671389

P/00/001 : Section 29

AUSTRALIA

Patents Act 1990

PATENT REQUEST : STANDARD PATENT

We, being the person(s) identified below as the Applicant, request the grant of a standard patent to the person identified below as the Nominated Person, for an invention described in the accompanying complete specification.

Full application details follow:

[71/70] Applicant/Nominated Person:
Rhone-Poulenc Agrochimie
Address: 14 a 20 Rue pierre Baizet,
B.P. 9163 Lyon 09, 69263 Lyon Cedex 1, France

[54] Invention Title:

"Process for the formation of intermediates and intermediates useful for the preparation of fungicidal 2-amidazolin-5-one and 2-amidazoline-5-thione derivatives"

[72] Names of actual inventors:

Guy LACROIX
Raymond PEIGNIER
Regis PEPIN

[74] Address for service in Australia:

DAVIES COLLISON CAVE, Patent Attorneys, of 1 Little Collins Street, Melbourne, Victoria, Australia. Attorney Code: DM

DIVISIONAL APPLICATION DETAILS:

[62] Original Application No. 651021 (30310/92)
Person by whom made: Rhone-Poulenc Agrochimie

DATED this 7th day of October, 1994

M 060814 071094

A member of the firm of DAVIES COLLISON CAVE for and on behalf of the Applicant

P/00/008 Section 29(1)
Regulation 3.1(2)

AUSTRALIA

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NOTICE OF ENTITLEMENT

We, **Rhone-Poulenc Agrochimie**, of 14 a 20 Rue pierre Baizet, B.P. 9163 Lyon 09, 69263 Lyon Cedex 1, France, the applicant in respect of the accompanying patent request, state the following:-

The Nominated person is entitled to the grant of the patent because the Nominated person would, on the grant of a patent for the invention to the inventors, be entitled to have the patent assigned to the Nominated person.

The Nominated person is the applicant of the original application with respect to which the present application is a further complete application under S.39 of the Patents Act 1990.

7 October, 1994

(A member of the firm of Davies Collison Cave for
and on behalf of the applicant)

AU9474499

(12) PATENT ABRIDGMENT (11) Document No. AU-B-74499/94
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 671389

(54) Title
PROCESS FOR THE FORMATION OF INTERMEDIATES AND INTERMEDIATES USEFUL FOR THE PREPARATION OF FUNGICIDAL 2-AMIDAZOLIN-5-ONE AND 2-AMIDAZOLINE-5-THIONE DERIVATIVES

International Patent Classification(s)
(51)^5 **C07D 233/84** **C07C 331/24** **C07C 331/26** **C07C 333/20**
C07D 233/86 **C07D 401/12** **C07D 405/06** **C07D 409/06**

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(62) Related to Division(s) : **30310/92**

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(74) Attorney or Agent
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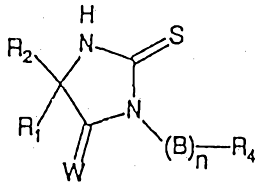
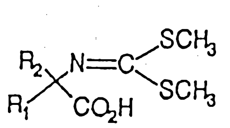
(56) Prior Art Documents
AU 64586/94 C07D 233/86 A01N 43/50

(57) Claim

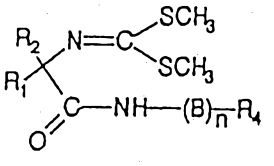
10. Compounds having the formulae II, III, IV, V, VI, VII and VIII



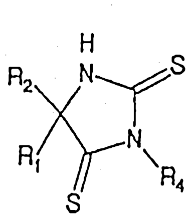
(II)



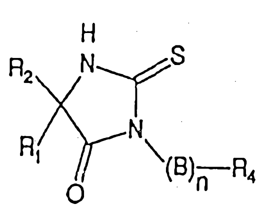
(III)



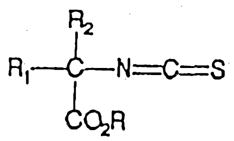
(V)



(VI)



(VII)


$R_1-C(R_2)(CO_2R)-N{=}C{=}S$

(VIII)

in which R_1, R_2, B, n and R_4 have the same meaning as in claim 1, W is a sulphur or oxygen atom or an S=O group and R is $C_{1\text{-}4}$ alkyl.

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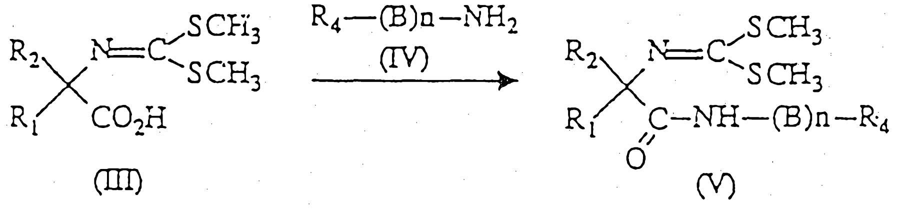
1. A process for the preparation of compounds of formula (V) wherein an imino dithiocarbonate of formula (III) is condensed with an amine or a hydrazine of formula (IV) according to the scheme:



in which:

- n = 0 or 1
- B represents NR_5 or O or S or CR_5R_6 or SO_2 or C=O

- R_1 and R_2, which are identical or different, represent:
  - H, provided that one of the 2 groups is different from H, or
  - an alkyl or haloalkyl radical containing 1 to 6 carbon atoms or
  - an alkoxyalkyl, alkylthioalkyl, alkylsulphonylalkyl, monoalkylaminoalkyl, alkenyl or alkynyl radical containing 2 to 6 carbon atoms or
  - a dialkylaminoalkyl or cycloalkyl radical containing 3 to 7 carbon atoms or
  - an aryl radical preferably phenyl, naphthyl, thienyl, furyl, pyridyl, benzothienyl, benzofuryl, quinolyl, isoquinolyl, or methylenedioxyphenyl, optionally substituted by 1 to 3 groups chosen from R_7 or
  - an arylalkyl, aryloxyalkyl, arylthioalkyl or arylsulphonylalkyl radical, or
  - R_1 and R_2 can form, with the carbon to which they are bonded on the ring, a carbocycle or a heterocycle having from 5 to 7 atoms, it being possible for these rings to be fused to a phenyl, optionally substituted by 1 to 3 groups chosen from R_7;
- R_4 represents:
  - a hydrogen atom when n is equal to 1 or
  - an alkyl group containing 1 to 6 carbon atoms or
  - an alkoxyalkyl, alkylthioalkyl, haloalkyl, cyanoalkyl, thiocyanatoalkyl, alkenyl or alkynyl group containing 2 to 6 carbon atoms or

. . ./3

- a dialkylaminoalkyl, alkoxycarbonylalkyl or N-alkylcarbamoylalkyl group containing 3 to 6 carbon atoms or
- a N,N-dialkylcarbamoylalkyl group containing 4 to 8 carbon atoms or
- an aryl radical, preferably phenyl, naphthyl, thienyl, furyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, benzothienyl, benzofuryl, quinolyl, isoquinolyl or methylenedioxyphenyl, optionally substituted by 1 to 3 groups chosen from R_7 or
- an arylalkyl, aryloxyalkyl, arylthioalkyl or arylsulphonylalkyl radical, or
- an amino group disubstituted by 2 identical or different groups chosen from:
    - an alkyl radical containing 1 to 6 carbon atoms
    - an alkoxyalkyl, alkenyl or alkynyl radical containing 3 to 6 carbon atoms
    - a cycloalkyl radical containing 3 to 7 carbon atoms
    - an arylalkyl, phenyl or naphthyl radical, optionally substituted by 1 to 3 groups chosen from R_7 or
    - a thienylmethyl or furfuryl radical
- a pyrrolidino, piperidino, morpholino or piperazino group, optionally substituted by alkyl containing 1 to 3 carbon atoms;
- R_5 represents:
- H, except when R_4 is H, or
- an alkyl, haloalkyl, alkylsulphonyl or haloalkylsulphonyl radical containing 1 to 6 carbon atoms or
- an alkoxyalkyl, alkylthioalkyl, acyl, alkenyl, alkynyl, haloacyl, alkoxycarbonyl, haloalkoxycarbonyl, alkoxyalkylsulphone or cyanoalkylsulphonyl radical containing 2 to 6 carbon atoms or
- an alkoxyalkoxycarbonyl, alkylthioalkoxycarbonyl or cyanoalkoxycarbonyl radical containing 3 to 6 carbon atoms or
- a formyl radical or
- a cycloalkyl, alkoxyacyl, alkylthioacyl, cyanoacyl, alkenylcarbonyl or alkynylcarbonyl radical containing 3 to 6 carbon atoms or
- a cycloalkylcarbonyl radical containing 4 to 8 carbon atoms or
- a phenyl; arylalkylcarbonyl, preferably phenylacetyl or phenylpropionyl; arylcarbonyl, preferably benzoyl, optionally substituted by 1 to 3 groups from R_7; thienylcarbonyl;furylcarbonyl;pyridylcarbonyl;benzyloxycarbonyl;furfuryloxycarbonyl;

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tetrahydrofurfuryloxycarbonyl; thienylmethoxycarbonyl; pyridylmethoxycarbonyl; phenoxycarbonyl or (phenylthio)carbonyl, the phenyl being itself optionally substituted by 1 to 3 groups from R_7; (alkylthio)carbonyl; (haloalkylthio)carbonyl; (alkoxyalkylthio)carbonyl; (cyanoalkylthio)carbonyl; (benzylthio)carbonyl; (furfurylthio)carbonyl; (tetrahydrofurfurylthio)carbonyl; (thienylmethylthio)carbonyl; (pyridylmethylthio)carbonyl; or arylsulphonyl radical or

- a carbamoyl radical, optionally mono- or disubstituted by
    - an alkyl or haloalkyl group containing 1 to 6 carbon atoms or
    - a cycloalkyl, alkenyl or alkynyl group containing 3 to 6 carbon atoms or
    - an alkoxyalkyl, alkylthioalkyl or cyanoalkyl group containing 2 to 6 carbon atoms or
    - a phenyl, optionally substituted by 1 to 3 R_7 groups;
- a sulphamoyl group, optionally mono- or disubstituted by
    - an alkyl or haloalkyl group containing 1 to 6 carbon atoms or
    - a cycloalkyl, alkenyl or alkynyl group containing 3 to 6 carbon atoms or
    - an alkoxyalkyl, alkylthioalkyl or cyanoalkyl group containing 2 to 6 carbon atoms or
    - a phenyl, optionally substituted by 1 to 3 R_7 groups;
- an alkylthioalkylsulphonyl group containing 3 to 8 carbon atoms or a cycloalkylsulphonyl group containing 3 to 7 carbon atoms;
- R_6 represents:
- a hydrogen atom or
- a cyano group or
- an alkyl group containing 1 to 6 carbon atoms or a cycloalkyl group containing 3 to 7 carbon atoms or
- an acyl or alkoxycarbonyl group containing 2 to 6 carbon atoms or
- a benzoyl group, optionally substituted by 1 to 3 R_7 groups;
- R_7 represents:
- a halogen atom or
- an alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio or alkylsulphonyl radical containing 1 to 6 carbon atoms or

.../5

- a cycloalkyl, halocycloalkyl, alkenyloxy, alkynyloxy, alkenylthio or alkynylthio radical containing 3 to 6 carbon atoms or

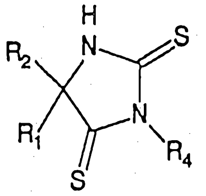
- a nitro or cyano group or

- an amino radical, optionally mono- or disubstituted by an alkyl or acyl radical containing 1 to 6 carbon atoms or an alkoxycarbonyl radical containing 2 to 6 carbon atoms

- a phenyl, phenoxy or pyridyloxy radical, these radicals optionally being substituted;

it being necessary for the acid (III) to be activated for this condensation in the acid chloride form, in the dicyclohexylisourea form using dicyclohexylcarbodiimide, or in the imidazolide form using carbonyldiimidazole.

