

Señor

SUPERINTENDENTE DELEGADO PARA LA
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

SUPERINDUSTRIA Y COMERCIO

Radicacion : 00050413 00010000

Folios: 2

Fecha, (AMB): 2004-00-31 11:56:32

Tramite : 002 PATENTES D 332 PRESENTAC 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Ref: P1.-GRUNENTHAL GmbH.-Expediente No. 00-058.413.-

1. Me refiero al asunto de la referencia.
2. Por medio del presente, atentamente me permito manifestar que hubo un cambio de apoderado para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **GRUNENTHAL GmbH**.
3. En consecuencia, atentamente solicito a ese Despacho reconocirme personería en este asunto, de conformidad con la sustitución de poder adjunta, otorgada a favor de la SUSCRITA.
4. Por lo tanto, ruego a usted notificarme de las providencias expedidas dentro de este expediente y notificadas al anterior apoderado, que actualmente se encuentran pendientes de cumplimiento o de respuesta.
5. Solicito a esé Despacho proceder de conformidad.

Atentamente,


ALICIA LLOREDA RICAURTE

T.P. 53215

Código 231

150 162 157

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES
E. _____ S. _____ D. _____

Ref: P1.-GRUNENTHAL GmbH.-Expediente No.00-058.413.-

Yo, **JOSE ANTONIO LLOREDA**, mayor de edad y vecino de esta ciudad, abogado titulado e Inscrito, Identificado como aparece al pie de mi firma, actuando en mi carácter de Representante Legal en Bogotá para asuntos relacionados con la propiedad Industrial de **GRUNENTHAL GmbH**, sociedad organizada y existente de conformidad con las leyes de Alemania, domiciliada en Aachen, Alemania, tal y como consta en este expediente, atentamente manifiesto a usted que **SUSTITUYO** el poder a mi conferido a la doctora **ALICIA LLOREDA RICAURTE**, abogada titulada e Inscrita, Identificada con la cédula de ciudadanía No. 39.690.713 de Usaquén, para que continúe representando a la mencionada sociedad en el expediente de la referencia.

De conformidad con el artículo 66 del C.P.C., manifiesto bajo la gravedad de juramento que los demás apoderados citados en el documento otorgado a mi favor no desean ejercer el poder a ellos conferido.

El mencionado apoderado tendrá las mismas facultades a mi conferidas, en especial, renunciar, recibir, sustituir, desistir, presentar recursos, conciliar, transigir, y en fin, para todo lo que se encamine a la correcta defensa de los Intereses de la sociedad en cuyo nombre actúo.

NOTARIA SEXTA DE BOGOTÁ
RECONOCIMIENTO Y PRESENTACION PERSONAL
Atentamente, D.O.

25 AGO 2004

Ante mí **PABLO MENDEZ BARAJAS**

NOTARIO SEXTO(E) DEL CIRCULO DE BOGOTÁ

JOSE ANTONIO LLOREDA

Compareció en mi oficina el Sr. **JOSE ANTONIO LLOREDA**, T.D. 118784, C.C. 17.159.681, quien me manifestó que es el Sr. **JOSE ANTONIO LLOREDA**, C.C. 17.159.681, quien (es) exhibió(eron) la(s) C.C.

quien (es) exhibió(eron) la(s) C.C.

y declaró(aron) que la(s) firma(s) que aparece(n)

en el presente documento es(son) la(s) suya (s) y

que el contenido del mismo es cierto.

Constatada se firma con diligencia y se imprime

JOSE ANTONIO LLOREDA
C.C. No. 17.159.681 de Bogotá



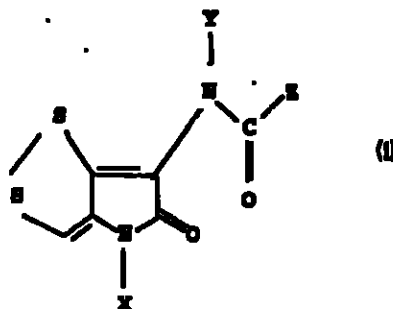
159 110
963

(12) **UK Patent Application** (10) **GB** (11) **2 170 498 A**
(43) Application published 8 Aug 1988

(21) Application No 8600180 (22) Date of filing 8 Jan 1988 (30) Priority data (31) 8582771 (32) 4 Feb 1988 (33) GB 8504870 28 Feb 1988	(51) INT CL⁴ C07D 486/04 (52) Domestic classification (Edition I): C2C 138X 200 214 220 228 22Y 247 258 26Y 281 282 305 30Y 311 313 31Y 338 342 34Y 351 352 384 388 389 38Y 801 803 824 825 828 82X 852 858 86X 882 885 888 805 AB KM KR KS U18 1306 C2C (56) Documents cited None (58) Field of search C2C
(71) Applicant Imperial Chemical Industries Plc (United Kingdom), Imperial Chemical House, Millbank, London SW1P 3JF (72) Inventors Christopher Richard Ayles Godfrey, Ian Thomas Dell (74) Agent and/or Address for Service Michael James Ficks, Imperial Chemical Industries Plc, Legal Dept: Patents, PO Box 8, Beecham Road, Welwyn Garden City, Herts	

(54) Processes for making fungicidal dithiopyrrolones

(57) Processes for making compounds of formula:



wherein X, Y and Z which may be the same or different are an optionally substituted alkyl, cycloalkyl, aryl, aralkyl (especially benzyl), alkenyl or heterocyclic group; or a hydrogen atom; provided that when Y is a hydrogen atom X is not methyl or hydrogen atom and when Y is methyl X is not a hydrogen atom, are described.

