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OLARTERAISBECK
OLARTE RAISBECK FRIERI MOURE & CASTRO LTDA.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 03-008178- -00006-0000
Fecha: 2008-01-16 16:57:05 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 8

Señores
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES
E. S. D.

Ref: Expediente No. 03.008.178
Solicitud de patente de invención titulada:
"SALES DE TARTRATO DERIVADOS DE TIAZOLIDINDIONA".
Solicitante: SMITHKLINE BEECHAM P.L.C.

RESPUESTA AL OFICIO No. 13292, NOTIFICADO POR FIJACIÓN EN LISTA No. 387, DE FECHA 19 DE OCTUBRE DE 2007.
(EXAMEN DE FONDO)

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 45 de la Decisión 486:

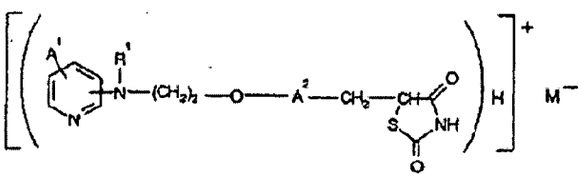
1. En primer lugar y con el ánimo de brindar mayor claridad a la presente solicitud, me permito adjuntar un Capítulo Reivindicatorio Modificado que reemplaza en su totalidad al Capitulo Reivindicatorio presentado al momento de radicar la presente solicitud. En el Capítulo Reivindicatorio Modificado se eliminaron las antiguas Reivindicaciones 10 y 11.

Valga anotar que las modificaciones efectuadas al Capítulo Reivindicatorio cumplen a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que éstas de ninguna manera implican una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial.

2. a- El Examinador establece que las Reivindicaciones 10 y 11 se refieren a usos, por lo que no serían patentables.

b- Considero superada la anterior objeción, en tanto que las Reivindicaciones 10 y 11 fueron eliminadas del Capítulo Reivindicatorio Modificado.

3. a- El Examinador argumenta que la patente WO94/05659 (D1) afecta la novedad de la presente solicitud, puesto que D1 previamente divulgó compuestos derivados de tiazolidindionas de Fórmula (I)



(I)

que comprende el compuesto 5-[4-[2-(N-metil-N-(2piridil)amino)etoxi]benciljtiazolidino-2,4-diona, donde el ión (-) corresponde a un ácido farmacéuticamente aceptable con un pKa en el rango entre 0.1 y 4.5. Los ácidos farmacéuticamente aceptables incluyen los ácidos minerales, como los ácidos bromhídrico, clorhídrico y sulfúrico, y los ácidos orgánicos, como el metanosulfónico, tartárico y maleato, especialmente tartárico y maleico. Asimismo, el Examinador argumenta que la presente solicitud no anexa datos comparativos de las ventajas y efectos inesperados en las propiedades de flujo y rendimiento, que demuestren el salto tecnológico alcanzado frente a los compuestos reportados en el estado de la técnica.

Por lo tanto, el Examinador concluye que la presente invención carece de novedad.

b- i) En primer lugar, deseo subrayar que el solicitante de la presente solicitud de patente reconoce la existencia de D1 y su cercanía con la invención desarrollada. De hecho, la Descripción de la invención cita a D1 como arte previo relevante (ver página 1, líneas 13 a 17).

ii) Ahora bien, D1 reveló sales de adición ácida de derivados de tiazolidinonas sustituidas de Fórmula I, donde los ácidos formadores de sales (página 4, líneas 14-16) incluyen ácidos minerales como los ácidos bromhídrico, clorhídrico y sulfúrico, y ácidos orgánicos como los ácidos metanosulfónico, tartárico y maléico. Sin embargo, D1 no revela de manera **específica** sales tartrato de ninguno de los compuestos de Fórmula I. De hecho, la única referencia específica incluida en D1 a sales de los compuestos de Fórmula I, es a sales del ácido maléico en los Ejemplos 1 y 2. Adicionalmente, nada en D1 enseña o siquiera sugiere que la sal tartrato podría cristalizar en las formas polimórficas específicas de las Reivindicaciones 2 y 3.