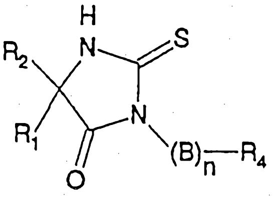
2. A process for the preparation of dithiohydantoins of formula (VI) (process E):



(VI)

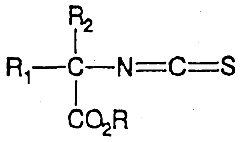
in which R_1, R_2 and R_4 have the same meaning as in Claim 1 with at least one of R_1 or R_2 being electron-withdrawing, characterised in that two isothiocyanates, of formulae R_1R_2CHNCS and R_4NCS in which R_4NCS is unable to form an anion, are reacted in the presence of a base, in a solvent and at a temperature below -60°C.

6. A process for the preparation of the 2-thiohydantoins of formula (VII) (process F):



(VII)

characterised in that, before cyclising, a compound of formula (IV) ($R_4(B)nNH_2$) is reacted with isothiocyanates derived from the amino acids of formula (VIII):



$$R_1-\overset{\displaystyle R_2}{\underset{\displaystyle CO_2R}{C}}-N=C=S$$

(VIII)

in which R_1, R_2, R_4, B and n have the same meaning as in claim 1 and R is C_{1-4}alkyl ~~or a benzyl group.~~

Regulation 3.2

AUSTRALIA

Patents Act 1990

COMPLETE SPECIFICATION

FOR A STANDARD PATENT

(ORIGINAL)

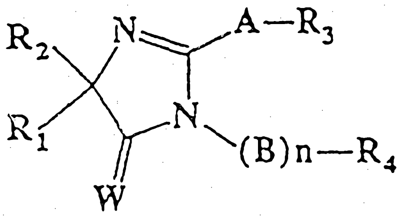
Name of Applicant:	Rhone-Poulenc Agrochimie
Address for Service:	DAVIES COLLISON CAVE, Patent Attorneys, 1 Little Collins Street, Melbourne, 3000.
Invention Title:	"Process for the formation of intermediates and intermediates useful for the preparation of fungicidal 2-amidazolin-5-one and 2-amidazoline-5-thione derivatives"

The following statement is a full description of this invention, including the best method of performing it known to us:

The present application is a divisional application of Australian Patent Application No. 30310/92, the entire disclosure of which is incorporated herein by reference.

AU 30310/92 relates to new imidazolinone or imidazolinthione compounds for use in plant protection. The present application relates to the processes for the preparation of intermediates and to the products which can optionally be used as intermediates in the preparation processes for the imidazolinone and imidazolinthione compounds.

AU 30310/92 claims 2-imidazolin-5-one or 2-imidazoline-5-thione derivatives of general formula (I)



(I)

in which:

- W is a sulphur or oxygen atom or an S=O group
- A represents O or S
- n = 0 or 1
- B represents NR_5 or O or S or CR_5R_6 or SO_2 or C=O.

- R_1 and R_2, which are identical or different, represent:

- H, provided that one of the 2 groups is different from H, or
- an alkyl or haloalkyl radical containing 1 to 6 carbon atoms or
- an alkoxyalkyl, alkylthioalkyl, alkylsulphonylalkyl, monoalkylaminoalkyl, alkenyl or alkynyl radical containing 2 to 6 carbon atoms or
- a dialkylaminoalkyl or cycloalkyl radical containing 3 to 7 carbon atoms or
- an aryl radical preferably phenyl, naphthyl, thienyl, furyl, pyridyl, benzothienyl, benzofuryl, quinolyl, isoquinolyl, or methylenedioxyphenyl, optionally substituted by 1 to 3 groups chosen from R_7 or
- an arylalkyl, aryloxyalkyl, arylthioalkyl or arylsulphonylalkyl radical, or
- R_1 and R_2 can form, with the carbon to which they are bonded on the ring, a carbocycle or a heterocycle having from 5 to 7 atoms, it being possible for these rings to be fused to a phenyl, optionally substituted by 1 to 3 groups chosen from R_7;

- R_3 represents:
  - an alkyl group containing 1 to 6 carbon atoms or
  - an alkoxyalkyl, alkylthioalkyl, alkylsulphonylalkyl, haloalkyl, cyanoalkyl, thiocyanatoalkyl, oxoalkyl, alkenyl or alkynyl group containing 2 to 6 carbon atoms or
  - a dialkylaminoalkyl, alkoxycarbonylalkyl or N-alkylcarbamoylalkyl group containing 3 to 6 carbon atoms or
  - a N,N-dialkylcarbamoylalkyl group containing 4 to 8 carbon atoms or
  - an arylalkyl group, the alkyl part being a radical containing 1 to 6 carbon atoms and the aryl part is phenyl, naphthyl, thienyl, furyl or pyridyl, optionally substituted by 1 to 3 groups chosen from R_7;
- R_4 represents:
  - a hydrogen atom when n is equal to 1 or
  - an alkyl group containing 1 to 6 carbon atoms or
  - an alkoxyalkyl, alkylthioalkyl, haloalkyl, cyanoalkyl, thiocyanatoalkyl, alkenyl or alkynyl group containing 2 to 6 carbon atoms or
  - a dialkylaminoalkyl, alkoxycarbonylalkyl or N-alkylcarbamoylalkyl group containing 3 to 6 carbon atoms or
  - a N,N-dialkylcarbamoylalkyl group containing 4 to 8 carbon atoms or
  - an aryl radical, preferably phenyl, naphthyl, thienyl, furyl, pyridyl, pyrimidyl, pyridazinyl,

pyrazinyl, benzothienyl, benzofuryl, quinolyl, isoquinolyl or methylenedioxyphenyl, optionally substituted by 1 to 3 groups chosen from R_7 or

- an arylalkyl, aryloxyalkyl, arylthioalkyl or arylsulphonylalkyl radical, or

- an amino group disubstituted by 2 identical or different groups chosen from:

    - an alkyl radical containing 1 to 6 carbon atoms

    - an alkoxyalkyl, alkenyl or alkynyl radical containing 3 to 6 carbon atoms

    - a cycloalkyl radical containing 3 to 7 carbon atoms

    - an arylalkyl, phenyl or naphthyl radical, optionally substituted by 1 to 3 groups chosen from R_7 or

    - a thienylmethyl or furfuryl radical

- a pyrrolidino, piperidino, morpholino or piperazino group, optionally substituted by alkyl containing 1 to 3 carbon atoms;

- R_5 represents:

    - H, except when R_4 is H, or

    - an alkyl, haloalkyl, alkylsulphonyl or haloalkylsulphonyl radical containing 1 to 6 carbon atoms or

    - an alkoxyalkyl, alkylthioalkyl, acyl, alkenyl, alkynyl, haloacyl, alkoxycarbonyl, haloalkoxycarbonyl, alkoxyalkylsulphonyl or cyanoalkylsulphonyl radical containing 2 to 6 carbon atoms or

- an alkoxyalkoxycarbonyl, alkylthioalkoxycarbonyl or cyanoalkoxycarbonyl radical containing 3 to 6 carbon atoms or
- a formyl radical or
- a cycloalkyl, alkoxyacyl, alkylthioacyl, cyanoacyl, alkenylcarbonyl or alkynylcarbonyl radical containing 3 to 6 carbon atoms or
- a cycloalkylcarbonyl radical containing 4 to 8 carbon atoms or
- a phenyl; arylalkylcarbonyl, preferably phenylacetyl and phenylpropionyl; arylcarbonyl, preferably benzoyl, optionally substituted by 1 to 3 groups from R_7; thienylcarbonyl; furylcarbonyl; pyridylcarbonyl; benzyloxycarbonyl; furfuryloxycarbonyl; tetrahydrofurfuryloxycarbonyl; thienylmethoxycarbonyl; pyridylmethoxycarbonyl; phenoxycarbonyl or (phenylthio)carbonyl, the phenyl being itself optionally substituted by 1 to 3 groups from R_7; (alkylthio)carbonyl; (haloalkylthio)carbonyl; (alkoxyalkylthio)carbonyl; (cyanoalkylthio)carbonyl; (benzylthio)carbonyl; (furfurylthio)carbonyl; (tetrahydrofurfurylthio)carbonyl; (thienylmethylthio)carbonyl; (pyridylmethylthio)carbonyl; or arylsulphonyl radical or
- a carbamoyl radical, optionally mono- or disubstituted by

- an alkyl or haloalkyl group containing 1 to 6 carbon atoms or
- a cycloalkyl, alkenyl or alkynyl group containing 3 to 6 carbon atoms or
- an alkoxyalkyl, alkylthioalkyl or cyanoalkyl group containing 2 to 6 carbon atoms or
- a phenyl, optionally substituted by 1 to 3 R_7 groups;

- a sulphamoyl group, optionally mono- or disubstituted by
  - an alkyl or haloalkyl group containing 1 to 6 carbon atoms or
  - a cycloalkyl, alkenyl or alkynyl group containing 3 to 6 carbon atoms or
  - an alkoxyalkyl, alkylthioalkyl or cyanoalkyl group containing 2 to 6 carbon atoms or
  - a phenyl, optionally substituted by 1 to 3 R_7 groups;
- an alkylthioalkylsulphonyl group containing 3 to 8 carbon atoms or a cycloalkylsulphonyl group containing 3 to 7 carbon atoms;

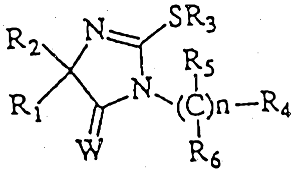
- R_6 represents:
  - a hydrogen atom or
  - a cyano group or
  - an alkyl group containing 1 to 6 carbon atoms or a cycloalkyl group containing 3 to 7 carbon atoms or
  - an acyl or alkoxycarbonyl group containing 2 to 6 carbon atoms or

- a benzoyl group, optionally substituted by 1 to 3 R_7 groups;

- R_7 represents:
  - a halogen atom or
  - an alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio or alkylsulphonyl radical containing 1 to 6 carbon atoms or
  - a cycloalkyl, halocycloalkyl, alkenyloxy, alkynyloxy, alkenylthio or alkynylthio radical containing 3 to 6 carbon atoms or
  - a nitro or cyano group or
  - an amino radical, optionally mono- or disubstituted by an alkyl or acyl radical containing 1 to 6 carbon atoms or an alkoxycarbonyl radical containing 2 to 6 carbon atoms
  - a phenyl, phenoxy or pyridyloxy radical, these radicals optionally being substituted;

and their salts.

Certain specific compounds of the formula I, of formula Ia, are known



Ia

in which W, R_1 to R_6 and n have the same meaning as in formula I.

Denoted S-alkylated derivatives of 5,5-diphenyl-2-thiohydantoin and of 5,5-diphenyldithiohydantoin, they have been especially studied for their pharmacological properties:

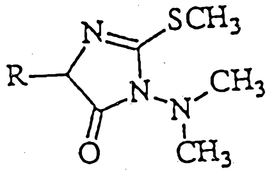
a) Zejc, A., Dissertationes Pharmaceuticae et pharmacologicae, Warsaw, <u>20</u> (5), 507-524 and 525-537 (1968)

b) Lucka-Sobstel, B. and Zejc, A., Dissertationes Pharmaceuticae et pharmacologicae, <u>22</u> (1), 13-19 (1970)

c) Fetter, J., Harsanyi, K., Nyitrai, J. and Lempert, K., Acta Chemica (Budapest), <u>78</u> (3), 325-333 (1973).

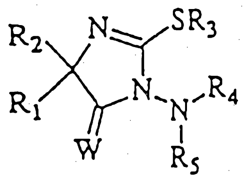
No agricultural fungicidal activity has been described for these compounds.

Other specific compounds of formula I have been described by Böhme, Martin and Strahl in Archiv der Pharmazie, <u>313</u>, 10-15 (1980) (ref. d). They are the 3 following compounds:



R=H, CH_3, phenyl

These compounds are thus included in the compounds of formula Ib, which form part of the invention:



Ib

in which W and R_1 to R_5 have the same meaning as in formula I.