160 161
164

1

1

SPECIFICATION

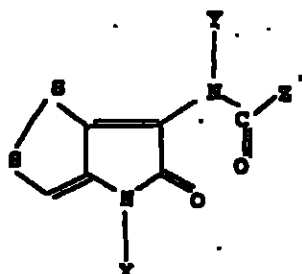
Processes for making heterocyclic compounds

5 This invention relates to processes for making heterocyclic compounds having biological activity and especially useful as fungicides.

5

The invention provides processes for making compounds having the general formula (I):

10



10

(I)

15

15

wherein X, Y and Z, which may be the same or different, are optionally substituted alkyl, cycloalkyl, aryl, aralkyl (especially benzyl), alkenyl or heterocyclic group; or a hydrogen atom; provided that when Y is a hydrogen atom X is not methyl or a hydrogen atom and when Y is methyl X is not a hydrogen atom, the processes comprising any of the reaction sequences 1 to 4 hereinafter set forth; or any part of, or combination of, these reaction sequences; or any individual step thereof.

20

Alkyl groups can be in the form of straight or branched chains, and preferably contain 1 to 6 carbon atoms.

25 Several compounds having the general formula (I), wherein Y is a hydrogen atom and X is either a hydrogen atom or a methyl group, which are naturally occurring compounds, some with fungicidal activity, have been described in the literature. Examples of these compounds are thiolutin (I, X=Z=CH₃, Y=H) (see The Merck Index, ninth edition, 1976, p 1206; and references therein), holomydin (I, X=Y=H, Z=CH₃) (see The Merck Index, ninth edition, 1976, p. 620; and references therein) and the Xenorhabdin antibiotics (see CSIRO (1984) Australian Patent Applic. No. 127365). Compounds (I) derived from naturally occurring thiolutin, wherein X is a methyl group and Y is a hydrogen atom are the subject of Brit. Pat. (1966) Pub. No. 753,331. Also compound (I), wherein Y is a methyl group and both X and Z are hydrogen atoms is a naturally occurring compound with antibiotic activity (see B. Jensen, *J. Antibiotics*, 1969, 22, 231).

25

30

Preferred alkyl groups for X, Y and Z from 1 to 6, especially 1 to 4, carbon atoms. Preferred cycloalkyl groups are cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl. The alkyl moiety in aralkyl groups preferably contains from 1 to 4 carbon atoms.

35

Preferred alkenyl groups contain from 3 to 6 carbon atoms and include allyl.

The compounds may contain chiral centres. Such compounds are generally obtained in the form of racemic mixtures. However, these and other mixtures can be separated into the individual isomers by methods known in the art.

40

Examples of suitable substituent groups for X, Y and Z when they represent aralkyl, aralkenyl or aryl, especially benzyl or phenyl, are halogen, haloalkyl, alkyl, alkoxy (especially containing 1 to 4 carbon atoms), optionally substituted phenyl and optionally substituted phenoxy.

Suitably the aryl, especially phenyl group, is unsubstituted or substituted with 1, 2 or 3 ring substituents, which may be the same or different, as defined above. Examples of X, Y and Z are phenyl, 2-, 3- or 4-chlorophenyl, 2,4- or 2,6-dichlorophenyl, 2,4- or 2,6-difluorophenyl, 2-, 3- or 4-fluorophenyl, 2-, 3- or 4-bromophenyl, 2-, 3- or 4-methoxyphenyl, 2,4-dimethoxyphenyl, 2-, 3- or 4-ethoxyphenyl, 2-fluoro-4-chlorophenyl, 2-chloro-4-fluorophenyl, 2-, 3- or 4-methylphenyl, 2-, 3- or 4-ethylphenyl, 2-, 3- or 4-trifluoro-methylphenyl, 4-phenylphenyl (4-biphenyl), 2-chloro-4-methoxyphenyl, 2-fluoro-4-methoxyphenyl, 2-chloro-4-methylphenyl, 2-fluoro-4-methylphenyl, 4-isopropylphenyl, 2-methyl-4-chlorophenyl or 2-methyl-4-fluorophenyl.

45

50

When X, Y and Z is alkyl it can be a straight or branched chain alkyl group having 1 to 6, eg. 1 to 4 carbon atoms; examples are methyl, ethyl, propyl (*n*- or *iso*-propyl) and butyl (*n*-, *sec*-, *iso*- or *t*-butyl); when X, Y and Z is alkenyl it can be allyl.

55 The salts can be salts with inorganic or organic acids eg. hydrochloric, nitric, sulphuric, acetic, 4-toluenesulphonic or oxalic acid.

55

Several total syntheses of compounds of type (I), wherein Y is a hydrogen atom and X is either a hydrogen atom or a methyl group have been described in the literature (Schmidt and Gelger, *Annaler*, 1963, 664, 166; G.Büchl and B.Lukas, *J.Amer.Chem.Soc.*, 1964, 86, 5654; K.Haglo and N.Yoneda, *Chem.Pharm.Bull.*, 1974, 47, 1484). The partial syntheses of compounds of type (I), wherein Y is a hydrogen atom and X is a methyl group, from naturally occurring thiolutin (I, X=Z=CH₃; Y=H) has also been described (Brit.Pat.No. 753,331).