Es importante recordar que el Manual Andino de Patentes establece que objeciones de novedad válidas deben basarse en referencias del arte previo que revelen explícitamente la invención,

incluyendo todas sus características, aún las más banales.[1] Así las cosas, es claro D1 no afecta la novedad de la presente invención, ya que allí no se revela de manera explicita la sal tartrato del compuesto D(-)-5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]benciljtiazolidino-2,4-diona, sus solvatos, ni los polimorfos de dicho compuesto desarrollados en la presente invención.

iii) D1 se refiere como compuesto preferido de Fórmula I a la sal del ácido maléico del compuesto D(-)-5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]benciljtiazolidino-2,4-diona (en la página 3,líneas 7-8). Así entonces, no hay razón alguna para que una persona medianamente versada en la materia desatienda dicha enseñanza directa y seleccione una sal diferente de dicho compuesto, en lugar de la sal maléica enseñada y sugerida por D1.

En gracia de discusión, aún si por alguna razón no evidente a partir de D1 una persona medianamente versada en la materia decidiera utilizar la sal tartrato, no hay enseñanza alguna en el arte previo que indique qué sal tartrato elegir, y aún menos que deba elegirse la sal tartrato específicamente.

Como lo reconoce toda persona medianamente versada en la materia, el ácido tartárico exhibe el fenómeno de estereoisomerismo y por lo tanto, existe en diferentes formas isoméricas, que de manera correspondiente dan origen a diferentes sales tartrato del compuesto de interés. Específicamente, el ácido tartárico puede existir como: ácido D-tartárico, que es ópticamente activo y levorotatorio; ácido L-tartárico, que es también ópticamente activo pero dextrogiratorio; mezcla racémica de ácido DL-tartárico, que no es ópticamente activo; y ácido meso-tartárico, que tampoco es ópticamente activo debido a que los centros quirales se compensan internamente. Por lo tanto, es claro que las sales del ácido tartárico del compuesto D(-)-5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]benciljtiazolidino-2,4-diona formadas con las diversas especies de ácido tartárico tendrán diferentes propiedades.

iv) En este punto deseo resaltar que la sal específica reivindicada en la presente invención despliega una combinación de propiedades que la hacen particularmente ventajosa para su procesamiento y producción a gran escala en la industria farmacéutica, en especial, para operaciones de molienda a gran escala.

- En primer lugar, la sal tartrato de la presente invención ventajosamente tiene un alto punto de ebullición. Un alto punto de fusión es deseable en operaciones de procesamiento farmacéutico a gran escala, debido a

[1] Manual Andino de Patentes. Sección 9.4.

que esto permite la utilización de altas temperaturas de secado. D1 no presenta datos de punto de ebullición para ninguna sal tartrato, sea del 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]benciljtiazolidino-2,4-diona u otro compuesto de Fórmula I. Sin embargo, se ha determinado experimentalmente que el punto de fusión de la sal D(-)-tartrado reivindicada es sorprendentemente mayor que el punto de fusión del la sal tartrato-meso correspondiente. Específicamente, el punto de fusión de la sal D(-)tartrato reivindicada de ha determinado en **181.6°C** y su T_{onset} determinado por calorimetría de barrido diferencial en un recipiente cerrado es de 187°C. Estas cifras comparadas con el punto de fusión de 149 a 155°C y un T_{onset} de 146°C de la sal tartrato-meso,[2] evidencian la superioridad del compuesto de la presente invención en cuanto al punto de fusión y por lo tanto, su conveniencia para el procesamiento farmacéutico a gran escala, que de ninguna manera hubiera podido preverse a partir de D1.

- En segundo lugar, la sal tartrato de la presente invención tiene muy buenas propiedades de flujo en volumen, lo que la hace particularmente adecuada para su preparación y manejo en grandes volúmenes. Un valor de Relación de Hausner bajo es un indicador de buenas propiedades de flujo (ver página 7, línea 9). El valor de Relación de Hausner, que es un término aceptado en el arte, es la relación entre la densidad del material a su volumen natural y la densidad del material compactado, que puede ser determinado mediante técnicas usuales. Así, el término "buenas propiedades de flujo" se caracteriza adecuadamente por compuestos que tienen una Relación de Hausner menor o igual que 1.5, especialmente menor o igual que 1.25. Ningún valor de Relación de Hausner se revela en D1, para alguna sal tartrato, sea del 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]benciljtiazolidino-2,4-diona u otro compuesto de Fórmula I. Sin embargo, se determinó experimentalmente que la sal D(-)-tartrato de la presente invención tiene un índice de Relación de Hausner de **1.2** que resulta de especial utilidad. Este valor particularmente bajo y ventajoso contrasta con el valor de Relación de Hausner de la sal tartrato-DL correspondiente, que se determinó en 3.2. La superioridad de las propiedades de flujo en

[2] Datos obtenidos de la solicitud WO02/12233, página 10.

volumen de la sal-D-tartrato de la presente invención, y por lo tanto, los beneficios para su manejo a gran escala para su procesamiento farmacéutico, no hubieran podido de ninguna manera predecirse a partir de D1.