The compounds of formula Ia can be prepared according to the processes known per se described in the abovementioned references and in the following references:

e) Biltz, H., Chemische Berichte 42, 1792-1801 (1909)

f) Chattelain, M. and Cabrier, P., Bulletin de la Société Chimique de France, 14 (1947), 639-642

g) Carrington, C.H. and Warring, W.S., Journal of the Chemical Society, (1950) 354-365

h) Lampert, K., Breuer, J. and Lemper-Streter, M., Chemische Berichte, 92, 235-239 (1959)

i) Shalaby, A. and Daboun, H.A., Journal für Praktische Chemie, 313 (6), 1031-1038 (1971)

j) Simig, G., Lemper, K. and Tamas, J., Tetrahedron, 29 (22), 3571-3578 (1973)

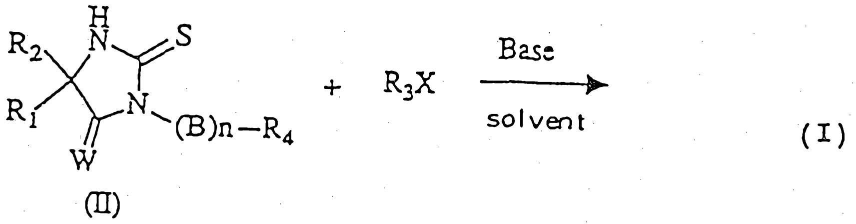
k) Schmidt, U., Heimgartner, H. and Schmidt, H., Helvetica Chemica Acta, 62 (1979), 160-170

l) Muraoka, M., Journal of the Chemical Society, Perkin Transactions I, (1990), 3003-3007 or according to one of the processes A, B, C or D described below.

The compounds of formula Ib can be obtained according to the process described by Böhme, Martin and Strahl in Archiv der Pharmazie, 313, 10-15 (1980) (reference d) or according to one of the processes described below.

Process A: Process for the preparation of the compounds of formula (I).

The preparation of the compounds of formula (I) by S-alkylation of the 2-thiohydantoins (II) is carried out according to the reaction scheme:



in which X represents a chlorine, bromine or iodine atom or a sulphate group, or an alkylsulphonyloxy or arylsulphonyloxy group, alkyl and aryl being as defined above for R_1 and R_2. It is possible to use, as base, an alkoxide, for example potassium tert-butoxide, an alkali metal or alkaline-earth metal hydroxide, an alkali metal carbonate or a tertiary amine. It is possible to use, as solvent, ethers, cyclic ethers, alkyl esters, acetonitrile, alcohols containing 1 to 3 carbon atoms, or aromatic solvents, for example tetrahydrofuran, at a temperature of between -5°C and +80°C.

This process is suitable for the compounds in which W represents a sulphur or oxygen atom.

The 2-thiohydantoins of formula (II) can be obtained according to the processes described in the literature such as, for example, in the following references:

e) Biltz, H., Chemische Berichte, 42, 1792-1801 (1909)

n) Eberly and Dains, Journal of the American Chemical Society, 58, (1936), 2544-2547

o) Carrington, C.H., Journal of the Chemical Society, (1947), 681-686

g) Carrington, C.H. and Warring, W.S., Journal of the Chemical Society, (1950), 354-365

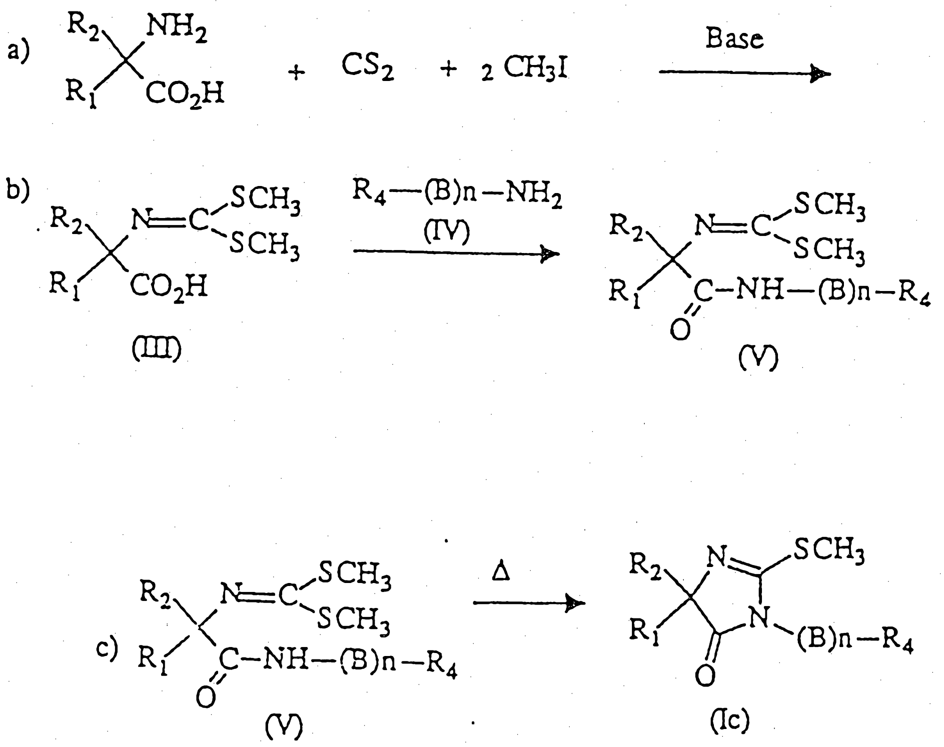
h) Lampert, K., Breuer, J. and Lemper-Streter, M., Chemische Berichte, 92, 235-239 (1959)

i) Koltai, E., Nyitrai, J., Lempert, K. and Burics, L., Chemische Berichte, 104, 290-300 (1971)

or alternatively according to one of processes E or F described below and which form part of the invention.

Process B: Preparation of the compounds Ic.

The preparation of the 2-methylthio-2-imidazolin-5-ones of formula (Ic) by cyclisation of the iminodithiocarbonates of formula (V) is carried out according to the overall scheme:

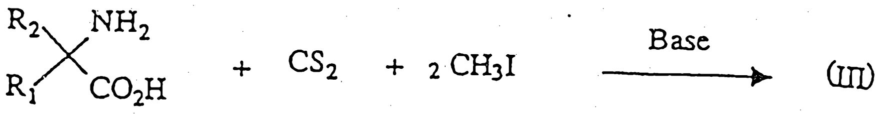


a) The iminodithiocarbonates (III) can be prepared by carrying out the preparation according to the conditions described in the literature for analogous compounds:

- C. Alvarez Ibarra et al., Tetrahedron Letters, 26 (2), 243-246 (1985)

- E. Melendez et al., Synthesis, 1981, 961

according to:



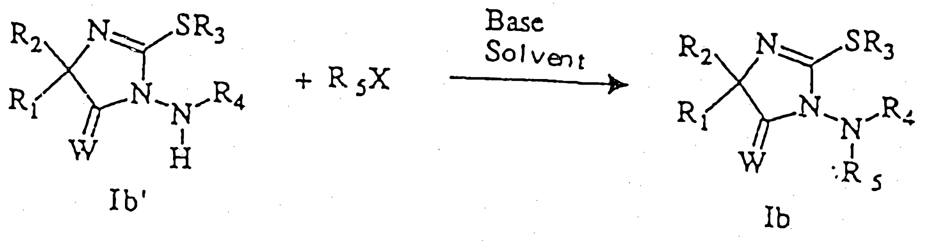
b) The compounds of formula (V) are obtained by condensing the compounds of formula (III) with amines or hydrazines of formula (IV). To carry out the condensation, the acid (III) must be activated in the acid chloride form, in the dicyclohexylisourea form using dicyclohexylcarbodiimide or in the imidazolide form using carbonyldiimidazole. Condensation is carried out under the usual conditions for this type of reaction.

c) Cyclisation of the compounds (V) is carried out by simple heating in an aromatic solvent at reflux. It is possible to use, as solvent, especially xylene, chlorobenzene or dichlorobenzene.

Process C: Derivatisation of the compounds (Ib') and (Id').

Process C1: Preparation of the compounds Ib by N-derivatisation of the compounds Ib'.

The compounds of formula (Ib') (compounds (Ib) in which R_5 is a hydrogen atom) can be alkylated, acylated, alkoxycarbonylated, carbamoylated or sulphamoylated according to the following general scheme:

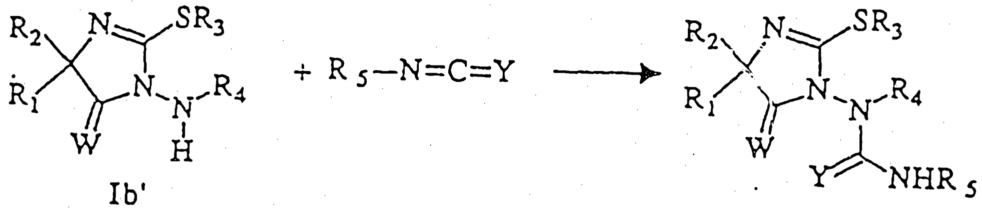


R_5 represents here an alkyl, alkoxycarbonyl, acyl, arylcarbonyl, alkylsulphonyl, arylsulphonyl, carbamoyl or sulphamoyl group, such as defined above.

X represents a halogen, a sulphate group or an optionally substituted phenoxy, or an alkylsulphonyl-oxy or arylsulphonyloxy group, or a group R_5O, when R_5 is acyl.

It is possible to use, as base, alkali metal hydrides, alkoxides or a tertiary amine. The reaction can be carried out at a temperature of between -30°C and +50°C. It is possible to use, as solvent, for example ethers, cyclic ethers, dimethylformamide, dimethyl sulphoxide or aromatic solvents.

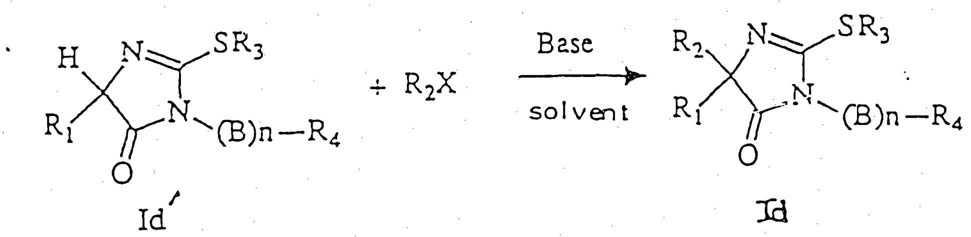
Carbamoylation of the compounds (Ib') can be carried out by reacting with isocyanates or isothiocyanates according to the scheme:



The reaction is carried out under the same conditons as those described above, it being possible for the base, however, to be used in catalytic quantity.

<u>Process C2</u>: Preparation of the compounds Id.

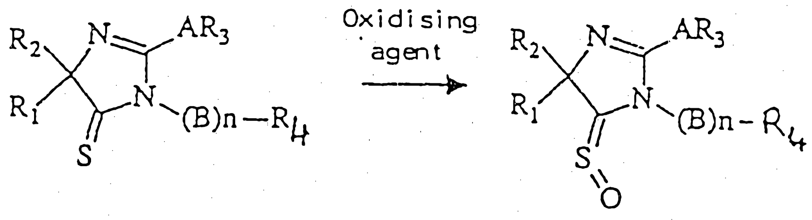
The compounds Id' (compounds Id in which R_2 is a hydrogen atom, can be alkylated in position 4 according to the scheme:



X represents a chlorine, bromine or iodine atom. It is possible to use, as base, an alkoxide, a metal hydride or an amide. The reaction can be carried out at a temperature of between -30°C and +80°C. It is possible to use, as solvent, ethers, cyclic ethers, dimethylformamide, dimethyl sulphoxide or aromatic solvents.

Process D: Preparation of the S-oxidised derivatives of the 2-imidazoline-5-thiones.

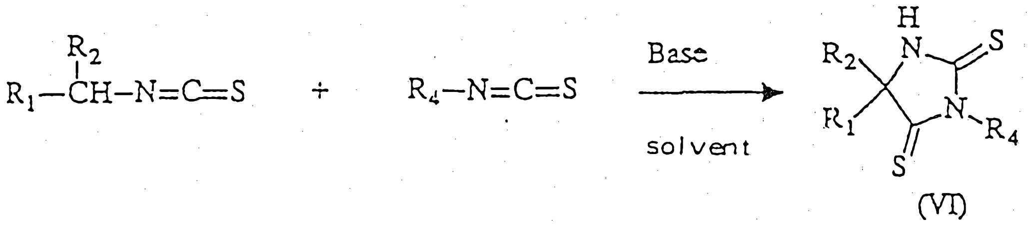
The compounds of formula (I) in which W represents a S=O group are obtained by oxidising the 2-imidazoline-5-thiones according to the scheme:



It is possible to use peroxides, especially peracids, as oxidising agent. The oxidising agent must be used in a stoichiometric quantity. Oxidation is carried out in chloroform or in methylene chloride at a temperature of between -20°C and +20°C.