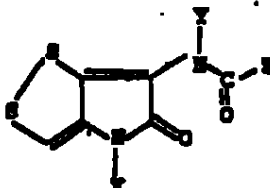
60

The processes described in this invention have several advantages over these existing methods. The starting materials used are relatively cheap and readily available. Furthermore, the synthetic sequences described herein are shorter and give better overall yields of final products even when carried out on a large scale. In addition, the processes are sufficiently versatile to permit the variation of the substituent groups X, Y and Z

65

as defined above. Examples of the compounds which can be prepared by the processes of the present invention are shown in Table I. These conform to formula I and in each instance the groups X, Y and Z are as shown in the table "Ph" stands for C_6H_5 i.e. for phenyl.

TABLE I



Compound numbers	X	Y	Z	Melting point (°C)
1	CH ₃	CH ₃	CF ₃	214 (dec)
2	CH ₃	CH ₃	CO ₂ C ₂ H ₅	85
3	CH ₃	CH ₃	CH ₃	216
4	CH ₃	CH ₃	CH ⁺ Ph	203-205
5	PhCH ₂ -	CH ₃	CH ₂ CH CH ⁺ Ph	86-88
6	PhCH ₂ -	CH ₃	CH ₂ CH	86-88
7	PhCH ₂ -	H	H	gum
8	PhCH ₂ -	H	CH ₃	186
9	PhCH ₂ -	H	CF ₃	214
10	PhCH ₂ -	H	H	207 (dec)
11	PhCH ₂ -	H	CO ₂ C ₂ H ₅	115
12	PhCH ₂ -	H	CO ₂ CH ₃	172
13	PhCH ₂ -	H	CH ⁺ Ph	225
14	PhCH ₂ -	H	CH ₂ CH	96-98
15	PhCH ₂ -	H	CH ₂ OCH ₃	142-144
16	Ph	H	(CH ₃) ₂ CH	Oil
17	C ₂ H ₅	H	C(CH ₃) ₃	267
18	C ₂ H ₅	H	CH ₃	223-226 (dec)
19	C ₂ H ₅	H	CF ₃	204-206
20	CH ₂ CH ₂	H	H	218-223
21	CH ₂ CH ₂ CH	H	CH ₃ CH ₃ C Cl CH ₃	228-231 154-156
22	p-CH ₃ O-C ₆ H ₄ -	H	CH ₃	
23	i-C ₃ H ₇	H	CH ₃	
24	i-C ₃ H ₇	CH ₃	H	
25	n-C ₆ H ₁₃	H	CF ₃	
26	n-C ₆ H ₁₃	H	COOC ₂ H ₅	
27	i-C ₃ H ₇	H	COOCH ₃	
28	CH ₃	Ph	COOC ₂ H ₅	
29	CH ₃	Ph	CF ₃	

The compounds of the invention having the general formula (I) can be prepared by the steps shown in Schemes 1-4. Throughout Schemes 1-4 the terms X, Y and Z are as defined above; R¹, R² and R³, which may be the same or different, are alkyl or aralkyl groups; R¹ and R² may be joined to form part of a ring; and A and B are halogen atoms or good leaving groups, which may be the same or different.

Thus, compounds of general formula (I) can be prepared by treatment of compounds of general formula (II) with an oxidizing agent such as iodine, (see, for example, Schmidt and Gelger, *Annalen*, 1963, 684, 166) or air, (see, for example, K. Hagio and N. Yoneda, *Chem. Pharm. Bull.*, 1974, 47, 1484) in a convenient solvent such as dichloromethane (see Scheme 1).

Compounds of general formula (II), which may exist as mixtures of geometric isomers, can be prepared from compounds of general formula (II) by treatment with an alkali metal, such as lithium (when R¹=R²=benzyl) in a convenient solvent, such as liquid ammonia, (see, for example, G. Büchi and G. Lüscher, *J. Amer. Chem. Soc.*, 1964, 86, 5654) or by treatment with transition metal salts, such as mercury (II) acetate or copper (II) acetate (when R¹=R²=Butyl; or R¹=R²=allyldene, for example methylene or isopropylidene) in a suitable solvent, such as trifluoroacetic acid, followed by treatment with hydrogen sulphide in a suitable

152 1.3

466

solvent, such as dimethylformamide, (see, for example, O.Nishimura, C.Kitada and M.Fujino, *Chem.Pharm. Bull.*, 1978, 26, 1576).

Compounds of general formula (III), which exist as mixtures of geometric isomers which can be separated, can be prepared from compounds of general formula (IV) by treatment with an acylating agent, such as acetylchloride, in the presence or absence of an acid-binding agent (such as triethylamine) in a suitable solvent, such as dichloromethane or chloroform or tetrahydrofuran, and at a convenient temperature (such as 0 to 80°C).

Compounds of general formula (IV), which exist as mixtures of geometric isomers which can be separated, can be prepared from compounds of general formula (V) by treatment with a salt of an amine YNH_2 , such as ammonium acetate or anilinium acetate, with or without a convenient solvent (such as acetic acid), and at a convenient temperature (such as 80 to 160°C).

Compounds of general formula (V), which exist as mixtures of geometric isomers which can be separated, can be prepared from compounds of type (VI)-A (which may exist as mixtures of geometric isomers and which are in equilibrium with compounds of type (VI)-B) by treatment with oxalyl chloride or bromide in the presence of an acid-binding agent (such as triethylamine) in a suitable solvent (such as dichloromethane or chloroform) and at a convenient temperature (such as -78°C to 25°C) (Scheme 2).

