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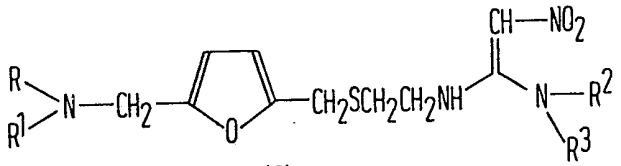
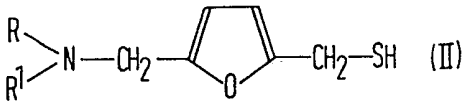
(54) Process for preparing N-[2-[[[5-dialkylaminomethyl-2-furamyl]-methyl]-thio]-ethyl]-N′-alkyl-2-nitro-1,1-ethene diamines

(57) The novel process for preparing the title compounds of the formula

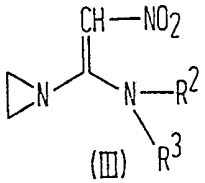


(I)

where R, R^1, R^2 and R^3 are independently H or C_{1-3} alkyl comprises reacting a compound II with a compound III



(II)

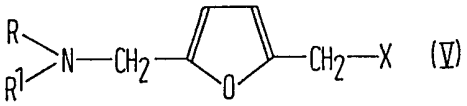


(III)

Compounds III, which are claimed *per se,* can be prepared by reaction of corresponding 1-methylthio-1-alkylamino-2-nitroethenes with ethyleneimine in the presence of thiophilic metal ions.

Compounds II, which are claimed *per se,* may be prepared by introduction of the mercapto group.

Processes for the preparation of compounds V:



(V)

where X is Cl, Br or —S—C(NH)NH_2 are also claimed.

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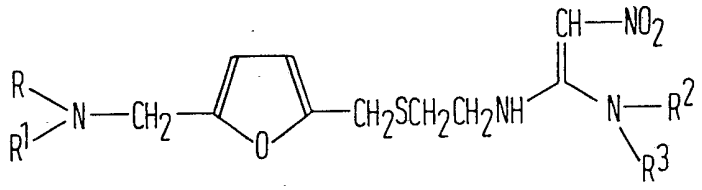
SPECIFICATION

Process for the preparation of N-[2[[[5-(Dialkylamino)-methyl-2-furanyl]-methyl]-thio]-ethyl]-N'-alkyl-2-nitro-1,1-ethenediamines and their intermediates

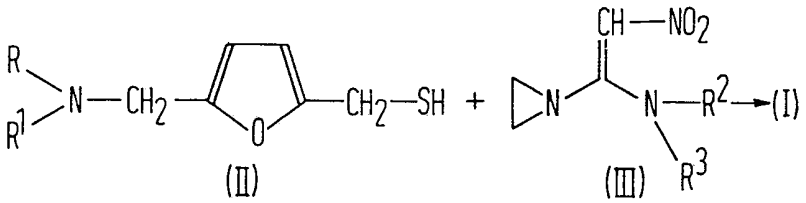
The present invention relates to a process for the production of compounds of the general formula



(I):

where R, R^1, R^2 and R^3, which can be either equal or different, represent an atom of hydrogen or a lower alkyl group containing no more than 3 atoms of carbon.

The compounds (I) are notoriously endowed with interesting pharmaceutical properties. Their preparation is described starting from N-alkyl-1-(methylthio)-2-nitro-etheneamines, and 2-[[[5-(dialkylamino)-methyl-2-furanyl]-methyl]-thio]-ethylamines (B. J. Price, J. W. Clitherow and J. Bradshau, Belgian Patent No. 857,388). The yields are not higher than 70% and moreover this procedure requires the use of the expensive cysteamine as source of the sequence S—C—C—N. According to the invention, the compounds (I) can be obtained with high yields, and in a much cheaper way, by means of the reaction between compounds of general formula (II) and (III):



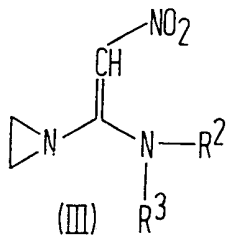
(II) (III)

where R, R^1, R^2 and R^3 have the above-mentioned meanings, in an inert solvent such as water, methanol, ethanol, dimethylformanide or acetonitrile, in the presence of a base such as hydroxide, methoxide or ethoxide ions, and at temperatures ranging from about −20°C to about +60°C.

It had already been found (V. Sunjic et al. Gazz. Chin. Ital. *110* (1980) 345—350, and Swiss Patent Applications Nos. 16340/77, 5237/78 and 10695/78) that heterocyclic methylenethiols yield, with ethyleneiminocyano-azomethine, the same sequence S—C—C—N. It has now surprisingly been observed that the same fundamental scheme of reaction can be applied also in the case of compounds of formula (III), in spite of the presence in them of the nitroethenic group, itself endowed with acid characteristics and with a general sensitivity (at this regard see A. Streitweiser and C. H. Heathcock, Introduction to Organic Chemistry, Collier Mac Millan Int. Editions, New York-London, 1976, pp. 800—801). Unexpectedly, in fact, this group remains stable also in basic medium, at least in the range of temperatures and with the order of addition of the reagents adopted by the process of the present invention.

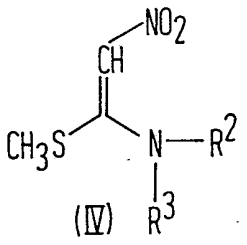
The condensation yields between (II) and (III) are generally of about 80%, which is considerably higher than those described in previous preparations of compounds of formula I.