4. Finalmente, deseo anotar que para el concepto inventivo comprendido en la presente solicitud, ha sido otorgado hasta el momento, el privilegio de patente por parte de las Oficinas de Patentes en Europa, Eurasia, Ucrania, Noruega y Nueva Zelanda.

Si bien es cierto que las concesiones de patentes en oficinas de otros países no son vinculantes en el sentido que obliguen a la SIC a tomar una decisión en el mismo sentido, sí considero que dichas concesiones sugieren el cumplimiento de los requisitos de patentabilidad de la materia revindicada, ya que los criterios de evaluación y estudio aplicados para concluir la aceptación de dichas patentes resultan equivalentes a los que la SIC debe emplear. Tan cierto es lo anterior, que el Manual Andino de Patentes, al comentar el Artículo 46 de la Decisión 486, establece que una Oficina nacional competente podrá reconocer los resultados de exámenes de novedad o de patentabilidad efectuados respecto a la solicitud extranjera equivalente, como suficientes para acreditar el cumplimiento de las condiciones de patentabilidad.[3]

5. Por todo lo anterior, considero que las objeciones presentadas por el Examinador han sido resueltas y por consiguiente solicito respetuosamente que se proceda a otorgar el privilegio de patente a la presente invención.

Atentamente,

CARLOS R. OLARTE
C.C. No. 79.782.747 de Bogotá
T.P. 74.295

Anexos:

- Capítulo Reivindicatorio Modificado.
- Recibo de pago correspondiente a la tasa de modificación.

[3] Manual Andino de Patentes. Sección 7.3.

85

6

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 2,722
FECHA : ENERO 9 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 03-008178- -00006-0000
Fecha: 2008-01-16 16:57:05 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIY!I Eve: 379 FASENACIONALII
Act. 444 RESPUESTAREQUE Folios: 8

***** C O N S I G N A C I O N *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
OLARTE RAISBEK	CONSIGNACION	BANCO DE BOGOTA	062754387	106793	09/01/2008	15,878,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	84 FUSION DE SOLICITUD	103,000.00
		TOTAL : $	103,000.00

SON: CIENTO TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

86

CAPÍTULO REIVINDICATORIO MODIFICADO

1.- Un compuesto, 5-[4-[2-(N-metil-N-(2-piridil)amino)-etoxi]bencil]tiazolidino-2,4-diona, sal D(-) tartrato, o un solvato del mismo.

2.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque provee: (i) un espectro infrarrojo sustancialmente de conformidad con la figura 1; (ii) un espectro de Raman sustancialmente de conformidad con la figura 2; (iii) un patrón de difracción de polvos de rayos X (XRPD) sustancialmente de conformidad con el cuadro 1 o la figura 3; o (iv) un espectro de ^{13}C RMN en estado sólido sustancialmente de conformidad con la figura 4.

3.- El compuesto de conformidad con la reivindicación 1, caracterizado además porque provee dos o más de: (i) un espectro infrarrojo sustancialmente de conformidad con la figura 1; y (ii) un espectro de Raman sustancialmente de conformidad con la figura 2; y (iii) un patrón de difracción de polvos de rayos X (XRPD) sustancialmente de conformidad con el cuadro 1 o la figura 3; y (iv) un espectro de ^{13}C RMN en estado sólido sustancialmente de conformidad con la figura 4.

4.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque está en forma purificada.

5.- El compuesto de conformidad con cualquiera de las

reivindicaciones 1 a 3, caracterizado además porque está en una forma sólida de dosificación.

6.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque está en una forma farmacéuticamente aceptable capaz de ser molida.

7.- El compuesto de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque está en una forma farmacéuticamente aceptable que tiene buenas propiedades de flujo.

8.- Un procedimiento para preparar el D(-) Tartrato, o un solvato del mismo, caracterizado porque 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]-bencil]tiazolidino-2,4-diona (compuesto (I)), o una sal del mismo, se hace reaccionar con una fuente de ión D(-) tartrato y después, si se requiere, se prepara un solvato del D(-) Tartrato resultante; y el D(-) Tartrato o un solvato del mismo, se recupera.