Alternatively, compounds of the general formula (V) can be prepared from esters of general formula (VII) by treatment with a suitable base (such as sodium hydride, lithium di-isopropylamide or lithium hexamethyldisilazide) in a suitable solvent (such as tetrahydrofuran or diethyl ether) and at a convenient temperature (-78°C to 25°C).

In addition, compounds of the general formula (V) can be prepared from compounds of general formula (IV) by hydrolysis in a suitable solvent (such as water or ethanol) in the presence of a suitable catalyst (such as hydrochloric acid) (see, for example, K.Heglo and N.Yoneda, *Chem.Pharm.Bull.*, 1974, 47, 1484) (Scheme 1).

Esters of general formula (VII), which exist as mixtures of geometric isomers which can be separated, can be prepared from compounds of general formula (VI)-A (which may exist as mixtures of geometric isomers and which are in equilibrium with compounds of type (VI)-B) by treatment with a suitable acylating agent, such as ethyl oxalyl chloride or methyl oxalyl chloride in the presence or absence of an acid-binding agent (such as triethylamine) in a suitable solvent such as dichloromethane or chloroform) and at a convenient temperature (such as 0°C).

Compounds of general formula (VI)-A (which may exist as mixtures of geometric isomers and which are in equilibrium with compounds of type (VI)-B) can be prepared from ketones of general formula VII by treatment with an amine $X-NH_2$ in the presence of a dehydrating agent (such as titanium tetrachloride) in a suitable solvent (such as diethyl ether) and at a convenient temperature (-78°C to 25°C).

Ketones of general formula (VII) can be prepared from ketones of general formula VIII by treatment with a thiol of general formula R^1SH or R^2SH in the presence of a base (such as sodium hydride, sodium methoxide) in a suitable solvent (such as diglyme, ethanol or tetrahydrofuran) and at a convenient temperature (such as -25°C to 50°C).

Alternatively ketones of general formula (VII) can be prepared from β -keto-esters of general formula (IX) by treatment with a salt (such as lithium chloride) in a suitable solvent (such as dimethylsulphoxide) and at a convenient temperature (such as 110°C to 180°C) (see, for example, A.P.Krapcho, J.F.Weimaster, J.M.Eldridge, E.G.E.Jehngen, Jr., A.J.Lovey, W.P. Stephens, *J.Org. Chem.*, 1978, 43, 138) or by decarboxylation of β -keto-acids of general formula (IX), using standard methods as set out in the chemical literature (see, for example, H.O.House, *Modern Synthetic Methods*, 2nd edition, p.511).

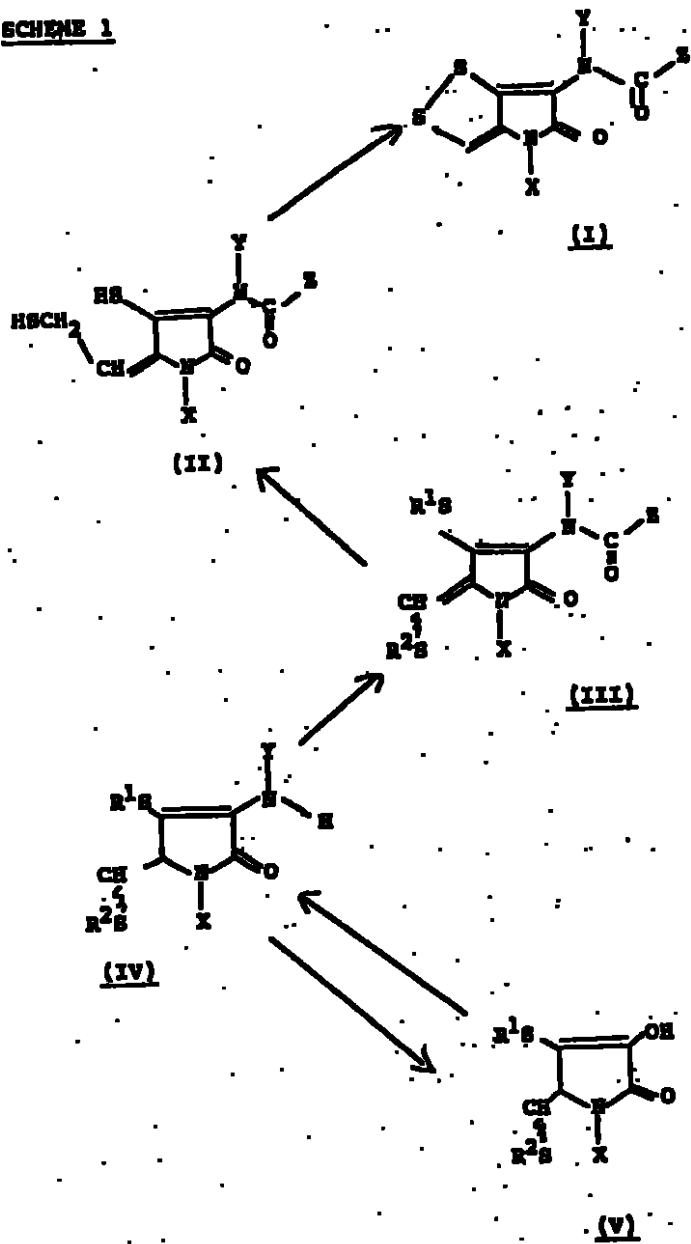
β -Keto-acids of general formula (IX) can be prepared from β -keto-esters of general formula (X) using standard methods as set out in the chemical literature (see, for example, H.O.House, *Modern Synthetic Methods*, 2nd edition, p.511).