The present invention also relates to a process for the preparation of new compounds of general formula (III)



(III)

where R^2 and R^3, which can be equal or different, represent an atom of hydrogen, or a lower alkyl group containing at the most 3 C-atoms, starting from compounds of general formula (IV):



(IV)

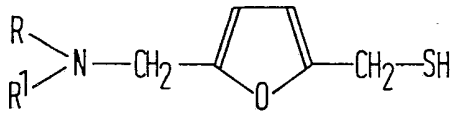
where R^2 and R^4 have the same meaning as in the formula III, and from ethyleneimine, in the presence of thiophilic metal ions, for example of Cu^+, Cu^{2+}, Zn^{2+} or Ag^+ as catalysts and in polar solvents such as acetonitrile, methanol or water, which on the one hand ensure the presence of metal ions in solution in sufficient concentration, and on the other hand the quantitative precipitation of metal mercaptides, with reaction temperatures usually ranging from 0°C to 60°C, and the recovery of the pure products after quantitative separation of metal mercaptides by filtration, saturation of the aqueous solution with ammonium chloride and treatment with ammonia until pH 10, extraction of the products with dichloromethane or chloroform, evaporation of the solvent and crystallization of the raw products from suitable solvents or solvent mixtures. The compounds of formula (III) are new, and their preparaiton has not been previously described. Therefore, the invention also relates to the compounds of formula (III).

The preparation described in this invention has the advantages that the alkylmercaptanic group in the compounds of formula (IV) can be replaced by ethyleneimine under mild conditions, such as to prevent the cleavage of the ethyleneiminic ring, notoriously unstable, in the presence of some metal ions, which are here defined "thiophilic", such as Cu^+, Cu^{2+}, Zn^{2+} or Ag^+.

It is well-known that nucleophilic substitutions to the trigonal carbon (sp^2-hybridation) are energetically unfavoured processes (see for example A. Streitweiser and C. H. Heathcock, Introduction to Organic Chemistry, Collier Macmillan Int. Ed., 1976, New York and London, pp. 893—898, and J. B. Hendrickson, D. J. Cram, G. S. Hammond, Organic Chemistry, 3rd ed., 1970, McGraw-Hill, pp. 445).

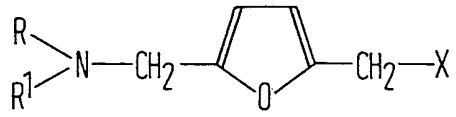
Surprisingly, the activating effect of metal ions on the carbon-sulphur bond in the compounds of general formula (IV) allows the nucleophilic substitution with ethyleneimine to the ethylenic carbon atom under very mild conditions.

The present invention also relates to a process of preparation of new furanic derivatives of general formula (II)



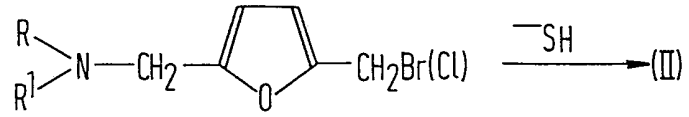
(II)

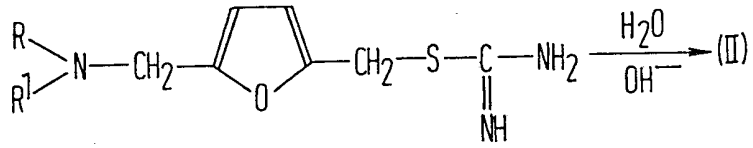
or of their stable salts, where R and R_1 represent at atom of hydrogen or a lower alkyl group, preferably bearing 1—3 atoms of carbon, starting from compounds of general formula (V)



(V)

where R and R_1 have the same meaning as in formula II, whereas X represents an atom of chlorine or bromine, or the thioureidic group (—SC(=NH)NH_2). If X represents an atom of chlorine or bromine, the process of the invention provides for the reaction of the respective compounds (V) with sodium or potassium hydrosulfide in protic solvents, such as lower alcohols or water; on the contrary, if X is the thioureidic group, a hydrolysis in potassium hydroxide in methanol or water is carried out, at temperatures preferably ranging from room temperature to the reflux temperature of the mixture; the compounds of general formula (II) are then isolated in the form of their stable salts such as hydrochlorides and hydrobromides. The two above-mentioned alternatives can be schematized as follows:

a) 

b) 

The above-mentioned compounds are useful intermediates in the synthesis of compounds effective in gastric ulcer therapy (see for instance H. G. Dammon et al., Deutsche Med. Wochenschr. *104*, 1676 (1979)). Although the literature mentions the preparation of 5-(N,N-dimethylamino)methyl-2-hydroxymethyl-furan by means of dimethylaminomethylation according to Mannich of 2-hydroxymethylfuran (see for example A. P. Dunlop and F. N. Peters, The Furanes, 1953, Reinhold Publ. Corp., New York, pp. 222; W. Holden, J. Amer. Chem. Soc. *69*, 464 (1947)), the low yields (11—45%) preclude the economic advantage of this compound as starting material. In a recent patent (U.S. Pat. 4,128,657) the preparation of some 2-hydroxymethylfurans in aqueous solution, but with yields of no higher than 50%, has been described. According to another preferred feature of the present invention, working with paraformaldehyde in methanolic solution at high temperature, the yield of 5-(N,N-dialkylamino)-methyl-2-hydroxymethyl-furans (V, where X=OH) is more than 90%.

As mentioned before, the compounds of general formula (I) are effective in gastric ulcer chemotherapy, in particular the compound in which R, R^1 and R^2 represent a methyl group, whereas R^3 is hydrogen (W. Domschke et. al. Lancet *1979*, 320).