Process E: Preparation of the dithiohydantoins of formula (VI).

The dithiohydantoins of formula (VI) can be obtained by trapping the alpha anions of the isothiocyanates with isothiocyanates which cannot form anions according to the scheme:

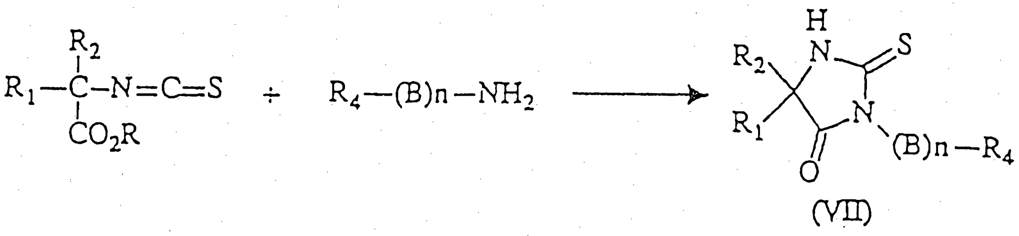


At least one of the groups R_1 or R_2 must be electron-withdrawing (aryl, substituted aryl, alkoxycarbonyl, and the like). The isothiocyanate R_4-NCS must not be able to form an anion; aryl isothiocyanates can be used in particular in this reaction.

It is possible to use, as base, potassium tert-butoxide, lithium or sodium bis(trimethylsilyl)amide or alkali metal hydrides. It is possible to use ethers or cyclic ethers as solvent. The reaction is carried out at a temperature below -60°C. The anion must be trapped as it is formed. To achieve this, the mixture of the 2 isothiocyanates is run onto the base in solution at a temperature below -60°C.

Process F: Preparation of the 2-thiohydantoins of formula (VII).

The preparation of the 2-thiohydantoins (VII) from the isothiocyanates derived from the amino acids (VIII) is carried out according to the reaction:



Cyclisation can be carried out in two ways:

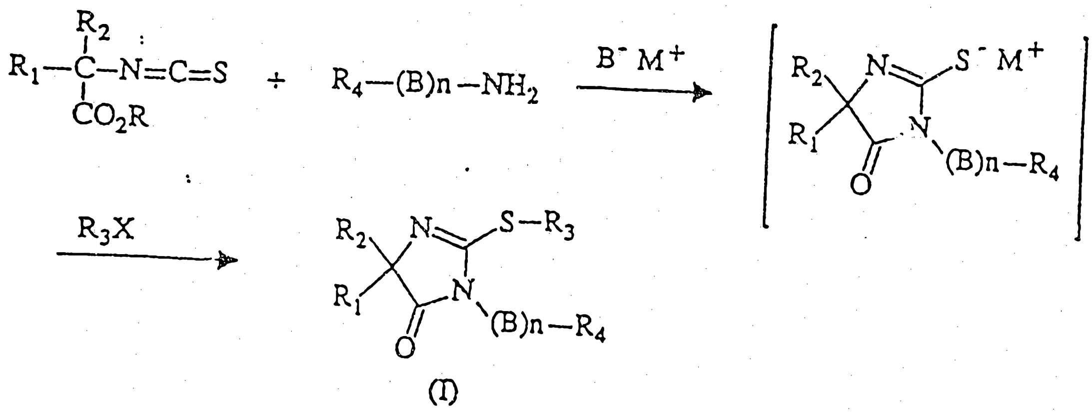
- thermally: in this case, the mixture of the reactants is heated at a temperature of between 110°C and 180°C in an aromatic solvent such as toluene, xylene or the chlorobenzenes;

- in basic medium: the cyclisation is carried out in the presence of one equivalent of a base such as an alkali metal alkoxide, an alkali metal hydroxide or a tertiary amine. Under these conditions, cyclisation takes place at a temperature of between -10 and +80°C. It is possible to use ethers, cyclic ethers, alcohols, esters, DMF, DMSO and the like as solvent.

The isothiocyanates can be prepared according to one of the processes mentioned in Sulfur Reports, Volume 8 (5), pages 327-375 (1989).

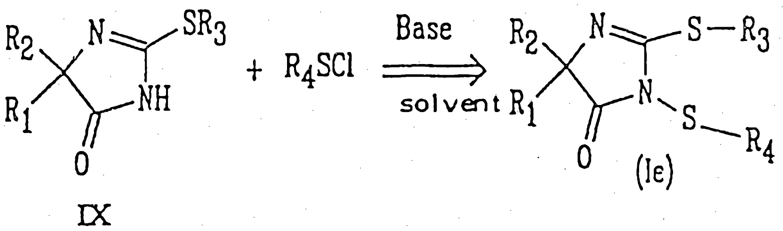
<u>Process G</u>: Preparation of the compounds of formula I in a single stage.

During cyclisation of the 2-thiohydantoins according to process F, if the cyclisation is carried out in basic medium, the thiohydantoin is in the thiolate form at the end of the reaction and can be reacted directly with an alkyl halide or alkyl sulphate R_3X or with R_3X in which X is an alkylsulphonyloxy or aryl-sulphonyloxy to form (I). Processes A and F are thus linked together according to the scheme:



<u>Process H</u>: Preparation of the compounds of formula Ie, in which (B)n is a sulphur atom.

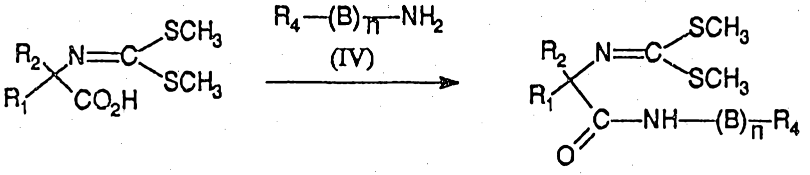
These compounds can be obtained by reacting a sulphuryl chloride R_4SCl with an imidazolinone of formula IX according to the scheme:



The reaction is carried out at a temperature of between -20°C and +30°C, in the presence of one molar equivalent of a base. As solvent, it is possible to use alkali metal hydrides, alkali metal alkoxides or tertiary amines as a base. As a solvent, it is possible to use polar solvents, for example, ethers, cyclic ethers, dimethylformamide, dimethyl sulphoxide or aromatic solvents. The imidazolinones (IX) can be prepared by processes analogous to process A.

Some of the intermediates used in the preparation of the compounds of general formula (I) of the present invention and the processes for their preparation are novel *per se*.

According to one aspect of the present invention there is provided a process for the preparation of compounds of formula (V) wherein an imino dithiocarbonate of formula (III) is condensed with an amine or a hydrazine of formula (IV) according to the scheme:



(III) (V)

in which:

- n = 0 or 1
- B represents NR_5 or O or S or CR_5R_6 or SO_2 or C=O

- R_1 and R_2, which are identical or different, represent:
  - H, provided that one of the 2 groups is different from H, or
  - an alkyl or haloalkyl radical containing 1 to 6 carbon atoms or
  - an alkoxyalkyl, alkylthioalkyl, alkylsulphonylalkyl, monoalkylaminoalkyl, alkenyl or alkynyl radical containing 2 to 6 carbon atoms or
  - a dialkylaminoalkyl or cycloalkyl radical containing 3 to 7 carbon atoms or
  - an aryl radical preferably phenyl, naphthyl, thienyl, furyl, pyridyl, benzothienyl, benzofuryl, quinolyl, isoquinolyl, or methylenedioxyphenyl, optionally substituted by 1 to 3 groups chosen from R_7 or
  - an arylalkyl, aryloxyalkyl, arylthioalkyl or arylsulphonylalkyl radical, or
  - R_1 and R_2 can form, with the carbon to which they are bonded on the ring, a carbocycle or a heterocycle having from 5 to 7 atoms, it being possible for these rings

to be fused to a phenyl, optionally substituted by 1 to 3 groups chosen from R_7;

- R_4 represents:
  - a hydrogen atom when n is equal to 1 or
  - an alkyl group containing 1 to 6 carbon atoms or
  - an alkoxyalkyl, alkylthioalkyl, haloalkyl, cyanoalkyl, thiocyanatoalkyl, alkenyl or alkynyl group containing 2 to 6 carbon atoms or
  - a dialkylaminoalkyl, alkoxycarbonylalkyl or N-alkylcarbamoylalkyl group containing 3 to 6 carbon atoms or
  - a N,N-dialkylcarbamoylalkyl group containing 4 to 8 carbon atoms or
  - an aryl radical, preferably phenyl, naphthyl, thienyl, furyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, benzothienyl, benzofuryl, quinolyl, isoquinolyl or methylenedioxyphenyl, optionally substituted by 1 to 3 groups chosen from R_7 or
  - an arylalkyl, aryloxyalkyl, arylthioalkyl or arylsulphonylalkyl radical, or
  - an amino group disubstituted by 2 identical or different groups chosen from:
    - an alkyl radical containing 1 to 6 carbon atoms
    - an alkoxyalkyl, alkenyl or alkynyl radical containing 3 to 6 carbon atoms
    - a cycloalkyl radical containing 3 to 7 carbon atoms
    - an arylalkyl, phenyl or naphthyl radical, optionally substituted by 1 to 3 groups chosen from R_7 or
    - a thienylmethyl or furfuryl radical
  - a pyrrolidino, piperidino, morpholino or piperazino group, optionally substituted by alkyl containing 1 to 3 carbon atoms;
- R_5 represents:
  - H, expect when R_4 is H, or
  - an alkyl, haloalkyl, alkylsulphonyl or haloalkylsulphonyl radical containing 1 to 6 carbon atoms or
  - an alkoxyalkyl, alkylthioalkyl, acyl, alkenyl, alkynyl, haloacyl, alkoxycarbonyl, haloalkoxycarbonyl, alkoxyalkylsulphone or cyanoalkylsulphonyl radical containing 2 to 6 carbon atoms or
  - an alkoxyalkoxycarbonyl, alkylthioalkoxycarbonyl or cyanoalkoxycarbonyl radical containing 3 to 6 carbon atoms or
  - a formyl radical or

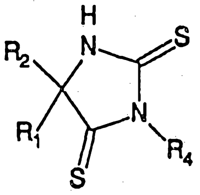
- a cycloalkyl, alkoxyacyl, alkylthioacyl, cyanoacyl, alkenylcarbonyl or alkynylcarbonyl radical containing 3 to 6 carbon atoms or
- a cycloalkylcarbonyl radical containing 4 to 8 carbon atoms or
- a phenyl; arylalkylcarbonyl, preferably phenylacetyl or phenylpropionyl; arylcarbonyl, preferably benzoyl, optionally substituted by 1 to 3 groups from R_7; thienylcarbonyl;furylcarbonyl;pyridylcarbonyl;benzyloxycarbonyl;furfuryloxycarbonyl; tetrahydrofurfuryloxycarbonyl; thienylmethoxycarbonyl; pyridylmethoxycarbonyl; phenoxycarbonyl or (phenylthio)carbonyl, the phenyl being itself optionally substituted by 1 to 3 groups from R_7; (alkylthio)carbonyl; (haloalkylthio)carbonyl; (alkoxyalkylthio)carbonyl; (cyanoalkylthio)carbonyl; (benzylthio)carbonyl; (furfurylthio)carbonyl; (tetrahydrofurfurylthio)carbonyl; (thienylmethylthio)carbonyl; (pyridylmethylthio)carbonyl; or arylsulphonyl radical or
- a carbamoyl radical, optionally mono- or disubstituted by
    - an alkyl or haloalkyl group containing 1 to 6 carbon atoms or
    - a cycloalkyl, alkenyl or alkynyl group containing 3 to 6 carbon atoms or
    - an alkoxyalkyl, alkylthioalkyl or cyanoalkyl group containing 2 to 6 carbon atoms or
    - a phenyl, optionally substituted by 1 to 3 R_7 groups;
- a sulphamoyl group, optionally mono- or disubstituted by
    - an alkyl or haloalkyl group containing 1 to 6 carbon atoms or
    - a cycloalkyl, alkenyl or alkynyl group containing 3 to 6 carbon atoms or
    - an alkoxyalkyl, alkylthioalkyl or cyanoalkyl group containing 2 to 6 carbon atoms or
    - a phenyl, optionally substituted by 1 to 3 R_7 groups;
- an alkylthioalkylsulphonyl group containing 3 to 8 carbon atoms or a cycloalkylsulphonyl group containing 3 to 7 carbon atoms;
- R_6 represents:
- a hydrogen atom or
- a cyano group or
- an alkyl group containing 1 to 6 carbon atoms or a cycloalkyl group containing

3 to 7 carbon atoms or

- an acyl or alkoxycarbonyl group containing 2 to 6 carbon atoms or
- a benzoyl group, optionally substituted by 1 to 3 R_7 groups;
- R_7 represents:
- a halogen atom or
- an alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio or alkylsulphonyl radical containing 1 to 6 carbon atoms or
- a cycloalkyl, halocycloalkyl, alkenyloxy, alkynyloxy, alkenylthio or alkynylthio radical containing 3 to 6 carbon atoms or
- a nitro or cyano group or
- an amino radical, optionally mono- or disubstituted by an alkyl or acyl radical containing 1 to 6 carbon atoms or an alkoxycarbonyl radical containing 2 to 6 carbon atoms
- a phenyl, phenoxy or pyridyloxy radical, these radicals optionally being substituted;

it being necessary for the acid (III) to be activated for this condensation in the acid chloride form, in the dicyclohexylisourea form using dicyclohexylcarbodiimide, or in the imidazolide form using carbonyldiimidazole.