β -Keto-esters of general formula (X) can be prepared from esters of general formula (XI) or (XII) by treatment with a base (such as sodium hydride) in a suitable solvent (such as tetrahydrofuran) and at a suitable temperature (such as 0°C to 100°C) (Scheme 3).

Compounds of general formula IV, where $X=Y$, which exist as mixtures of geometric isomers which can be separated, can be prepared from compounds of general formula (V), where X is an aryl substituent (such as a phenyl group) on treatment with a salt of an amine $Y-NH_2$, such as ammonium acetate, with or without a convenient solvent (such as acetic acid), and at a convenient temperature (such as 80°C to 160°C) (Scheme 4).

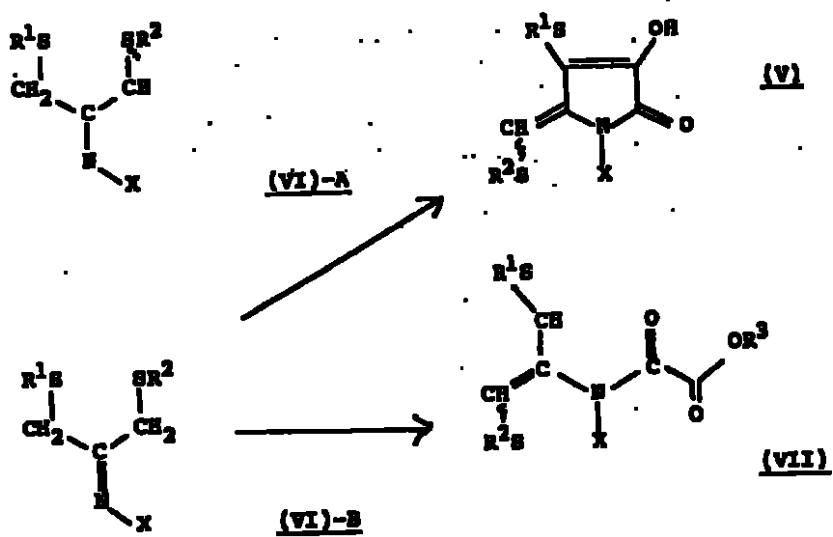
167 64
167

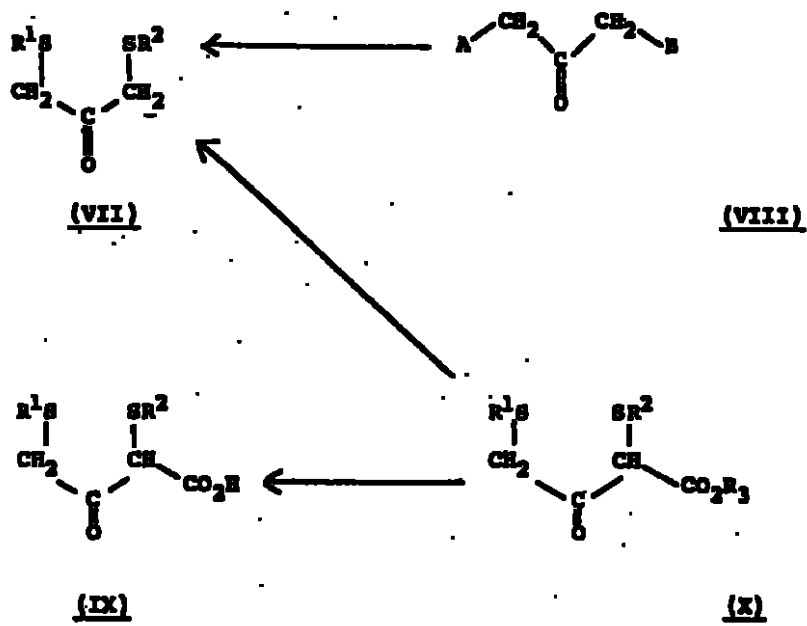
SCHEME 1



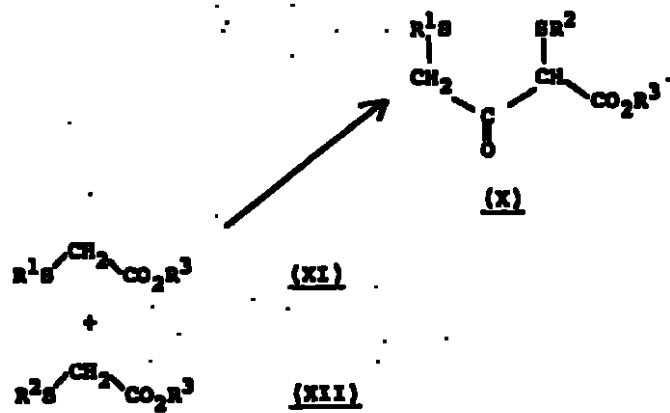
~ a III de la sollicitud

SCHEME 2

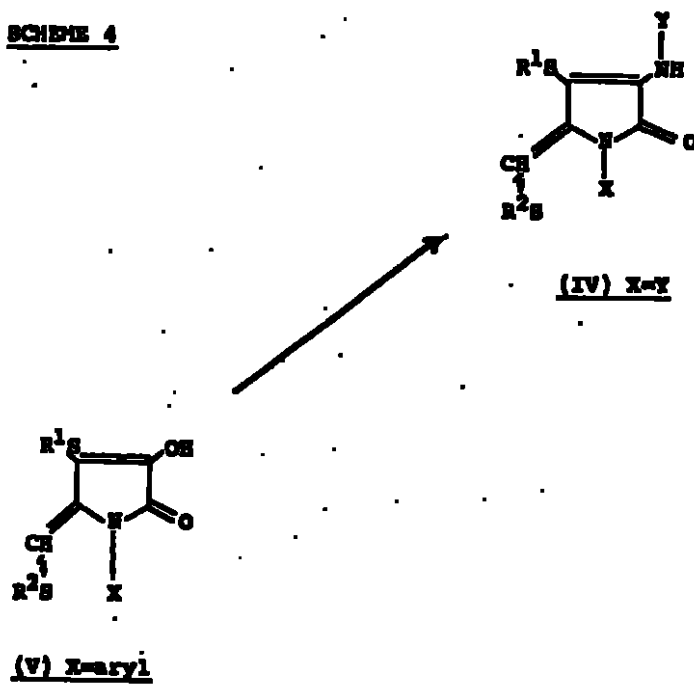




SCHEME 3



SCHEME 4



The following Examples illustrate the invention; the temperatures are given in degrees Centigrade (°C).

Example 1

This example illustrates the preparation of 5-(methoxyacetylamino)-4-benzyl-1,2-dithiolo[4,3-b]pyrrol-5(4H)-one (Compound No. 13 of Table I).

To a solution of sodium methoxide in dry methanol (formed by the addition of sodium (10.58g) to dry methanol (200ml)) was slowly added a solution of *t*-butylmercaptan (41.5g) in dry methanol (50ml). The resultant solution was cooled to 0°C and a solution of 1,3-dichloroacetone (29.21g) in dry methanol (50ml) was added over a period of 1 hour. The resultant mixture was stirred for a further 16 hours at room temperature and then partitioned between dichloromethane and dilute sodium hydroxide solution. The organic phase was dried over magnesium sulphate, filtered and evaporated to give a liquid. Distillation at 96°C/1mm afforded 1,3-di(*t*-butylthio)acetone (VII, $R^1=R^2=t\text{-Bu}$ - see Scheme 2) (28.42g, 49%). In an alternative procedure, *t*-butylmercaptan (500g) was added drop-wise over 6½ hours to a slurry of sodium hydride (80% dispersion in oil, 163g) in dry diglyme (2.22 litres) under an atmosphere of nitrogen. The reaction was exothermic and the rate of addition was set to hold the temperature below 40°C. A white suspension formed which thickened as the reaction progressed. After stirring overnight, the suspension was diluted with a further 400ml of diglyme and cooled to 0-5°C. A solution of 1,3-dichloroacetone in diglyme (710ml) was then added drop-wise over a period of 6 hours. The reaction mixture