The following examples are illustrations, but not limitative, of the process according to the present invention.

EXAMPLE 1

1-Methylamino-1-methylthio-2-nitroethene

1,1-Bis-methylthio-2-nitroethene (16.4 g, 0.10 mole) is dissolved in hot toluene (200 ml) and an ethanolic solution of methylamine (25 ml of a 30% solution; 0.25 moles of methylamine) diluted with 40 ml of toluene, is added in 30 minutes, at the reflux temperature. After an hour of stirring under reflux, the crystals which precipitate are separated from the hot solution by means of filtration. In this way about 1 gr. of secondary pure product is obtained 1,1-bis-methylamino-2-nitroethane, m.p. 214—215°C (from 2-propanol). IR(KBr): 3180—3300 (broad band), 1625—1580, 1428, 1360—1380 (broad band), 1230 (broad band), 995, 752, 645 cm^{-1}. NMR ($CDCl_3$): 2.88 (d, 6H, collapses in s by addition of D_2O), 6.55 (s, 1H).

Elemental analysis: for $C_4H_9N_3O_2$ (131.14)

Calc. %: C 36.65; H 6.91; N 32.05

found: C 36.68; H 6.84; N 31.80.

The filtered liquid is evaporated to a volume of about 150 ml, and it is cooled by ice overnight long. The crystals are separated by means of filtration, and dried to give 11.8 g (80%) of the pure 1-methylamino-1-methylthio-2-nitroethene, m.p. 105—106°C. By re-crystallization from ethyl acetate m.p. 109—110°C.

IR (KBr): 3200, 1620, 1465, 1395, 1340, 1230—1250 (broad band), 995, 820, 760, 660 cm^{-1}.

NMR($CDCl_3$): 2.51 (s, 3H), 3.20 (d, 3H, collapses in s by addition of D_2O), 6.68 (s, 1H).

Elemental analysis: for $C_4H_8N_2SO_2$ (148.18)

Calc.% C 32.41; H 5.44; N 18.98

found: C 32.41; H 5.51; N 19.28.

EXAMPLE 2

1-N-Propylamino-1-methylthio-2-nitroethene

Using the same conditions as in Example 1, and starting from 1.64 g (10.0 mmol) of 1,1-dimethylthio-2-nitroethene and 3.0 ml of a 50% ethanolic solution of n-propylamine, the reaction is carried out for 70 minutes. Then the solvent is dry-evaporated and the residue is crystallized from ethyl acetate (about 10 ml), obtaining about 200 mg of bis-1,1-n-propylamino-2-nitroethene, m.p. 120—121°C.

IR(KBr): 3250, 2840—2880 (three bands), 1620, 1575 (broad band), 1380—1410 (broad band), 1220 (broad band), 1010, 755 cm^{-1}.

NMR($CDCl_3$): 1.0 (t, 6H), 1.2—2.0 (m, 4H), 3.0—3.6 (m, 4H), 6.72 (s, 1H).

Elemental analysis for: $C_8H_{17}N_3O_2$ (187.24)

Calc.% : C 51.31; H 9.15; N 22.44

found: C 51.31; H 9.25; N 22.34.

The filtered solution is evaporated and the residue oil is crystallized from n-heptane, giving thus 1.12 g (63.6%) of pure 1-n-propylamino-1-methylthio-2-nitroethene, m.p. 64—65°C.

IR(KBr): 3140, 2840—3000 (four bands), 1560, 1455, 1420, 1330, 1305, 1210, 970, 825, 765, 680 cm^{-1}.

NMR($CDCl_3$); 1.05 (t, 3H), 1.3—2.0 (m, 2H), 2.50 (s, 3H), 3.48 (q, 2H), 6.70 (s, 1H).

Elemental analysis for: $C_6H_{12}N_2O_2S$ (176.24)

Calc.% : C 40.88; H 6.86; N 15.89
found : C 40.91; H 6.98; N 15.91.

EXAMPLE 3

1-Dimethylamino-1-methylthio-2-nitroethene

1,1-Dimethylthio-2-nitroethene (3.30 g, 20.0 mmol) is dissolved in dichloromethane (150 ml) and then dimethylamine hydrochloride (4.08 g, 50.0 mmoles) and sodium methoxide (2.67 g, 50.0 moles) are added. The reaction mixture is heated to reflux for 1 hour. It is then cooled and acetic acid 2 M (50 ml) is added. The organic phase is separated, and the water phase extracted with dichloromethane (3 x 60 ml). The organic extract is dried (Na_2SO_4), evaporated and the residue oil is purified with a silica-gel column, using ethyl acetate as eluting solvent.

The first fraction contains about 5% of the starting compound, then 2.20 g (68%) of the pure 1-dimethylamino-1-methylthio-2-nitroethene, m.p. 60—61°C.

IR(KBr): 2900—3040 (three bands), 1572, 1450, 1410, 1395, 1335, 1205, 942, 680 cm^{-1} is obtained.

NMR($CDCl_3$): 2.52 (s, 3H), 3.31 (s, 6H), 6.66 (s, 1H).

Elemental analysis for: $C_5H_{10}N_2O_2S$ (162.21)
Calc.% : C 37.01; H 6.21; N 17.27
found : C 36.88; H 6.17; N 17.44.

EXAMPLE 4

1-Ethyleneimino-1-methylamino-2-nitroethene

1-Methylamino-1-methylthio-2-nitroethene (37.0 g, 0.25 mole) is added at small doses to ethyleneimine (150 ml) silver nitrate (42.5 g), and 2 M NaOH (125 ml) in water (1.5 l) solution.