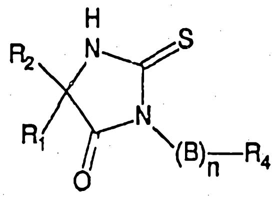
According to another aspect of the present invention there is provided a process for the preparation of dithiohydantoins of formula (VI) (process E):



(VI)

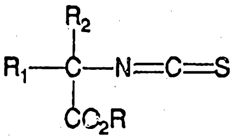
in which R_1, R_2 and R_4 have the same meaning as defined above with at least one of R_1 or R_2 being electron-withdrawing, characterised in that two isothiocyanates, of formulae R_1R_2CHNCS and R_4NCS in which R_4NCS is unable to form an anion, are reacted in the presence of a base, in a solvent and at a temperature below -60°C.

The present invention also provides a process for the preparation of the 2-thiohydantoins of formula (VII) (process F):



(VII)

characterised in that, before cyclising, a compound of formula (IV) ($R_4(B)nNH_2$) is reacted with isothiocyanates derived from the amino acids of formula (VIII):

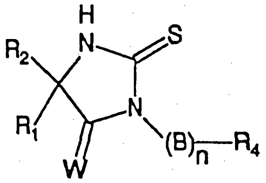


$$R_1-\overset{R_2}{\underset{CO_2R}{C}}-N=C=S$$

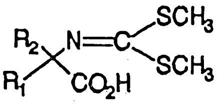
(VIII)

in which R_1, R_2, R_4, B and n have the same meaning as defined above and R is C_{1-4}alkyl or a benzyl group.

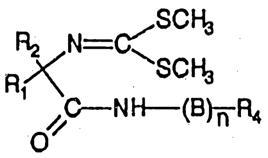
The present invention further provides compounds having the formulae II, III, IV, V, VI, VII and VIII



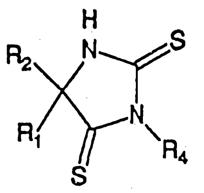
(II)



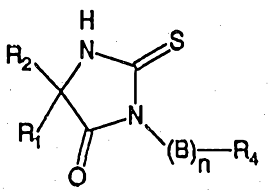
(III)



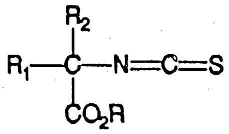
(V)



(VI)



(VII)



$$R_1-\overset{R_2}{\underset{CO_2R}{C}}-N=C=S$$

(VIII)

in which R_1, R_2, B, n and R_4 have the same meaning as in claim 1 and W is a sulphur or oxygen atom or an S=O group.

The compounds which are preferred for their better fungicidal activity and/or for their ease of synthesis are:

1) the compounds of formula Ib,

2) the compounds of formula I, in particular Ib, in which R_5 is a hydrogen atom,

3) the compounds in which R_1 and R_2 are different from H,

4) the compounds in which R_2 represents an alkyl group containing 1 to 3 carbon atoms,

5) the compounds in which R_1 represents a phenyl ring, optionally substituted by R_7,

6) the compounds in which R_3 represents an alkyl group containing 1 to 3 carbon atoms,

7) the compounds in which R_4 represents a phenyl ring, optionally substituted by R_7,

8) the compounds in which R_3 represents a methyl group.

The examples below are given by way of

illustration of the compounds according to the invention, of the processes for their preparation and of their antifungal properties.

The structures of all the products were established by at least 1 of the following spectral techniques: proton NMR spectrometry, carbon-13 NMR spectrometry, infrared spectrometry and mass spectrometry.

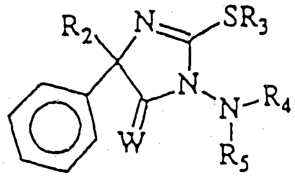
In the tables below, the methyl and phenyl radicals are represented respectively by Me and Ph, and Cst means a physical constant, that is to say either a melting point (M.p.) or the refractive index (n_D^{20}).

Example 1: Preparation of compound No. 34 according to process A.

0.9 g (3 mmol) of 3-benzyl-5-methyl-5-phenyl-2-thiohydantoin is dissolved in 30 ml of anhydrous tetrahydrofuran. The mixture is cooled to 0°C and then 0.34 g (3 mmol) of potassium tert-butoxide is added. The mixture is left to react for 10 min at 0°C and then 0.46 g (3.3 mmol) of methyl iodide is run in dropwise at this temperature: potassium iodide is observed to precipitate. The temperature of the mixture is allowed to return to room temperature. The mixture is diluted with 100 ml of ethyl acetate. The solution is washed 2 times with 100 ml of water on each occasion. The solution is dried over sodium sulphate and is then treated with active charcoal. The solution is concentrated under reduced pressure: 0.6 g of

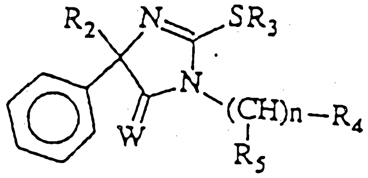
1-benzyl-4-methyl-2-methylthio-4-phenyl-2-imidazolin-5-one (compound No. 34) is recovered in the form of a pale-yellow solid melting at 68°C.

The compounds described below were prepared in the same way:



No.	R_2	R_3	R_4	R_5	W	Cst
1	Me	Me	Ph	H	S	M.p.= 127°C
3	Me	2-oxopropyl	Ph	H	S	M.p.= 130°C
9	Me	Me	Ph	H	O	M.p.= 149°C
10	Me	Me	meta-tolyl	H	O	M.p.= 124°C
11	Me	Me	para-tolyl	H	O	M.p.= 150°C
12	Me	Et	Ph	H	O	M.p.= 118°C
13	Me	Me	4-fluoroPh	H	O	M.p.= 144°C
14	Me	allyl	Ph	H	O	M.p.= 92°C
15	Me	Me	ortho-tolyl	H	O	M.p.= 92°C
16	Me	Me	3-chloroPh	H	O	M.p.= 120°C
17	Me	iso-propyl	Ph	H	O	M.p.= 95°C
18	Me	Me	4-chloroPh	H	O	M.p.= 149°C
19	Me	Me	tert-butyl	H	O	M.p.= 73°C
20	Me	Me	2-chloroPh	H	O	M.p.= 134°C
22	Me	Me	Ph	Me	O	M.p.= 124°C
23	Me	Me	Ph	acetyl	O	M.p.= 132°C
24	Me	Me	4-methoxyPh	H	O	M.p.= 138°C
25	Me	n-propyl	Ph	H	O	M.p.= 90°C
40	Me	Me	2-methoxyPh	H	O	M.p.= 110°C
41	Me	Me	acetyl	H	O	M.p.= 55°C

No.	R_2	R_3	R_4	R_5	W	Cst
43	Me	Me	4-NO_2-Ph	H	O	M.p.= 133°C
44	Me	Me	2-pyridyl	H	S	M.p.= 114°C
45	Me	Me	2-pyridyl	H	O	M.p.= 147°C
46	Me	Me	3-pyridyl	H	O	M.p.= 140°C
47	Me	Me	3-pyridyl	H	S	M.p.= 176°C
54	Me	Me	2,6-Me_2Ph	H	S	M.p.= 146°C
73	Me	Me	2-thiazolyl	Me	O	M.p.= 116°C
75	Me	CHF_2	Ph	H	O	M.p.= 80°C
82	Me	Me	4-Me-SO_2-Ph	H	O	M.p.= 130°C



No.	R_2	R_3	R_4	n	R_5	W	Cst
26	Me	Me	Ph	0	-	S	M.p.= 123°C
27	Ph	Me	Ph	0	-	S	M.p.= 120°C
28	Me	Me	Me	0	-	S	M.p.= 85°C
29	Ph	Me	Me	0	-	S	M.p.= 144°C

No.	R_2	R_3	R_4	n	R_5	W	Cst
30	Me	Me	Ph	0	-	O	M.p.= 70°C
31	Me	Me	Me	0	-	O	M.p.= 58°C
32	Ph	Me	Me	0	-	O	M.p.= 170°C
33	H	Me	Ph	0	-	O	M.p.= 250°C
34	Me	Me	Ph	1	H	O	M.p.= 68°C
35	Me	Me	2-thienyl	1	H	O	M.p.= 76°C
36	Me	Me	Me	1	Me	O	n_D^{20} = 1.553
37	Me	Me	2-furyl	1	H	O	"honey-like consistency"
38	Me	Me	3-pyridyl	0	-	O	"honey-like consistency"
50	Ph	MeS	Me	0	H	S	M.p.=144°C
52	Me	MeS	Ph	1	CO_2Me	O	"honey-like consistency"
57	Me	MeS	2-MePh	0	-	O	"honey-like consistency"

The following were also prepared:

- 4-(3-pyridyl)-4-methyl-1-(N-phenylamino)-2-methylthio-2-imidazolin-5-one (compound 51: M.p. 156°C);

- 4-phenyl-4-methyl-1-(benzyloxy)-2-methylthio-2-imidazolin-5-one (compound 56: honey-like consistency).

Example 2: Preparation of compound No. 7 according to process B.

a) N-[bis(methylthio)methylene]-2-phenylglycine (compound (III) with R_1 = phenyl and R_2 = H):

100 g (0.66 mol) of phenylglycine are dissolved at +5°C in 335 g of 22 % aqueous potassium hydroxide (1.3 mol). 55.3 g of carbon disulphide are added while stirring the mixture vigorously: a precipitate appears and the mixture turns orange in colour. The mixture is left to react for 3 h at room temperature and then 103 g (0.73 mol) of methyl iodide are run in while keeping the temperature of the mixture below 30°C. The mixture is left to react for 0.5 h and then 74 g (0.66 mol) of a 50 % potassium hydroxide solution are added. The mixture is left to react for 0.5 h and then 103 g of methyl iodide are again run in and left to react for 1 h. The mixture is diluted with 300 ml of water. The mixture is acidified to pH = 4 with 1N hydrochloric acid. The product is extracted with 500 ml of ethyl acetate. The solution is dried over magnesium sulphate and then concentrated under

reduced pressure. 49.5 g of N-[bis(methylthio)-methylene]-2-phenylglycine (yield = 31 %) are recovered in the form of a yellow solid melting at 112°C.