was allowed to warm up to room temperature over 1 hour and then methanol (50ml) was added to destroy excess sodium hydride. The resultant mixture was partitioned between water (4 litres) and toluene (3 litres). The aqueous layer was back-extracted with toluene (2 litres) and the combined organic layers were washed with water (2x3 litres), dried and concentrated *in vacuo* to afford 1,3-di(*t*-butylthio)acetone (VII, $R^1=R^2=t\text{-Bu}$ - see Scheme 2) (570g, 88%) which could if desired be used in the next stage of the synthesis without further purification.

To a solution of 1,3-di(*t*-butylthio)acetone (25g) in sodium-dried diethyl ether (150ml) at room temperature was added a solution of benzylimine (29.8g) in sodium-dried diethyl ether (50ml). After 1 hour, titanium tetrachloride (10.1g) was added slowly and stirring was continued at room temperature for a further 3 hours. The resultant mixture was filtered through celite and the solvent removed *in vacuo* to afford the benzylimine of 1,3-di(*t*-butylthio)acetone (VI-B, $X=Bz$, $R^1=R^2=t\text{-Bu}$ - see Scheme 2) as a brown oil (23.07g) which was used immediately in the next stage of the synthesis without further purification.

To a solution of oxalyl chloride (8.91g) in dry dichloromethane (300ml) at 50°C was added a solution containing the benzylimine of 1,3-di(*t*-butylthio)acetone (22.7g) and triethylamine (7.1g) in dry dichloromethane (800ml). The mixture was stirred for 2 hours, allowed to warm up to room temperature and then washed with water, sodium bicarbonate solution and saturated brine. The organic phase was dried over sodium sulphate, filtered and evaporated to give a brown oil. Titration with petrol followed by chromatography of the residue on silica (eluent: dichloromethane-diethyl ether mixtures) afforded compound (V, $X=Bz$, $R^1=R^2=t\text{-Bu}$ - see Scheme 1) as a brown solid (14.8g, 56%, m.p. 158°C).

Compound (V, $X=Bz$, $R^1=R^2=t\text{-Bu}$ - see Scheme 1) (1.4g) and ammonium acetate (2.86g) were ground together into a fine powder and then fused at ca 140°C for 2 hours. The mixture was allowed to cool and then taken up into dichloromethane. The organic phase was basified with sodium bicarbonate solution, washed with water and brine, and the dried over anhydrous magnesium sulphate. The resultant solution was filtered through a silica plug (eluent: diethyl ether) to afford, after evaporation, compound (IV, $X=Bz$, $Y=H$, $R^1=R^2=t\text{-Bu}$ - see Scheme 1) as a brown solid (1.27g 91%, m.p. 119-120°C).