After 2 hours of stirring at room temperature, the silver mercaptide is filtered and washed with water; the filtered solution is saturated with ammonium chloride and treated to pH 10 with concentrated ammonia. It is then extracted with dichloromethane (3 x 500 ml); the organic extracts are dried (Na_2SO_4), and the residue oil is crystallized from ethyl acetate; 30.7 g (86%) of pure 1-ethyleneimino-1-methylamino-2-nitroethene, m.p. 133—134°C.

IR(KBr): 3220, 1615, 1508, 1405, 1380, 1290, 1240, 1155, 1110, 825, 755, 660 cm^{-1}.

NMR(DMSO-d_6): 2.40 (s, 4H, 3.10 (d, 3H, collapses in s by adding D_2O), 6.62 (s, 1H), are obtained.

Elemental analysis for: $C_5H_9N_3O_2$ (143.15)
Calc.% : C 41.95; H 6.34; N 29.35
found : C 41.93; H 6.47; N 29.68.

EXAMPLE 5

1-Ethyleneimino-1-methylamino-2-nitroethene

Starting from 7.4 g (0.05 mols) of 1-methylamino-1-methylthio-2-nitroethene, 3.0 ml of ethyleneimine, 25 ml of 2M sodium hydroxide solution and 4.0 g of copper (I) chloride, the reaction is carried out in acetonitrile (180 ml) at 40—50°C for three hours. After filtration of the copper mercaptide the solvent is distilled at 30—40°C under vacuum and the raw product crystallizes from ethyl acetate giving 7.1 g of the above-mentioned pure compound, m.p. 132—134°C.

EXAMPLE 6

1-Ethyleneimino-1-n-propylamino-2-nitroethene

3.50 g (20.0 mmol) of 1-n-propylamino-1-methylthio-2-nitroethene, in 150 ml of 1% ethyleneimine aqueous solution, to which silver nitrate (4.25 g) and sodium hydroxide 2M (12.5 ml) are added, are reacted for 30 minutes at room temperature. Silver mercaptide is afterwards filtered and washed with water; the filtrate is saturated with NH_4Cl and treated to pH 10 with concentrated ammonia. The mixture is extracted with CH_2Cl_2 (3 x 10 ml), the organic extracts are dried (Na_2SO_4) and evaporated to dryness. The residue oil is crystallized from 2-propanol, giving 2.21 g (64.9%) of pure 1-ethyleneimino-1-n-propylamino-2-nitroethene, m.p. 77—78°C.

IR(KBr): 3130, 2850—2970 (four bands), 1595, 1505, 1410, 1290, 1220, 1160 (two bands), 1060, 1112, 830 cm^{-1}.

NMR(DMSO-d_6): 2.40 (s, 4H), 3.10 (d, 3H, collapses in s by adding D_2O), 6.62 (s, 1H).

Elemental analysis for: $C_7H_{13}N_3O_2$ (171.19)
Calc.% : C 49.10; H 7.05; N 24.54
found : C 49.37; H 7.44; N 24.49.

EXAMPLE 7
1-Ethyleneimino-1-n-propylamino-2-nitroethene

1-n-Propylamino-1-methylthio-2-nitroethene (7.0 g, 40.0 mmol) is dissolved in acetonitrile and added to an aqueous ethyleneimine solution (30 ml of 10% H_2O solution). Zinc (II) chloride (3.80 g) and sodium hydroxide are subsequently added and the resulting mixture is stirred at 35°C for 8 hours. Precipitated zinc mercaptide zinc is pump-filtered and the filtered solution is treated as described in Example 6, giving 6.22 g of the pure above-mentioned product, m.p. 77—78°C.

EXAMPLE 8
1-Ethyleneimino-1-dimethylamino-2-nitroethane

1-Dimethylamino-1-methylthio-2-nitroethene (8.1 g, 50 mmol) is dissolved in an ethyleneimine 10% aqueous solution (40 ml) and added to silver nitrate (8.5 g, 50 mmol) and sodium hydroxide (25 ml of 2M aqueous solution). After 4 hours of stirring at 0°C, silver mercaptide is pump-filtered and the filtered solution treated as described in Example 5. The raw product (9.4 g) is crystallized from ethyl acetate, giving 8.1 g of pure product, m.p. 82—84°C.

IR(KBr): 1610, 1515, 1400, 1392, 1228, 1170—1790 (broad band), 8.20, 665 cm^{-1}.
NMR(DMSO-d_6): 2.42 (s, 4H), 3.14 (s, 6H), 6.60 (s, 1H).
Elemental analysis for: $C_6H_{11}N_3O_2$ (157.15)

Calc.%	:	C 51.07;	H 7.86;	N 29.78
found	:	C 50.90;	H 7.73;	N 29.49.

EXAMPLE 9
5-(N,N-Dimethylamino)methyl-2-hydroxymethyl-furan

2-Hydroxymethyl-furan (49.0 g, 0.50 mol) is added to a suspension of 21 g (0.70 moles) of paraformaldehyde in a solution (about 25%) of dimethylamine hydrochloride in methanol (44.8 g, 0.55 mol, in 200 ml of methanol). The resulting mixture is stirred for 0.5 h. at room temperature, then it is heated with slight reflux for 12 hours. Methanol is distilled off under vacuum and the residue oil is treated with 0.5 l of 5% sodium hydroxide solution saturated with sodium chloride (90—100 g), and extracted with ethyl acetate (400 + 2 x 200 ml). Organic extracts are collected, dried (Na_2SO_4) and evaporated; 77 g (99.4%) of raw product (red oil) are obtained, which can be used without further purifying in the following preparations.