9.- Una composición farmacéutica, caracterizada porque comprende D(-) tartrato de 5-[4-[2-(N-metil-N-(2-piridil)amino)etoxi]-bencil]tiazolidino-2,4-diona, o un solvato del mismo, y un vehículo farmacéuticamente aceptable para el mismo.

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US005910592A

United States Patent [19]

Pool et al.

[11] **Patent Number: 5,910,592**

[45] **Date of Patent: *Jun. 8, 1999**

D1

88

[54] **SUBSTITUTED THIAZOLIDINEDIONE DERIVATIVES**

[75] Inventors: **Colin Ripley Pool**, Cranleigh; **Robin Sherwood Roman**, Fetcham; **Malcolm David Brightwell**, Redhill; **Alan William Tremper**, Edenbridge, all of United Kingdom

[73] Assignee: **SmithKline Beecham plc**, Brentford, United Kingdom

[*] Notice: This patent is subject to a terminal disclaimer.

[21] Appl. No.: **08/892,045**

[22] Filed: **Jul. 14, 1997**

Related U.S. Application Data

[63] Continuation of application No. 08/464,990, Jun. 5, 1995, abandoned, which is a continuation of application No. 08/392,878, Mar. 3, 1995, which is a continuation of application No. PCT/GB93/01853, Sep. 1, 1993.

[30] **Foreign Application Priority Data**

Sep. 5, 1992 [GB] United Kingdom 9218830

[51] **Int. Cl.**[6] **C07D 417/10**

[52] **U.S. Cl.** **546/269.7**; 514/342

[58] **Field of Search** 546/269.7; 514/342

[56] **References Cited**

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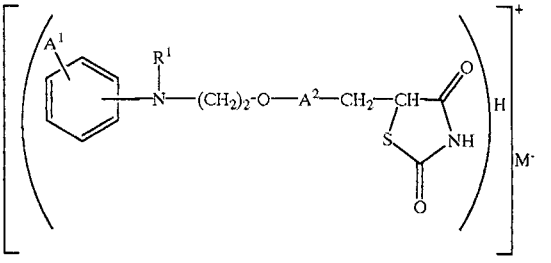
Primary Examiner—Jane Fan

Attorney, Agent, or Firm—Charles M. Kinzig

[57] **ABSTRACT**

A compound of formula (I):

(I)



wherein:

R^1 represents a hydrogen atom, C_{1-12} alkyl, C_{1-12} alkoxy, C_{1-12} alkylcarbonyl or arylC_{1-12} alkyl;

A^1 represents hydrogen or 1 to 4 optional substituents selected from the group consisting of: C_{1-12} alkyl, C_{1-12} alkoxy, aryl and halogen; aryl represents phenyl or naphthyl optionally substituted with up to five groups selected from halogen, C_{1-12} alkyl, phenyl, C_{1-12} alkoxy, haloC_{1-12} alkyl, hydroxy, nitro, C_{1-12} alkoxycarbonyl, C_{1-12} alkoxycarbonyl C_{1-12} alkyl, C_{1-12} alkoxycarbonyloxy, or C_{1-12} alkylcarbonyl;

A^2 represents a benzene ring having 1 to 3 optional substituents selected from hydrogen, halogen, C_{1-12} alkyl, C_{1-12} alkoxy; and

M represents a counter-ion other than the maleate ion.

2 Claims, No Drawings

SUBSTITUTED THIAZOLIDINEDIONE DERIVATIVES

This is a continuation of Ser. No. 08/464,990, filed Jun. 5, 1995, now abandoned, which is a continuation of Ser. No. 08/392,878, filed Mar. 3, 1995, which is a §371 of PCT/GB93/01853 filed Sep. 1, 1993.

This invention relates to certain novel compounds, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

European Patent Application, Publication Number 0,30628 relates to certain thiazolidinedione derivatives disclosed as having hypoglycemic and hypolipidaemic activity.

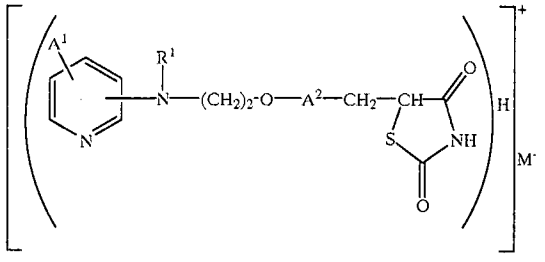
It is now surprisingly indicate that a specific group of compounds from within formula (I) of EP-A-0,306,228 have improved selectivity of action and are therefore of particular use in the treatment of Type II diabetes. These compounds are also indicated to be of particular use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia, hypertension and cardiovascular disease, especially atherosclerosis. In addition these compounds are considered to be useful for treating certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervous, and disorders associated with over-eating, such as obesity and anorexia bulimia

These compounds show good aqueous stability and good stability in the solid form, certain of these compounds are indicated to be particularly stable. In addition these compounds are significantly more soluble in water than the corresponding free base.