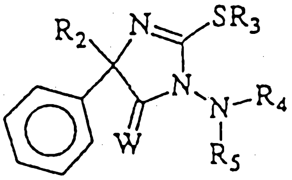
b) 2'-(metachlorophenyl)[N-(bis(methylthio)-methylene)-2-phenylglycyl]hydrazide (compound V with R_1 = phenyl, R_2 = H, R_4 = metachlorophenyl, n = 1, B = NH):

3.38 g (16.4 mmol) of dicyclohexylcarbodiimide are added to a solution of 2.95 g (16.4 mmol) of N-[bis(methylthio)methylene]-2-phenylglycine in methylene chloride (40 ml), and the mixture is then left to react for 0.5 h at room temperature. 2.34 g (16.4 mmol) of metachlorophenylhydrazine are added. The mixture is heated for 0.5 h at 30°C. The insoluble material is filtered off. The filtrate is washed with 2 times 30 ml of water on each occasion. The solution is concentrated: a honey-like product is obtained which is purified by chromatography on a silica column. After purification, 2.5 g of 2'-(metachlorophenyl)[N-(bis(methylthio)methylene)-2-phenylglycyl]hydrazide are recovered in the form of a pinkish powder melting at 146°C.

c) 1-Metachlorophenylamino-2-methylthio-4-phenyl-2-imidazolin-5-one (compound No. 7):

1.92 g (5 mmol) of 2'-(metachlorophenyl)[N-(bis(methylthio)methylene)-2-phenylglycyl]hydrazide is dissolved in 30 ml of xylene. The reaction mixture is heated for 4 h at reflux. The mixture is concentrated under reduced pressure. The resulting honey-like product is triturated with 10 ml of ether: the product crystallises. The precipitate is filtered and the product is dried in a desiccator under vacuum. Compound No. 7 is thus obtained, with a yield of 56 %, in the form of a yellow powder melting at 196°C.

By carrying out the preparation in a similar way, the compounds which appear in the following table were prepared:



No.	R_2	R_3	R_4	R_5	W	Cst
4	H	Me	2-chloroPh	H	O	M.p.= 130°C
5	H	Me	Ph	H	O	M.p.= 190°C
6	H	Me	4-chloroPh	H	O	M.p.= 162°C
7	H	Me	3-chloroPh	H	O	M.p.= 196°C
8	H	Me	meta-tolyl	H	O	M.p.= 182°C
59	H	MeS	2,4-$(CH_3)_2$Ph	H	O	M.p.= 64°C
61	H	MeS	2,5-$(CH_3)_2$Ph	H	O	M.p.= 162°C
63	H	MeS	2-EtPh	H	O	M.p.= 126°C
69	H	MeS	2,5-$(Cl)_2$Ph	H	O	M.p.= 144°C
71	H	MeS	3,5-$(Cl)_2$Ph	H	O	M.p.= 146°C

4-Phenyl-1-(N-phenylamino)-2-methylthio-2-imidazolin-5-one (compound 120) was also prepared.

Example 3: Preparation of 4-methyl-1-(N-methyl-N-phenylamino)-2-methylthio-4-phenyl-2-imidazolin-5-one (compound No. 22) by alkylation (methylation) according to process C1.

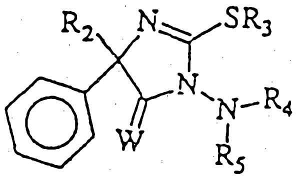
0.4 g (3.5 mmol) of potassium tert-butoxide is added to a solution of 4-methyl-1-phenylamino-2-

methylthio-4-phenyl-2-imidazolin-5-one (compound No. 9) (1 g, 3.2 mmol) in anhydrous tetrahydrofuran (30 ml), cooled beforehand to 0°C. The mixture is left to react for 0.5 h at 0°C. 0.5 g (3.5 mmol) of methyl iodide is then added and then the mixture is left to react for 0.5 h at room temperature. The reaction mixture is poured into 100 ml of water and the product is extracted with 100 ml of diethyl ether. The ethereal solution is dried over magnesium sulphate and then concentrated. The product crystallises when triturated in 10 ml of diisopropyl ether. It is filtered and then dried under vacuum. 0.73 g (yield: 70 %) of compound 22 is thus obtained in the form of a pale-yellow powder melting at 124°C.

<u>Example 4</u>: Preparation of 4-methyl-1-(N-acetyl-N-phenylamino)-2-methylthio-4-phenyl-2-imidazolin-5-one (compound No. 23) by acylation (acetylation) according to process C1.

0.4 g (3.5 mmol) of potassium tert-butoxide is added to a solution of 4-methyl-1-phenylamino-2-methylthio-4-phenyl-2-imidazolin-5-one (compound No. 9) (1 g, 3.2 mmol) in anhydrous tetrahydrofuran (30 ml), cooled beforehand to 0°C. The mixture is left to react for 0.5 h at 0°C. 0.25 g (3.5 mmol) of acetyl chloride is then added and the mixture is left to react for 0.5 h at room temperature. The reaction mixture is poured into 100 ml of water and the product is extracted with 100 ml of diethyl ether. The ethereal solution is washed with water to neutrality. The solution is dried over magnesium sulphate and then concentrated. A honey-like product is obtained which is purified by chromatography on a silica column. The purified product crystallises from diisopropyl ether. 0.25 g of compound No. 23 is obtained in the form of a white powder melting at 132°C.

By carrying out the preparation in the same way, compounds No. 39 and 42 were obtained.

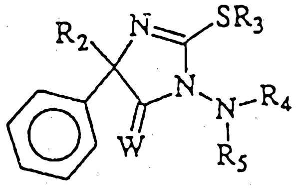


No.	R_2	R_3	R_4	R_5	W	Cst
23	Me	Me	Ph	acetyl	O	M.p.= 132°C
39	Me	Me	Ph	formyl	O	"honey-like consistency"
42	Me	Me	Ph	tBuOCO	O	"honey-like consistency"

Example 5: Preparation of 4-ethyl-2-methylthio-4-phenyl-1-phenylamino-2-imidazolin-5-one (compound 48) according to process C2.

0.55 g of potassium tert-butoxide is added to a solution of 1.5 g (5.05 mmol) of 2-methylthio-4-phenyl-1-phenylamino-2-imidazolin-5-one (compound No. 5) in 50 ml of anhydrous tetrahydrofuran. The mixture is left to react for 30 min at room temperature and then 0.8 g (5.05 mmol) of ethyl iodide is added. The mixture is left to react for 1 h at room temperature. The mixture is diluted with 150 ml of ethyl acetate. The solution is washed with water and then concentrated under reduced pressure. The product is purified by chromatography on a silica column (Merck 60H silica; eluent: 25 % ethyl acetate/75 % heptane). 0.65 g of compound No. 48 is obtained in the form of a beige powder melting at 147°C.

By carrying out the preparation in the same way, compound No. 49 was obtained.



No.	R_2	R_3	R_4	R_5	W	Cst
48	Et	Me	Ph	H	O	M.p.= 147°C
49	iso-Pr	Me	Ph	H	O	M.p.= 135°C
60	Me	MeS	2,4-(Me)$_2$Ph	H	O	"honey-like consistency"
62	Me	MeS	2,5-(Me)$_2$Ph	H	O	M.p.= 160°C
64	Me	MeS	2-EtPh	H	O	"honey-like consistency"
65	Me	MeS	2,4-(Cl)$_2$Ph	H	O	
66	Me	MeS	1-naphthyl	H	O	M.p.= 174°C
70	Me	MeS	2,5-(Cl)$_2$Ph	H	O	M.p.= 180°C
72	Me	MeS	3,5-(Cl)$_2$Ph	H	O	M.p.= 200°C
74	CHF$_2$	MeS	Ph	H	O	M.p.= 124°C
79	Me	MeS	2-CF$_3$-Ph	H	O	M.p.= 91°C

4-Methyl-2-methylthio-4-(4-fluorophenyl)-1-phenylamino-2-imidazolin-5-one (compound 68) was also prepared.

Example 6: Preparation of compound 2 according to process D.

1.7 g (5.2 mmol) of 4-methyl-2-methylthio-4-phenyl-1-phenylamino-2-imidazoline-5-thione (compound No. 1) is dissolved in 20 ml of chloroform. The solution is cooled to -10°C and then a solution of 1.35 g (5.5 mmol) of metachloroperbenzoic acid and 30 ml of chloroform is added over 10 min. On completion of addition, the temperature is allowed to return to room temperature. The mixture is washed with a saturated aqueous sodium bicarbonate solution and then with distilled water. The organic phase is treated with active charcoal and then concentrated. The resulting honey-like product is taken up in 20 ml of ether: the product dissolves and then a beige solid precipitates. The precipitate is filtered. The product is dried under reduced pressure. 0.4 g (yield: 25 %) of compound No. 2 is thus obtained in the form of a beige powder melting at 150°C.

No.	R_2	R_3	R_4	R_5	W	Cst
2	Me	Me	Ph	H	S=O	M.p.= 150°C

Example 7: Preparation of 3,5-diphenyl-5-methyldithiohydantoin according to process E.

15.1 g (122 mmol) of potassium tert-butoxide are dissolved in 200 ml of tetrahydrofuran in a 500 ml, three-necked, round-bottomed flask under a dry argon atmosphere. The solution is cooled to -70°C. A solution containing 20 g (122 mmol) of alpha-methylbenzyl isothiocyanate, 16.55 g (122 mmol) of phenyl isothiocyanate and 50 ml of tetrahydrofuran is run in dropwise while keeping the temperature of the mixture below -60°C. On completion of addition, the mixture is held for 0.5 h at -70°C and then is left to return to room temperature. The mixture is poured into 500 ml of water. The mixture is acidified to pH = 1 by addition of N hydrochloric acid. The product is extracted with ethyl acetate (2 extractions, each with 150 ml of solvent). The solution is dried over magnesium sulphate. The solution is concentrated under reduced pressure. The product is crystallised from 50 ml of ether. The precipitate is filtered. 21 g (yield: 58 %) of 3,5-diphenyl-5-methyldithiohydantoin are thus obtained, a yellow powder melting at 157°C.

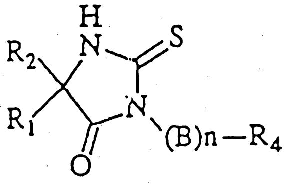
Example 8: Preparation of 3,5-diphenyl-5 methyl-2-thiohydantoin according to process F.

4.7 g (20 mmol) of ethyl 2-isothiocyanato-2-phenylpropionate are dissolved in 40 ml of xylene. 2.16 g (20 mmol) of phenylhydrazine are added and the mixture is heated for 4 h at reflux. The mixture is cooled to room temperature and a beige solid precipitates. The precipitate is filtered, washed with 5 ml of diisopropyl ether and then dried under vacuum. 4.6 g (yield = 77 %) of 3,5-diphenyl-5-methyl-2-thiohydantoin are thus obtained in the form of a beige powder melting at 164°C.

Example 9: Preparation of 5-methyl-5-phenyl-3-(2-pyridylamino)-2-thiohydantoin according to process F.

2 g (9 mmol) of methyl 2-isothiocyanato-2-phenylpropionate are dissolved in 30 ml of tetrahydrofuran. A solution containing 0.99 g of 2-hydrazinopyridine and 10 ml of tetrahydrofuran is added: the temperature of the mixture rises from 20 to 30°C and a solid precipitates. The mixture is allowed to react for 0.5 h at 30°C and then is cooled to 5°C. A solution containing 1 g of potassium tert-butoxide and 10 ml of tetrahydrofuran is then added: the mixture becomes violet in colour. The mixture is left to return to room temperature and is left to react for 2 h. The mixture is poured into 150 ml of water. The mixture is neutralised with acetic acid. The product is extracted with 150 ml of ethyl acetate. The solution is washed with water, dried over magnesium sulphate and then treated with active charcoal. The solution is concentrated and the product is crystallised from 20 ml of diethyl ether. The abovementioned product is filtered and is dried under vacuum. 1.6 g (yield: 60 %) of 5-methyl-5-phenyl-3-(2-pyridylamino)-2-thiohydantoin is obtained, a pale-yellow solid melting at 80°C.

The compounds of formula (VII) collated in the following table, which are intermediates of the compounds of formula I and are numbered from number 1001, were prepared according to this process:



(VII)

R_1 = methyl and R_2 = phenyl.