The pure product (72.9 g, 94.2%) is obtained by distillation (100—110°C/0.5—0.7 mmHg).
NMR (MeOH-d_4): 2.29 (s, 6H), 3.54 (s, 2H), 4.55 (s, 2H), 6.30 (s, 2H).

EXAMPLE 10
5-(N,N-Diethylamino)methyl-2-hydroxymethyl-furan

Starting from 2-hydroxymethyl-furan (24.5 g, 0.26 mol), formaldehyde (125 g), and diethylamine hydrochloride (32.8 g, 0.30 moles), the reaction is carried out in methanol (120 ml), following the conditions described in Example 9. 42 g (92%) of pure product are obtained, b.p.: 140—144°/0.6—0.9 mmHg.

Elemental analysis for: $C_{10}H_{17}NO_2$ (183.25)

Calc.%	:	C 65.57;	H9.33;	N 7.64
found	:	C 65.41;	H 9.09;	N 7.59.

EXAMPLE 11
5-(N,N-Dimethylamino)-methyl-2-bromomethyl-furan hydrobromide

To a 5-(N,N-dimethylamino)methyl-2-hydroxymethyl-furan (6.20 g, 0.04 mol) in $CHCl_3$ (100 ml), a 40% hydrobromic acid solution in acetic acid (5 ml) is slowly added at room temperature with stirring. The organic solvent is subsequently distilled off and the obtained solid product, dissolved in 2-propanol (60 ml), filtered with charcoal (0.5 g) and cooled to 0°C, gives the above-mentioned compound with a 87% yield. (10.5 g), m.p. 176—177°C (from acetonitrile).

IR(KBr): 3000—2500, 3110, 1540, 1470, 1415, 1250, 1240, 1230, 1205, 1030, 1010, 975, 820, 760, 660 cm^{-1}.

NMR (MeOH-d_4): 2.95 (s, 6H), 4.50 (s, 2H), 4.70 (s, 2H), 6.65 (d, 1H, J=3.5 Hz), 6.87 (d, 1H, J=3.5 Hz).

Elemental analysis for: $C_8H_{13}NOBr_2$ (299.02)

Calc.%	:	C 32.13;	H 4.38;	N 4.68
found	:	C 32.06;	H 4.48;	N 4.66.

EXAMPLE 12
5-(N,N-Dimethylamino)methyl-2-chloromethyl-furan hydrochloride

To a solution of 5-(N,N-dimethylamino)methyl-2-hydroxymethyl-furan (6.20 g, 0.04 mol) in $CHCl_3$ (100 ml), a solution of $SOCl_2$ (4.8 g, 0.042 mol) in $CHCl_3$ (30 ml) is added dropwise in 30 minutes at room temperature. The organic solvent is subsequently evaporated and the solid residue is dissolved in boiling 2-propanol (50 ml). From the solution, cooled at 0°C, the above-mentioned compound crystallizes with a 90% yield (7.5 g), m.p. 174—175°C (from ethanol).

IR(KBr): 3200—2500, 1550, 1480, 1420, 1260, 1230, 1205, 1020, 1050, 980, 820, 755 cm^{-1}.

NMR (MeOH-d_4): 2.95 (s, 6H), 4.70 (s, 2H), 4.62 (s, 2H), 6.65 (d, 1H, J=3.5 Hz), 6.87 (d, 2H, J=3.5 Hz).

Elemental analysis for: $C_8H_{13}NOCl_2$ (210.10)

Calc.%	:	C 45.73;	H 6.23;	N 6.66
found	:	C 45.61;	H 6.19;	N 6.51.

EXAMPLE 13
5-(N,N-Dimethylamino)methyl-2-S-isothioureyl-methyl-furan dihydrochloride

To a solution of thiourea (38.06 g, 0.50 mol) in 650 ml of 22% hydrochloric acid in 2-propanol, the compound 5-(dimethylamino)methyl-2-hydroxymethyl-furan (77.5 g; 0.50 mol) is added.

The resulting solution is heated to reflux for 10 hours. By cooling, under strong stirring, the reaction product crystallizes in the form of little prismatic crystals. The filtered raw product is washed with 3 x 30 ml of 2-propanol. After vacuum drying, 138 g (96.5%) of product with m.p. 172—174°C are obtained. By re-crystallization from absolute ethanol 128 g of product are obtained with m.p. 174—175°C.

IR(KB): 3020, 1668, 1440, 1255, 1115, 1002, 975, 935, 820, 690 cm^{-1}.

NMR (D_2O): 2.96 (s, 6H), 4.50 (s, 2H), 4.62 (s, 2H), 6.68 dd, 2H, J=4Hz).

Elemental analysis for: $C_9H_{17}N_3OSCl_2$ (286.22)

Calc.%	:	C 37.76;	H 5.98;	N 14.67
found	:	C 37.49;	H 6.07;	N 14.55.

EXAMPLE 14
5-(N,N-Dimethylamino)methyl-2-thiomethyl-furan hydrobromide

To a solution of sodium methoxide (2.97 g; 0.055 mol) in methanol (100 ml), saturated with hydrogen sulfide, a 5-(N,N-dimethylamino)methyl-2-bromomethyl-furan hydrobromide (7.47 g, 0.025 mol) in methanol (30 ml) solution is added in 30 min. at 0°C, with bubbling of hydrogen sulfide.