To a solution of (IV, $X=Bz$, $Y=H$, $R^1=R^2=t\text{-Bu}$ - see Scheme 1) (1.0g) in sodium-dried tetrahydrofuran (50ml) was added methoxyacetyl chloride (0.57g). The resultant solution was stirred at room temperature for 16 hours. The tetrahydrofuran was evaporated off and replaced by dichloromethane. The resultant solution was washed with sodium bicarbonate solution and dried over anhydrous magnesium sulphate. Filtration through a silica plug (eluent: diethyl ether) gave compound (III, $X=Bz$, $Y=H$, $Z=CH_2OCH_3$, $R^1=R^2=t\text{-Bu}$ - see Scheme 1) as an oil (0.87g, 73%), ($CDCl_3$) 1.37 (18H); 3.48 (3H,S); 4.04 (2H,S); 5.22 (2H,S); 6.80 (1H,S); 7.25 (5H, n); 8.18 (1H, br.s).

To a solution of compound (II, $X=Bz$, $Y=H$, $Z=CH_2OCH_3$, $R^1=R^2=t\text{-Bu}$) (0.85g) in trifluoroacetic acid (20ml) was added mercury (II) acetate (0.80g). The resultant solution was stirred at room temperature for one hour and the trifluoroacetic acid then removed by evaporation *in vacuo*. The solid residue was redissolved in *N,N*-dimethylformamide (20ml) and treated with hydrogen sulphide at room temperature for two hours. Nitrogen was then bubbled through the reaction mixture to remove traces of hydrogen sulphide and the black suspension was filtered through celite. A solution of iodine (0.48g) in chloroform (20ml) was added at room temperature and the solution stirred at room temperature for thirty minutes. The solvents were removed by evaporation *in vacuo*, and the residue was separated on silica (eluent: diethyl ether) to afford 5-(methoxyacetylamino)-4-benzyl-1,2-dithiolo[4,3-b]pyrrol-5(4H)-one (Compound No. 13 of Table I) as a yellow solid. (408mg, 84%, m.p. 98-99°C, ($CDCl_3$) 3.48 (3H,S); 4.02 (2H,S); 4.99 (2H,S); 6.48 (1H,S); 7.26 (5H, M); 8.50 (1H, br.s); m/e 334 M^+), 288, 276, 261, 241, 91, 45.

166
170

CLAIMS

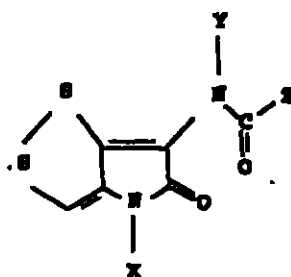
1. Processes for making compounds having the general formula (I):

5

5

1

10



(I)

10

15

15

wherein X, Y and Z, which may be the same or different, are optionally substituted alkyl, cycloalkyl, aryl, aralkyl (especially benzyl), alkenyl or heterocyclic group; or a hydrogen atom; provided that when Y is a hydrogen atom X is not methyl or a hydrogen atom and when Y is methyl X is not a hydrogen atom, the processes comprising any of the reaction sequences 1 to 4 hereinafter set forth; or any part of, or combination of, these reaction sequences; or any individual step thereof.

20

20

167 152

478

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

2020
Bogotá, D.C., Diciembre 9 de 2005

Doctora
ALICIA LLORED A RICAURTE

ASUNTO	Radicación No.	00 058 413
	Trámite	002
	Evento	001
	Actuación	430
	Oficio No.	15475
	Folios	0

Como resultado del examen de patentabilidad de la solicitud de patente de invención, realizado según lo establece el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se notifica el siguiente concepto técnico:

1. Documentos estudiados

Para el presente estudio se tuvieron en cuenta el capítulo descriptivo comprendido en los folios 6 - 41 y el nuevo capítulo reivindicatorio de los folios 42 - 63 de la solicitud en estudio.

2. Objeto de la invención

El objeto de la presente solicitud de patente de invención consiste en:

Las reivindicaciones 1 - 21 se refieren a derivados de 1,5-dihidropirrol-2-ona sustituidos de fórmula I.

Las reivindicaciones 22 - 29 se refieren a un procedimiento de preparación de derivados de 1,5-dihidropirrol-2-ona sustituidos de fórmula I.

Las reivindicaciones 30 - 32 se refieren a un medicamento que contiene derivados de 1,5-dihidropirrol-2-ona sustituidos de fórmula I.

Las reivindicaciones 33 - 75 se refieren al uso de derivados de 1,5-dihidropirrol-2-ona sustituidos de fórmula I.

El problema planteado en esta solicitud es la necesidad de proporcionar una composición para tratamiento del dolor, reacciones inflamatorias y alérgicas, depresiones, abuso de drogas y alcohol, gastritis, diarrea, incontinencia urinaria, afecciones cardiovasculares, de las vías respiratorias, psíquicas y epilepsia.

Para resolver este problema técnico la solicitud en estudio proporciona derivados de 1,5-dihidropirrol-2-ona sustituidos de fórmula I.

172 168

El objeto de la invención definido anteriormente se clasificó de acuerdo con la IPC: A 61 K 31/40 // 31/16 // 31/12 // 31/075 // 31/10 // 31/13.

También se reivindica prioridad de la Solicitud de Patente de Alemania DE 199 36719.1 de agosto 6 de 1999, con respecto a la cual la fecha de presentación de la actual solicitud cumple el plazo máximo permitido.

3. Usos

El artículo 21 de la Decisión 486 de la Comisión de la Comunidad Andina establece que: *"Los productos o procedimientos ya patentados, comprendidos en el estado de la técnica, de conformidad con el artículo 16 de la presente Decisión, no serán objeto de nueva patente, por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial"*.