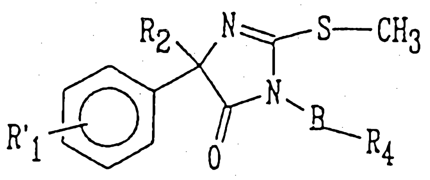
No.	n	B	R_4	Yield	M.p.
1001	1	NH	Ph	66 %	164°C
1002	1	NH	meta-tolyl	62 %	174°C
1003	1	CH_2	Ph	46 %	125°C
1004	1	NH	para-tolyl	13 %	162°C
1005	1	CH_2	2-thienyl	49.5 %	134°C
1006	1	NH	4-fluoroPh	30 %	162°C
1007	1	NH	ortho-tolyl	38 %	162°C
1008	0	-	iso-propyl	60.5 %	146°C
1009	1	NH	3-chloroPh	32 %	78°C
1010	1	NH	tert-butyl	18 %	120°C
1011	1	NH	4-chloroPh	24 %	196°C
1012	1	NH	2-chloroPh	69 %	172°C
1013	0	-	piperidino	32 %	206°C
1014	1	NH	4-methoxyPh	27 %	146°C
1015	1	NH	2-methoxyPh	29 %	214°C
1016	1	CH_2	2-furyl	39 %	105°C
1017	1	NH	acetyl	42 %	200°C
1018	1	NH	4-NO_2-Ph	41 %	234°C
1019	1	NH	2-pyridyl	60 %	80°C
1020	1	NH	3-pyridyl	17 %	

Example 10: Preparation of compound 9 according to process G.

11.1 g (50 mmol) of methyl 2-isothiocyanato-2-phenylpropionate are dissolved in 150 ml of anhydrous tetrahydrofuran. A solution containing 5.4 g (50 mmol) of phenylhydrazine and 50 ml of anhydrous tetrahydrofuran is added progressively over 10 min: the temperature of the mixture rises to 35°C. On completion of addition, the mixture is left to react for 0.5 h at 30°C and the mixture is then cooled to -5°C. A solution containing 5.6 g (50 mmol) of potassium tert-butoxide and 50 ml of anhydrous tetrahydrofuran is added at this temperature: the mixture turns violet in colour and then a precipitate forms. The mixture is left to react for 0.5 h at 0°C and then 8.5 g (60 mmol) of methyl iodide are added. The mixture is left to react for 1 h at room temperature. The mixture is diluted with 200 ml of ethyl acetate. The mixture is washed 2 times with 150 ml of water on each occasion. The solution is dried over magnesium sulphate and then treated with active charcoal. The solution is concentrated: a purplish-brown honey-like product is obtained which is crystallised from 50 ml of ether. The precipitate is washed and then dried under vacuum. A second crop of product is recovered after concentrating the mother liquors and taking up the residual honey-like product in 50 ml of diisopropyl ether. 12 g (yield = 77 %) of 4-methyl-2-methylthio-4-phenyl-1-phenylamino-2-

imidazolin-5-one (compound 9) are thus obtained in the form of a beige powder melting at 149°C.

By carrying out the preparations as above, the following compounds were obtained:

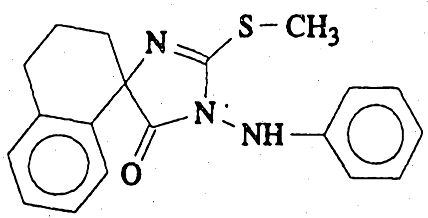


No.	R'_1	R_2	R_3	B	R_4	M.p.
58	-	Me	MeS	NH	2,3-$(Me)_2$Ph	116°C
67	-	Me	MeS	$(CH_2)_2$	Ph	honey-like consistency
76	-	Me	MeS	CH_2	3-pyridyl	67°C
77	-	Me	MeS	CH_2	2-pyridyl	honey-like consistency
78	-	Me	MeS	N	PhCH=	95°C
83	4-Me	Me	MeS	NH	Ph	179°C
84	-	Me	MeS	NH	3-Me-2-pyridyl	148°C
85	4-Cl	Me	MeS	NH	Ph	173°C
86	3,4-$(MeO)_2$	Me	MeS	NH	Ph	165°C
87	3,4-$(MeO)_2$	Me	MeS	NH	2-Me-Ph	151°C
88	4-Me	Me	MeS	NH	2-Me-Ph	52°C
89	4-PhO	Me	MeS	NH	Ph	146°C
90	4-Cl	Me	MeS	NH	3-Me-2-pyridyl	133°C
91	4-Cl	Me	MeS	NH	2-pyridyl	172°C
92*	R_1 = $PhCH_2$	Me	MeS	NH	Ph	166°C
93	4-PhO	Me	MeS	NH	2-Me-Ph	130°C
94	4-F	Me	MeS	NH	2-Me-Ph	120°C
96	4-Cl	Me	MeS	NH	2-Cl-Ph	145°C
97*	-	$(CH_2)_3$	MeS	NH	Ph	158°C
98*	-	$(CH_2)_2$	MeS	NH	Ph	85°C
99	4-Cl	H	MeS	NH	4-Cl-Ph	163°C
100	4-Cl	Me	MeS	NH	4-Cl-Ph	172°C

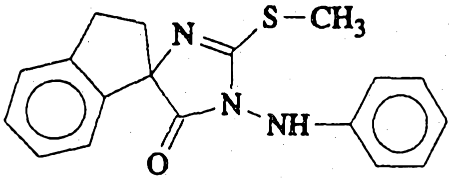
No.	R'_1	R_2	R_3	B	R_4	M.P.
101	4-Cl	Me	MeS	NH	4-F-Ph	170°C
102	4-Cl	Me	MeS	NH	3-Cl-Ph	146°C
103	4-Cl	Me	MeS	NH	4-Me-Ph	178°C
104*	-	$(CH_2)_3$	MeS	NH	2-Cl-Ph	168°C
105	4-Cl	Me	MeS	NH	2-Me-Ph	124°C
106	4-Cl	Me	MeS	NH	3-Me-Ph	136°C
107	4-F	Me	MeS	NH	3-Me-Ph	121°C
108	-	Me	MeS	NH	3-F-Ph	163°C
109	-	Me	MeS	NH	2,5-F_2-Ph	141°C
110	4-Me	Me	MeS	NH	4-Cl-Ph	168°C
111	4-Me	Me	MeS	NH	2-Cl-Ph	168°C
112*	-	$(CH_2)_3$	MeS	NH	4-Cl-Ph	191°C
113*	-	$(CH_2)_3$	MeS	NH	2-Me-Ph	174°C
114	4-Me	Me	MeS	NH	3-Cl-Ph	184°C
115	4-F	Me	MeS	NH	3-Cl-Ph	124°C
116	4-Me	Me	MeS	NH	4-F-Ph	186°C
117	4-Me	Me	MeS	NH	4-Me-Ph	157°C
118	4-F	Me	MeS	NH	4-Me-Ph	158°C
119	4-Me	Me	MeS	NH	3-Me-Ph	178°C
121	4-F	Me	MeS	NH	4-Cl-Ph	159°C
122	-	Me	MeS	NH	2,4-$(Me)_2$-Ph	63°C
123	-	Me	MeS	NH	3-Cl-2-Pyr	127°C
124	4-Cl	Me	MeS	NH	2-F-Ph	120°C
125	4-F	Me	MeS	NH	2-F-Ph	112°C
126	4-Me	Me	MeS	NH	2-F-Ph	156°C

* These compounds have the following formulae:

Compound 97:



Compound 98:



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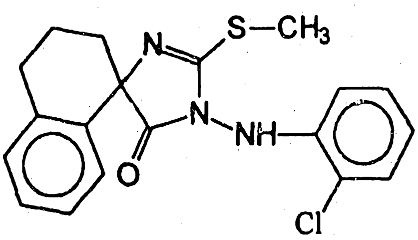

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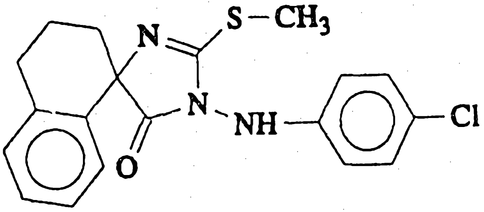

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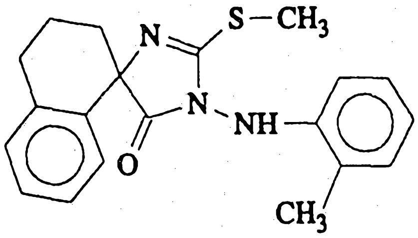
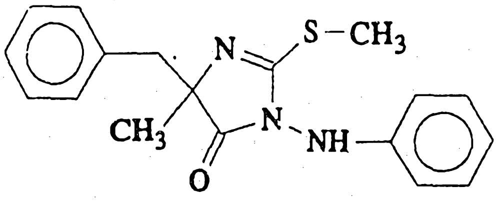


Compound 92:

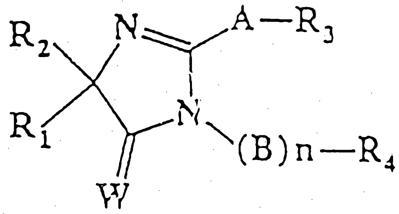


This compound does not follow the general formula on page 38.

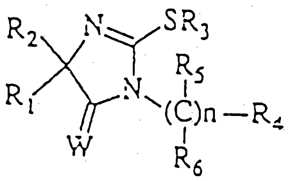
Example 11: Preparation of 4-phenyl-4-methyl-1-(phenylthio)-2-methylthio-2-imidazolin-5-one (compound 95: M.p. 112°C).

0.6 g (2.7 mmol) of 2-methylthio-4-methyl-4-phenyl-2-imidazolin-5-one in solution in 50 ml of anhydrous tetrahydrofuran (THF) is charged to a 100 ml, three-necked, round-bottomed flask under an inert atmosphere. The solution is stirred with a magnetic stirrer and is cooled to 0°C (ice bath + acetone). 0.30 g (1 molar equivalent) of potassium tert-butoxide is added and the mixture is stirred for 10 min at 0°C. A solution containing 0.40 g of phenylsulphenyl chloride and 10 ml of anhydrous THF is then run in. The mixture is then left to return to room temperature for one hour. The reaction mixture is run into 100 ml of water. Extraction is carried out with 100 ml of ethyl acetate. The organic phase is washed 4 times with water and dried over sodium sulphate.

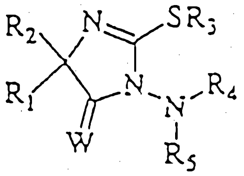
The organic phase is concentrated under vacuum. A yellow honey-like product is obtained which crystallises from isopropyl ether after purification on silica with a yield of 68% (melting point: 112°C).



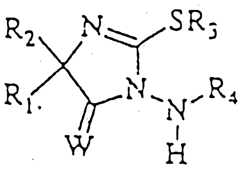
(I)



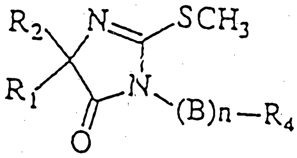
Ia



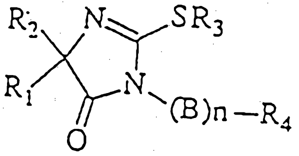
Ib



Ib'



(Ic)



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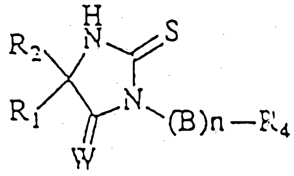
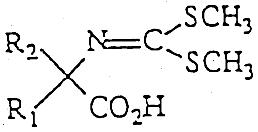


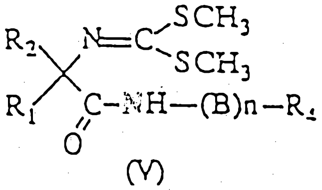
(II)



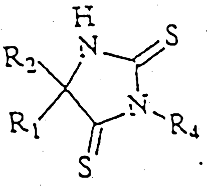
(III)

R_4—(B)n—NH_2

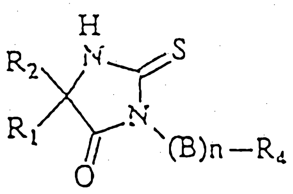
(IV)



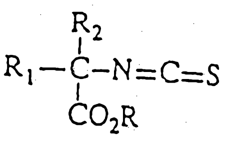
(V)



(VI)



(VII)



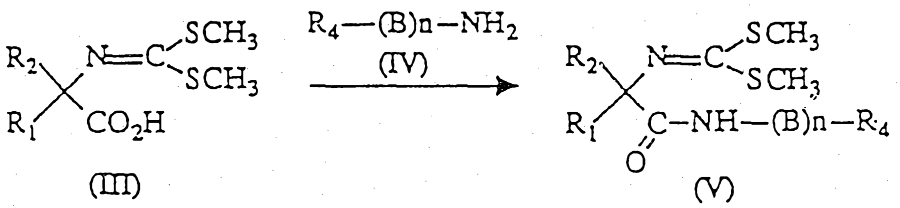
$$R_1-\overset{\displaystyle R_2}{\underset{\displaystyle CO_2R}{C}}-N=C=S$$

(VIII).