The resulting solution is acidified with a 30% HBr solution in 2-propanol (16 ml) and subsequently treated with charcoal (0.5 g). The organic solvent is distilled off and the oily residue is dissolved in 2-propanol. The inorganic salts are filtered, and the alcoholic solution is concentrated to small volume. 5.6 g of the above-mentioned compound are obtained, m.p. 129—130°C. (Yield 90%).

IR (KBr): 2700—2500, 1550, 1475, 1415, 1385, 1235, 1140, 1030, 1010, 980, 935, 820, 760 cm^{-1}.

NMR (MeOH-d_4): 2.95 (s, 6H), 3.85 (s, 2H), 4.50 (s, 2H), 6.42 (d, 1H, J=3.5 Hz), 6.79 (d, 1H, J=3.5 Hz).

Elemental analysis for: $C_8H_{14}BrNOS$ (252.18)

Calc.%	:	C 38.06;	H 5.59;	S 12.71
found	:	C 38.00;	H 5.51;	S 12.80.

EXAMPLE 15
5-(N,N-Dimethylamino)methyl-2-thiomethyl-furan hydrochloride

As described in the previous example, this compound is obtained with a 80% yield (4.15 g), starting from 5-(N,N-dimethylamino)methyl-2-chloromethyl-furan hydrochloride (5.25 g, 0.025 mol). The compound, which melts at 133—134°C (from 2-propanol) has the same spectrum characteristics of the previous compound.

Elemental analysis for: $C_8H_{14}ClNOS$ (207.68)

Calc.%	:	C 46.25;	H 6.79;	S 15.43
found	:	C 46.30;	H 6.81;	S 15.54.

EXAMPLE 16
5-(N,N-Dimethylamino)methyl-2-thiomethyl-furan hydrobromide

5-(N,N-Dimethylamino)methyl-2-thioureylmethyl-furan dihydrochloride (28.6 g, 0.1 mol) is dissolved in a 10% potassium hydroxide solution in methanol. After 50 minutes of reflux, the solution is cooled and titrated with a 30% hydrobromic acid solution in 2-propanol until pH 1 is reached. The

inorganic salts are filtered and the solvent is distilled under vacuum. The oily residue thus obtained crystallizes by addition of acetonitrile, giving 92% of the required compound, with m.p. 128—130°C.

EXAMPLE 17

5-(N,N-Diethylamino)methyl-2-thiomethyl-furan hydrobromide

Starting from 5-(N,N-diethylamino)methyl-2-bromomethylfuran hydrobromide (1.63 g, 5 mmol), and from a sodium methoxide solution in methanol (5.95 g, 11 mmol), previously saturated with hydrogen sulfide, the abovementioned compound is obtained with a 92% yield (1.28 g, m.p. 114—117°C), as described in the process of Example 14.

EXAMPLE 18

5-(N-Propylamino)methyl-2-thiomethyl-furan hydrochloride

By hydrolyzing 5-(N-propylamino)methyl-2-thioureylmethyl-furan dihydrochloride (1.2 g, 4.0 mmol) in 10 ml of 5% methanolic potassium hydroxide, with reflux heating for 30 minutes, the abovementioned compound is obtained with a 96% yield.

EXAMPLE 19

N-[2-[[[5-(Dimethylamino)-methyl-2-furanyl]-methyl]-thio]-ethyl]-N'-methyl-2-nitro-1,1-ethenediamine

To a solution of 2-[[5-(dimethylamino)methyl]-2-thiomethyl-furan (17.1 g, 0.1 mol) in acetonitrile (120 ml), a 5N aqueous sodium hydroxide solution is added dropwise at 0°C (20.0 ml, 0.1 mol). 1-Ethyleneimino-1-methylamino-2-nitro-ethene (14.3 g, 0.1 mol) is subsequently added little by little. It is stirred for 24 hours, then the solvent is distilled off and the residue oil is crystallized from an acetone-cyclohexane mixture, obtaining 25.4 g (82%) of pure product, m.p. 70—72°C.

IR (KBr): 3200—3300, 2980, 1620, 1590, 1540, 1335 cm^{-1}.

NMR (δ in ppm): 2.3 (s, 3H), 2.5—3.6 (m, 8H), 2.4 (s, sharp, 6H), 6.4—6.9 (m, 3H).

Elemental analysis for: $C_{13}H_{22}N_4O_3S$ (314.40)

Calc.%	:	C 49.66;	H 7.05; N 17.82
found	:	C 49.39;	H 6.89; N 17.76

EXAMPLE 20

N-[2-[[[5-(Dimethylamino)methyl-2-furanyl]-methyl]thio]-ethyl]-N'-propyl-2-nitro-ethenediamine

To a solution of 2-[[5-(dimethylamino)-methyl]-2-thiomethyl-furan (3.42 g, 20.0 mmol) in methanol (60 ml) under stirring, and in a nitrogen current at —5°C—0°C, solid KOH is added (1.12 g, 20.0 mmol). A solution of 1-ethyleneimino-1-propylamino-2-nitroethene (3.08 g, 18.0 mmol) in methanol (80 ml) is subsequently added dropwise. After 14 hours at room temperature the solvent is distilled off. The residue oil, dissolved in 200 ml of ethylmethylketone, is hot-filtered on charcoal and distilled until initial crystallization. G 5.67 (92%) of pure product are obtained, m.p. 54—56°C.

IR(KBr): 3150—3400 (broad), 2970, 2940, 1610, 1585, 1535, 1330 cm^{-1}.