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*.

El Artículo 19 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *"Se considerará que una invención es susceptible de aplicación industrial, cuando su objeto pueda ser producido o utilizado en cualquier tipo de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios"*.

Las reivindicaciones 33 - 75 se refieren al uso de derivados de 1,5-dihidropirrol-2-ona sustituidos de fórmula I.

Se aclara que, de acuerdo con el Art 14, no se puede otorgar patente a usos porque estos no son un producto ni un procedimiento tecnológico.

De otro lado, de acuerdo con el Art 19, se considera que los usos no tienen aplicación industrial porque no se refiere a un tipo de producción ó utilización en ningún tipo de industria.

Además los usos de los derivados de 1,5-dihidropirrol-2-ona sustituidos de fórmula I reivindicados no pueden ser objeto de nueva patente, aunque el solicitante los considere distintos a los originalmente comprendidos por la patente inicial, porque estos se conocían originalmente en la Pat GB 2 170 498 como intermediarios en la preparación de compuestos fungicidas.

4. Determinación del Estado de la Técnica

El artículo 16 de la decisión 486 de la comisión de la Comunidad Andina que establece que *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida."*

Solo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

Considerando que la fecha de presentación de la primera solicitud de patente de la cual se reivindica prioridad es agosto 6 de 1999, se consultaron las bases de datos y los archivos con que cuenta la entidad con fecha de publicación

anterior y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

No.	Documento	Título	Fecha de Publicación
D1	GB 2 170 498	Proceso para hacer ditiopirrolonas fungicidas	Agosto 6, 1986

5. Evaluación de los requisitos de Patentabilidad

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*.

En cumplimiento del artículo 14 de la Decisión 486, se procedió a evaluar el cumplimiento de los requisitos de novedad, nivel inventivo y aplicación industrial, con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación del Nivel Inventivo

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece que *Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*

Las reivindicaciones 1 – 21 se refieren a derivados de 1,5-dihidropirrol-2-ona sustituidos de fórmula I.

Las reivindicaciones 22 - 29 se refieren a un procedimiento de preparación de derivados de 1,5-dihidropirrol-2-ona sustituidos de fórmula I.

Las reivindicaciones 30 - 32 se refieren a un medicamento que contiene derivados de 1,5-dihidropirrol-2-ona sustituidos de fórmula I.

D1 enseña derivados de 1,5-dihidropirrol-2-ona sustituidos de fórmula I.

Se observa que los derivados 1,5-dihidropirrol-2-ona, objeto de esta solicitud, se obtienen de manera evidente a partir de lo enseñado en D1, donde se encuentran compuestos 1,5-dihidropirrol-2-ona como los de esta solicitud (ver folio 167, estructuras IV y V):

Cuando en esta solicitud los radicales R₂, R₃ son alquil C1-10, aril heteroaril, alquilen C1-6 aril ó juntos son =O, no hay nivel inventivo porque en la anterioridad corresponde a Y que es H, alquil, cicloalquil, aril, arilalquil, alquenil ó heterociclo.

Cuando en esta solicitud el radical R₄ es alquil C1-10, aril heteroaril, alquilen C1-6 aril ó juntos son =O, no hay nivel inventivo porque en la anterioridad corresponde a R₁ que es alquil ó arilalquil.

Cuando en esta solicitud los radicales R₂, R₃ son SR₁₁, donde R₁₁ es alquil C1-10, aril, heteroaril ó alquenil C1-6 aril ó alquenil C1-6 heteroaril, no hay nivel inventivo porque en la anterioridad corresponde a SR₂ donde R₂ es alquil ó arilalquil.

Cuando en esta solicitud el radical R₁ es alquil C1-10, aril, alquilen C1-6 heteroaril ó alquilen C1-6 heteroaril, no hay nivel inventivo porque en la anterioridad corresponde a X que es H, alquil, cicloalquil, aril, arilalquil, alquenil, ó heterociclo.

174
130

Se observa que: (a) debido a que los compuestos de esta solicitud eran conocidos en las anterioridades; para una persona conocedora de la materia era evidente el elaborar los medicamentos de manera similar, teniendo en cuenta estos compuestos; (b) las reivindicaciones de esta solicitud no mencionan una característica que conceda un efecto diferente o especial a los compuestos, que pueda considerarse como un aporte a la técnica, así que son obvios para una persona versada en la materia y (c) el problema planteado en esta solicitud que era la necesidad de proporcionar una composición para tratamiento del dolor, reacciones inflamatorias y alérgicas, depresiones, abuso de drogas y alcohol, gastritis, diarrea, incontinencia urinaria, afecciones cardiovasculares, de las vías respiratorias, psíquicas y epilepsia se resuelve proporcionando derivados 1,5-dihidropirrol-2-ona sustituidos de fórmula I que eran conocidos en la anterioridad; las reivindicaciones son obvias y evidentes para una persona versada en la materia. De manera que no tienen nivel inventivo.

6. Conclusión

En conclusión, los requisitos de patentabilidad de la presente solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	GB 2 170 498	1 - 32	Nivel Inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No. 10 de 2001.

Clara C. de Jaimes
CLARA C. DE JAIMES (E)
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista, de fecha
22 DIC 2005

CONCEPTO TÉCNICO No. 1986	EXAMINADOR TÉCNICO Código 202007
------------------------------	-------------------------------------