The surprising and advantageous stability and aqueous solubility of these, compounds provides for significant formulation and bulk handling advantages.

Accordingly, the present invention provides a compound of formula (1):

(I)



or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof, wherein:

R^1 represents a hydrogen atom, an alkyl group, a acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstiuted, or a substituted or unsubstituted aryl group, A^1 represents hydrogen or 1 to 4 optional substituents selected from the group consisting of alkyl, alkoxy, aryl and halogen or A^1 represents two substituents on adjacent carbon atoms, which substituents together with the carbon atoms to which they are attached form a substituted or unsubstituted aryl group; A^2 represents a benzene ring having 1 to 3 optional substituents; and M^- represents a counter-ion.

Suitable counter-ions M^- include ions provided by pharmaceutically acceptable acids.

A suitable source of counter-ions M^- is provided by those pharmaceutically acceptable acids having a pK_a in the range of from 0.1 to 4.5 and especially in the range of from 1.75 to 2.5.

Favoured pharmaceutically acceptable acids include mineral acids, such as hydrobromic, hydrochloric, and sulphuric acids, and organic acids, such as methanesulphonic, tartaric and malcic acids, especially tartaric and malcic acid.

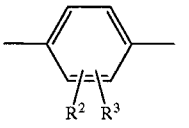
A preferred counter-ion is the maleate-ion $HOOC.CH{=}CH.COO^-$.

Preferably, A^1 is hydrogen.

Suitable optional substituents for the moiety A^2 include up to three substituents selected from halogen, substituted or unsubstituted alkyl or alkoxy.

Favourably, A^2 represents a moiety of formula (e):

(e)



wherein R^2 and R^3 each independently represent hydrogen, halogen, substituted or unsubstituted akyl or alkoxy.

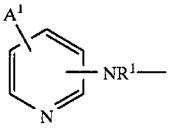
Suitably, R^2 and R^3 each independently represent hydrogen, halogen, alkyl or alkoxy.

Preferably, R^2 and R^3 each represent hydrogen.

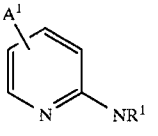
Suitably, R^1 represents hydrogen, alkyl, acyl, especially acetyl, or benzyl.

Preferably, R^1 represents an alkyl group, for example a methyl group.

Preferably the moiety:



in formula (I) is a moiety of formula:



wherein A^1 and R^1 are as defined above

A preferred compound of formula (I) is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione maleic acid salt.

The compounds of formula (I) are salts. The present invention extends to all forms of such salts including those provided by association of the salting hydrogen with all possible salt forming parts of the molecule and especially that provided by association with the pyridin nitrogen.

As indicated above a compound of formula (I) may exist in one of several tantomeric forms, all of which are encompassed by the present invention. It will be appreciated that the present invention encompasses all of the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof, including any stereoisomeric forms thereof, whether as individual isomers or as mixtures of isomers.

When used herein the term 'aylr' includes phenyl and naphthyl optionally substituted with up to five, preferably up

to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, nitro, alkoxycarbonyl, aloxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine; preferably chlorine.

Suitable alkyl groups, including alkyl groups per se and alkyl groups that form part of other groups such as alkoxy groups, are C_{1-12} groups having straight or branched carbon chains, especially C_{1-6} alkyl groups e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

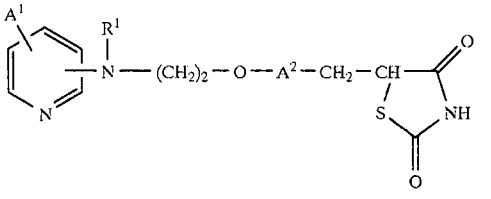
Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

Suitable acyl groups include alkylcarbonyl groups.

Suitable pharmaceutically acceptable solvates include hydrates.

In a further aspect the present invention also provides a process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable solvate thereof, which process comprises reacting a compound of formula (II):

(II)



wherein R^1. A^1 and A^2 are as defined in relation to formula (I) with a source of above defined counter-ion M^-; and thereafter if required preparing a pharmaceutically acceptable solvate thereof.