NMR (δ in ppm): 2.2—3.7 (m, 15H), 2.5 (s, sharp, 6H), 6.5—6.9 (m, 3H).

Elemental analysis for: $C_{15}H_{26}N_4O_3S$ (342.25)

Calc.%	:	C 52.61;	H 7.65; N 16.36
found	:	C 52.89;	H 7.92; N 16.60.

EXAMPLE 21

N-[2-[[[5-(dimethylamino)-methyl-2-furanyl]-methyl]-thio]-ethyl]-N'-methyl-2-nitro-ethenediamine

To a 2-[[5-(dimethylamino)-methyl]-2-thiomethyl-furan (9.42 g, 55.0 mmol) suspension in water (100 ml) a sodium hydroxide 5N solution (11.6 ml, 58.0 mmol) is added, keeping the temperature from —10°C to —5°C.

1-ethyleneimino-1-methylamino-2-nitroethene (7.87 g, 55.0 mmol) is subsequently added little by little in 30 minutes. After 6 hours at —5°C the mixture is heated to room temperature and the reaction mixture is stirred for 18 hours.

The thus obtained precipitate is collected by filtration, washed with water, dissolved in methyl-isobutylketone and hot-filtered with charcoal. By concentration of the clear solution the product crystallizes yielding 13.6 g (79%) m.p. 70—73°C.

EXAMPLE 22

N-[2-[[[5-(dimethylamino)-methyl-2-furanyl]-methyl]-thio]-ethyl]-N'-methyl-2-nitro-ethenediamine

The reaction is carried out in dimethylformamide (40 ml) starting from 2-[5-(dimethylamino)-methyl]-2-thiomethyl-furan (1.71 g, 10.0 mmol) and 1-ethyleneimino-1-methylamino-2-nitroethene (1.43 g, 10.0 mmol). The recovery of the product is carried out by means of the process described in

Example 19. 2.76 g (88%) of pure product are obtained, m.p. 71—73°C.

As described with this example, from the suitable N-dialkylamino-methyl-2-thiomethyl-furans and 1-ethyleneimino-1-alkylamino-2-nitro-ethenes the following compounds are obtained:

-N-[2-[[[5-dimethylamino)-methyl-2-furanyl]-methyl]-thio]-ethyl]-N'-methyl-2-nitro-1,1-ethenediamine, m.p. 124—126°C.

Elem. analysis for: $C_{15}H_{26}N_4O_3S$ (342.45)

calc.%	:	C 52.61	H 7.65	N 16.36
found%	:	C 52.38	H 7.41	N 16.09

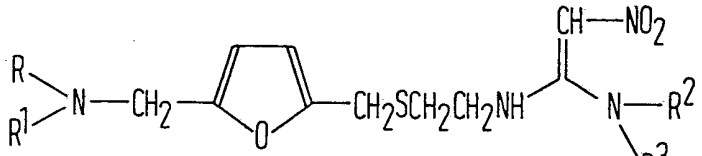
-N-[2-[[[5-(dimethylamino)-methyl-2-furanyl]-methyl]-thio]-ethyl]-N'-ethyl-2-nitro-1,1-ethenediamine, m.p. 141—144°C

Elem. analysis for: $C_{16}H_{28}N_4O_3S$ (356.48)

calc.%	:	C 53.90	H 7.92	N 15.72
found%	:	C 53.63	H 7.82	N 16.01.

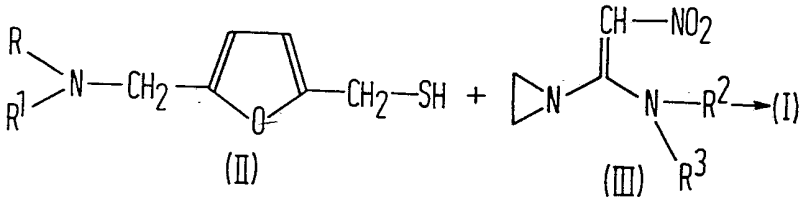
CLAIMS

1. Process for the preparation of a N-[2-[[[5-(dialkylamino-methyl-2-furanyl]-methyl]-thio]-ethyl]-N'-alkyl-2-nitro-1,1-ethenediamines of formula (I) and their physiologically acceptable salts



(I)

where R, R^1, R^2 and R^3, which can be either equal or different, represent an atom of hydrogen or a lower alkyl group containing no more than 3 atoms of carbon, wherein compounds of formula (II) are reacted with compounds of formula (III) according to the scheme



(II) (III)

where R, R^1, R^2 and R^3 have the above-explained meanings.

2. Process according to claim 1, wherein the compounds of formula (I) are prepared in the form of their hydrochlorides, hydrobromides, sulphates, fumarates or maleates.

3. Process according to claim 1 or 2, wherein the reaction between (II) and (III) is carried out in an aqueous solution, or in a lower-alcohol solution, or in dimethylformamide or acetonitrile.

4. Process according to claim 3 wherein the reaction is carried out in methanol or ethanol.

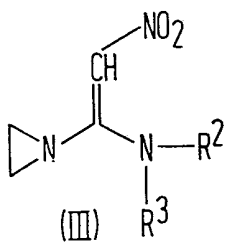
5. Process according to any one of claims 1 to 4, wherein the reaction is catalysed by basic ions.

6. Process according to claim 5, wherein the basic ions are hydroxide ions, methoxide ions or ethoxide ions.

7. Process according to any one of the preceding claims wherein the reaction is carried out at temperatures ranging from −20°C to +50°C.