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A process for the preparation of compounds of formula (V) wherein an imino dithiocarbonate of formula (III) is condensed with an amine or a hydrazine of formula (IV) according to the scheme:



(III) (V)

in which:

- n = 0 or 1
- B represents NR_5 or O or S or CR_5R_6 or SO_2 or C=O

- R_1 and R_2, which are identical or different, represent:
  - H, provided that one of the 2 groups is different from H, or
  - an alkyl or haloalkyl radical containing 1 to 6 carbon atoms or
  - an alkoxyalkyl, alkylthioalkyl, alkylsulphonylalkyl, monoalkylaminoalkyl, alkenyl or alkynyl radical containing 2 to 6 carbon atoms or
  - a dialkylaminoalkyl or cycloalkyl radical containing 3 to 7 carbon atoms or
  - an aryl radical preferably phenyl, naphthyl, thienyl, furyl, pyridyl, benzothienyl, benzofuryl, quinolyl, isoquinolyl, or methylenedioxyphenyl, optionally substituted by 1 to 3 groups chosen from R_7 or
  - an arylalkyl, aryloxyalkyl, arylthioalkyl or arylsulphonylalkyl radical, or
  - R_1 and R_2 can form, with the carbon to which they are bonded on the ring, a carbocycle or a heterocycle having from 5 to 7 atoms, it being possible for these rings to be fused to a phenyl, optionally substituted by 1 to 3 groups chosen from R_7;
- R_4 represents:
  - a hydrogen atom when n is equal to 1 or
  - an alkyl group containing 1 to 6 carbon atoms or
  - an alkoxyalkyl, alkylthioalkyl, haloalkyl, cyanoalkyl, thiocyanatoalkyl, alkenyl or alkynyl group containing 2 to 6 carbon atoms or

- a dialkylaminoalkyl, alkoxycarbonylalkyl or N-alkylcarbamoylalkyl group containing 3 to 6 carbon atoms or
- a N,N-dialkylcarbamoylalkyl group containing 4 to 8 carbon atoms or
- an aryl radical, preferably phenyl, naphthyl, thienyl, furyl, pyridyl, pyrimidyl, pyridazinyl, pyrazinyl, benzothienyl, benzofuryl, quinolyl, isoquinolyl or methylenedioxyphenyl, optionally substituted by 1 to 3 groups chosen from R_7 or
- an arylalkyl, aryloxyalkyl, arylthioalkyl or arylsulphonylalkyl radical, or
- an amino group disubstituted by 2 identical or different groups chosen from:
  - an alkyl radical containing 1 to 6 carbon atoms
  - an alkoxyalkyl, alkenyl or alkynyl radical containing 3 to 6 carbon atoms
  - a cycloalkyl radical containing 3 to 7 carbon atoms
  - an arylalkyl, phenyl or naphthyl radical, optionally substituted by 1 to 3 groups chosen from R_7 or
  - a thienylmethyl or furfuryl radical
- a pyrrolidino, piperidino, morpholino or piperazino group, optionally substituted by alkyl containing 1 to 3 carbon atoms;
- R_5 represents:
- H, except when R_4 is H, or
- an alkyl, haloalkyl, alkylsulphonyl or haloalkylsulphonyl radical containing 1 to 6 carbon atoms or
- an alkoxyalkyl, alkylthioalkyl, acyl, alkenyl, alkynyl, haloacyl, alkoxycarbonyl, haloalkoxycarbonyl, alkoxyalkylsulphone or cyanoalkylsulphonyl radical containing 2 to 6 carbon atoms or
- an alkoxyalkoxycarbonyl, alkylthioalkoxycarbonyl or cyanoalkoxycarbonyl radical containing 3 to 6 carbon atoms or
- a formyl radical or
- a cycloalkyl, alkoxyacyl, alkylthioacyl, cyanoacyl, alkenylcarbonyl or alkynylcarbonyl radical containing 3 to 6 carbon atoms or
- a cycloalkylcarbonyl radical containing 4 to 8 carbon atoms or
- a phenyl; arylalkylcarbonyl, preferably phenylacetyl or phenylpropionyl; arylcarbonyl, preferably benzoyl, optionally substituted by 1 to 3 groups from R_7; thienylcarbonyl;furylcarbonyl;pyridylcarbonyl;benzyloxycarbonyl;furfuryloxycarbonyl;

tetrahydrofurfuryloxycarbonyl; thienylmethoxycarbonyl; pyridylmethoxycarbonyl; phenoxycarbonyl or (phenylthio)carbonyl, the phenyl being itself optionally substituted by 1 to 3 groups from R_7; (alkylthio)carbonyl; (haloalkylthio)carbonyl; (alkoxyalkylthio)carbonyl; (cyanoalkylthio)carbonyl; (benzylthio)carbonyl; (furfurylthio)carbonyl; (tetrahydrofurfurylthio)carbonyl; (thienylmethylthio)carbonyl; (pyridylmethylthio)carbonyl; or arylsulphonyl radical or

- a carbamoyl radical, optionally mono- or disubstituted by
    - an alkyl or haloalkyl group containing 1 to 6 carbon atoms or
    - a cycloalkyl, alkenyl or alkynyl group containing 3 to 6 carbon atoms or
    - an alkoxyalkyl, alkylthioalkyl or cyanoalkyl group containing 2 to 6 carbon atoms or
    - a phenyl, optionally substituted by 1 to 3 R_7 groups;
- a sulphamoyl group, optionally mono- or disubstituted by
    - an alkyl or haloalkyl group containing 1 to 6 carbon atoms or
    - a cycloalkyl, alkenyl or alkynyl group containing 3 to 6 carbon atoms or
    - an alkoxyalkyl, alkylthioalkyl or cyanoalkyl group containing 2 to 6 carbon atoms or
    - a phenyl, optionally substituted by 1 to 3 R_7 groups;
- an alkylthioalkylsulphonyl group containing 3 to 8 carbon atoms or a cycloalkylsulphonyl group containing 3 to 7 carbon atoms;
- R_6 represents:
- a hydrogen atom or
- a cyano group or
- an alkyl group containing 1 to 6 carbon atoms or a cycloalkyl group containing 3 to 7 carbon atoms or
- an acyl or alkoxycarbonyl group containing 2 to 6 carbon atoms or
- a benzoyl group, optionally substituted by 1 to 3 R_7 groups;
- R_7 represents:
- a halogen atom or
- an alkyl, haloalkyl, alkoxy, haloalkoxy, alkylthio, haloalkylthio or alkylsulphonyl radical containing 1 to 6 carbon atoms or

- a cycloalkyl, halocycloalkyl, alkenyloxy, alkynyloxy, alkenylthio or alkynylthio radical containing 3 to 6 carbon atoms or

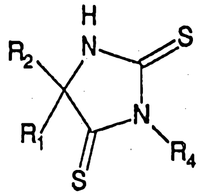
- a nitro or cyano group or

- an amino radical, optionally mono- or disubstituted by an alkyl or acyl radical containing 1 to 6 carbon atoms or an alkoxycarbonyl radical containing 2 to 6 carbon atoms

- a phenyl, phenoxy or pyridyloxy radical, these radicals optionally being substituted;

it being necessary for the acid (III) to be activated for this condensation in the acid chloride form, in the dicyclohexylisourea form using dicyclohexylcarbodiimide, or in the imidazolide form using carbonyldiimidazole.

2. A process for the preparation of dithiohydantoins of formula (VI) (process E):



(VI)

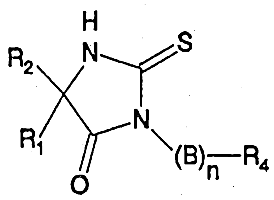
in which R_1, R_2 and R_4 have the same meaning as in Claim 1 with at least one of R_1 or R_2 being electron-withdrawing, characterised in that two isothiocyanates, of formulae R_1R_2CHNCS and R_4NCS in which R_4NCS is unable to form an anion, are reacted in the presence of a base, in a solvent and at a temperature below -60°C.

3. A process according to claim 2, characterised in that the base is chosen from potassium tert-butoxide, sodium or lithium bis(trimethylsilyl)-amide and/or alkali metal hydrides and the solvent is chosen from ethers and cyclic ethers.

4. A process according to claim 2 or claim 3, characterised in that R_1 and/or R_2 is an aryl or substituted aryl.

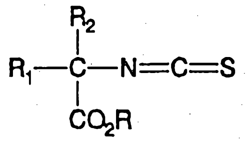
5. A process according to any one of claims 2 to 4 characterised in that the isothiocyanate R_4NCS is an aryl isothiocyanate.

6. A process for the preparation of the 2-thiohydantoins of formula (VII) (process F):



(VII)

characterised in that, before cyclising, a compound of formula (IV) ($R_4(B)nNH_2$) is reacted with isothiocyanates derived from the amino acids of formula (VIII):



$$R_1-\underset{CO_2R}{\overset{R_2}{C}}-N=C=S$$

(VIII)

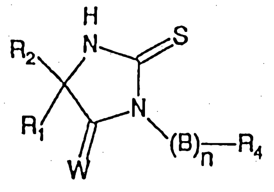
in which R_1, R_2, R_4, B and n have the same meaning as in claim 1 and R is C_{1-4}alkyl~~or a benzyl group.~~

7. A process according to claim 6, characterised in that the cyclisation is carried out thermally by heating the mixture of the reactants at a temperature of between 110 and 180°C in an aromatic solvent preferably toluene, xylene or the chlorobenzenes.

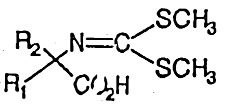
8. A process according to claim 6, characterised in that cyclisation is carried out with one equivalent of base, in a solvent and at a temperature of between -10 and +80°C, the mixture being subsequently neutralised at room temperature.

9. A process according to claim 8, characterised in that the base is chosen from the group comprising an alkali metal alkoxide, an alkali metal hydroxide or a tertiary amine; the solvent is chosen from the group comprising ethers, cyclic ethers, alcohols, esters, DMF and DMSO.

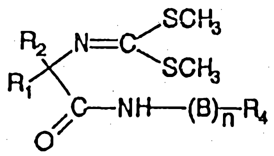
10. Compounds having the formulae II, III, IV, V, VI, VII and VIII



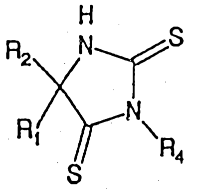
(II)



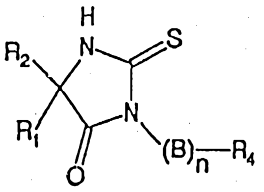
(III)



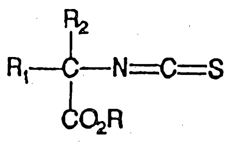
(V)



(VI)



(VII)



(VIII)

in which R_1, R_2, B, n and R_4 have the same meaning as in claim 1, W is a sulphur or oxygen atom or an S=O group and R is C_{1-4} alkyl.

11. A process according to any one of claims 1 to 9 or a compound according to claim 10 substantially as hereinbefore described with reference to any one of the examples.

DATED this 6th day of June, 1996

Rhone-Poulenc Agrochimie

By DAVIES COLLISON CAVE

Patent Attorneys for the Applicants.

ABSTRACT

The invention relates to intermediates useful in processes for preparation of fungicidal 2-amidazolin-5-one and 2-amidazoline-5-thione and processes for the preparation of said intermediates.