insoluble oily residue). On cooling, 3.4 g. (68%) of di-N-ethyl- $\beta$ -aminoethyl 3-methyl-5-(5'-nitro-2'-furyl)isoxazol-4-carboxylate, M.P. 65–67°, was obtained as yellow crystals. The infrared and n.m.r. spectra are in agreement with the assigned structure.

## EXAMPLE 7

Di-N-methyl- $\beta$ -amino- $\alpha$ -methylethyl 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate

A solution of 1-di-N-methylamino-2-propanol (1.7 g., 16 mmole) in acetone (10 ml.) was added to a stirred ice-cold solution of 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carbonyl chloride (2.05 g., 8 mmole), in acetone (50 ml.), and the reaction mixture was left at room temperature overnight and concentrated under reduced pressure. The residue was mixed with water (50 ml.) and extracted with ethyl acetate (3 × 50 ml.). The combined ethyl acetate layers were extracted with brine (2 × 25 ml.), dried over magnesium sulfate, and the solvent removed under reduced pressure. The residue, an oil which crystallized on scratching, was recrystallized from hexane to give 1 g. (40%) of light-sensitive crystals, M.P. 46°. The infrared and n.m.r. spectra were in agreement with the assigned structure.

## EXAMPLE 8

Di-N-ethyl- $\beta$ -amino- $\alpha$ -methylethyl 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate

A solution of 1-di-N-ethylamino-2-propanol (2.1 g., 16 mmole) in acetone (10 ml.) was added to a stirred ice-cold solution of 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carbonyl chloride (2.05 g., 8 mmole) in acetone (50 ml.) and the reaction mixture left overnight at room temperature. The acetone was removed under reduced pressure, water (50 ml.) added, and the mixture extracted with ethyl acetate (3 × 50 ml.). The combined ethyl acetate layers were extracted with brine (2 × 25 ml.), dried over magnesium sulfate, filtered, and ethyl acetate removed under reduced pressure. The residue, an oil which crystallizes on scratching, crystallized from hexane as yellow crystals, M.P. 43–45°, weight 1.0 g. (35%). The infrared and n.m.r. spectra were in agreement with the assigned structure.

## EXAMPLE 9

Di-N-methyl- $\beta$ -amino- $\beta$ -dimethylethyl 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carboxylate

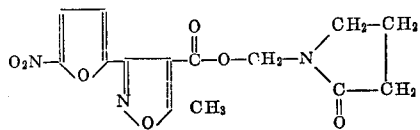
A solution of 2-di-N-methylamino-2-methyl-1-propanol (1.0 g., 16 mmole) in acetone (10 ml.) was added to a stirred, ice-cold solution of 5-methyl-3-(5'-nitro-2'-furyl)isoxazol-4-carbonyl chloride (2.05 g., 8 mmole) in acetone (50 ml.), and the reaction mixture left overnight at room temperature. The acetone was removed under reduced pressure, water (50 ml.) added and the mixture extracted with ethyl acetate (3 × 50 ml.). The combined



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14. The compound having the formula



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ALTON D. ROLLINS, Primary Examiner

U.S. Cl. X.R.

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