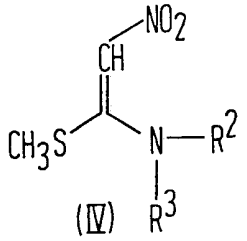
8. Process according to claim 7, wherein the reaction is carried out at temperatures of from −10°C to +10°C.

9. Method for the preparation of 1-ethyleneimino-1-alkylamino-2-nitroethenes of the formula (III)



(III)

in which R^2 and R^3, which can be either equal or different, and represent hydrogen or a lower alkyl group, bearing at the most 3 carbon atoms, wherein compounds of formula (IV)



(IV)

are reacted with ethyleneimine in presence of thiophilic metal ions.

10. Method according to claim 9, wherein as thiophilic metal ions Cu^+, Cu^{2+}, Zn^{2+} or Ag^+ ions are used.

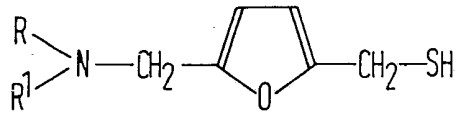
11. Method according to claim 9 or 10, wherein the reaction is carried out in polar solvents.

12. Method according to claim 11, wherein acetonitrile methanol or water are used as solvents.

13. Method according to any one of claims 9 to 12, wherein the reaction is carried out at temperatures ranging from about 0°C to about 60°C.

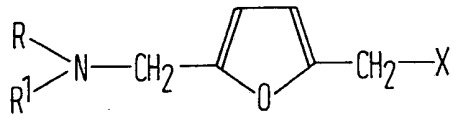
14. Method according to any one of claims 9 to 13, wherein the reaction products are isolated after quantitative separation of the metal mercaptides by filtration, saturation of the solution with ammonium chloride and treatment with ammonia until pH 10 is reached, and final extraction of the products themselves with hydro-immiscible solvents.

15. Method for the preparation of 5-substituted 2-thiomethyl-furans of general formula (II)



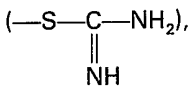
(II)

in which R and R_1, which can be either equal or different, represent hydrogen or a lower alkyl group, or of their addition salts with acids, wherein compounds of general formula (V)



(V)

in which R and R_1 have the above-explained meanings, whereas X represents an atom of chlorine or bromine, or the isothioureidic group



are reacted with alkali metal hydrosulfides (when X=chlorine or bromine) or hydrolyzed (when X is the isothioureidic group).

16. Method according to claim 15, wherein R and R_1 are hydrogen or lower alkyl having 1 to 3 carbon atoms.

17. Method according to claim 15 or 16, wherein sodium or potassium hydrosulfides are used as alkali metal hydrosulfides.

18. Method according to claim 15 or 16, wherein the hydrolysis of the isothioureidic group is carried with sodium or potassium hydroxide.

19. Method according to any one of claims 15 to 18, wherein the reaction is carried out in protic solvents.

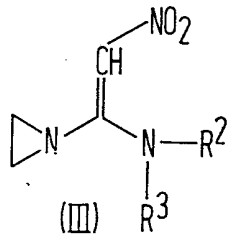
20. Method according to claim 19, wherein the protic solvents are selected from lower alcohols and/or water.

21. Method according to any one of claims 15 to 19, wherein the temperature ranges from room temperature to the reflux temperature of the reaction mixtures.

22. Method according to any one of claims 15 to 21, wherein the compounds of formula (II) are isolated in the form of stable salts.

23. Method according to claim 22, wherein the compounds of formula (II) are isolated as hydrochlorides or hydrobromides.

24. As new compounds, 1-ethyleneimino-1-alkylamino-2-nitroethenes of formula (III)



(III)

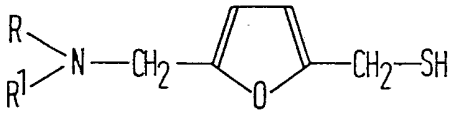
in which R^2 and R^3, which can be either equal or different, represent hydrogen or a lower alkyl group, bearing at the most 3 carbon atoms.

25. 1-ethyleneimino-1-methylamino-2-nitroethene.

26. 1-ethyleneimino-1-n-propylamino-2-nitroethene.

27. 1-ethyleneimino-1-dimethylamino-2-nitroethene.

28. As new compounds, compounds of formula (II)



(II)

where R and R_1 have the meanings explained in claim 1, and their addition salts with acids.

29. 5-(N,N-dimethylamino)-methyl-2-thiomethyl-furan and its addition salts with acids.

30. 5-(N-propylamino)methyl-2-thiomethyl-furan and its addition salts with acids.

31. 5-(N,N-diethylamino)methyl-2-thiomethyl-furan and its addition salts with acids.

32. A process according to claim 1 substantially as described herein.

33. A process for the preparation of a compound of formula (I) substantially as described herein with reference to any one of Examples 19 to 22.

34. A method according to claim 9 substantially as described herein.

35. A method for the preparation of a compound of formula (III) substantially as described herein with reference to any one of Examples 4 to 8.

36. A method according to claim 15 substantially as described herein.

37. A method for the preparation of a compound of formula (V) substantially as described herein with reference to any one of Examples 14 to 17.

38. Compounds of formula (III) substantially as described herein and exemplified.

39. Compounds of formula (II) and their acid addition salts substantially as described herein and exemplified.

40. Compounds of formula (I) and their physiologically acceptable salts, when prepared by the process of any one of claims 1 to 7, 32 or 33.

41. A pharmaceutical composition, comprising as an active ingredient, at least one compound according to claim 40.

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