A suitable source of a counter-ion M^- is a pharmaceutically acceptable acid.

A suitable source of counter-ions includes pharmaceutically acceptable acids having a pK_a in the range of from 1.5 to 4.5; especially in the range of from 1.75 to 2.5.

Favoured pharmaceutically acceptable acids include mineral acids, such as hydrobromic, hydrochloric and sulphuric acids, and organic acids, such as methanesulphonic, tartaric and maleic acids.

A preferred source of a counter-ion is maleic acid.

The reaction between the compound of formula (I) and the source of counter-ion M^- is generally carried out under conventional salt forming conditions, for example by admixing the compound of formula (I) and the source of counter-ion M^-, suitably in approximately equimolar amounts but preferably using a slight excess of the source of counter-ion M^-, in a solvent, generally a C_{1-4} alkanolic solvent such as ethanol, at any temperature which provides a suitable rate of formation of the required product, generally at an elevated temperature for example at the reflux temperature of the solvent and thereafter crystallising the required product.

Pharmaceutically acceptable solvates of the compound of formula (I) may be prepared using conventional chemical procedures.

The compound of formula (II) may be prepared according to methods disclosed in EP-A-0306228.

Suitable sources of counter-ion are known commercially available sources, such as malcic acid, or the required source may be prepared according to known procedures.

Where appropriate the isomeric forms of the compounds of formula (I) and the pharmaccutically acceptable salts thereof may be prepared as individual isomers using conventional chemical procedures.

The stability of the compounds of the invention may be determined using conventional quantiative analytical methods: For example the stability of the compounds in the solid form may be determined by using accelerated stability test such as differential scanning calorimetry (I) (DSC), thermogravimetric analysis (TGA) and isothermal testing at elevated temperatures including conventional storage test wherein the test compounds are stored under controlled conditions of temperature and humidity over known periods of time. Quantitative analysis of the test compounds, against appropriate reference standards before, during and after the storage period allows the stability of the test compound to be determined.

As stated the compounds of the invention are significantly more soluble in water than the corresponding free base. Thus a convenient method for determing the stability of the compounds of the invention in aqueous solution involves determining the degree of precipitation of the parent free base from an aqueous solution of the test compound at known conditions of temperature and over known periods of time. We have found that the compounds of formula (I) show good aqueous stability. In particular the compounds of formula (I) wherein M^- represents maleate or tarrate are particularly stable in aqueous solution. Most surprisingly, the compounds of formula (I) wherein M^- represents a maleate-ion, $HOOC.CH{=}CH.COO^-$, were found to be particularly stable in aqueous solution.

The quantitative analysis of the test compounds in the above mentioned tests may be carried out using conventional methods, generally chromatographic methods such as high pressure liquid chromatography.

As mentioned above the compounds of the invention are indicated as having useful therapeutic properties:

The present invention accordingly provides a compound of formula (I), and/or a pharmaceutically acceptable solvate thereof. for use as an active therapeutic substance.

Thus the present invention provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia.

In a further aspect the present invention also provides compound of formula (I). or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of hyperlipidaemia.

As indicated hereinbefore the present invention also provides a compound of formula (I) or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof for use in the treatment of hypertension, cardiovascular disease and certain eating disorders.

Cardiovascular disease includes in particular atherosclerosis.

Certain eating disorders include in particular the regulation of appetite and food intake in, subjects suffering from disorders associated with under-eating, such as anorexia nervosa and disorders associated with over-eating, such as obesity and anorexia bulimia

A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof, may be administered per se or, preferably as a pharmaceutically composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of formula (I), or a tautomeric form thereof a pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable 'embraces compounds, compositions and ingredients for

both human and veterinary use: for example the term 'pharmaceutically acceptable salt'embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate. polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium, stearate or sodium lauryl sulphate.

Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg. and more especially 0.1 to 250 mg.

The, present invention further provides a method for the treatment and/or prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof to a hyperglycaemia human or non-human mammal in need thereof.

The present invention further provides a method for the treatment of hyperlipidaemia in a human or non-human mammal, which comprises administering an effective, non toxic, amount of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof, to a hyperlipidaemic human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of hyperglycaemic humans, and/or the treatment and/or prophylaxis of hyperlipidaemic human, the compound of formula (I), or a tautomeric form, thereof and/or a pharmaceutically acceptable solvate thereof, may be taken in doses, such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and more usually about 1 to 1500 mg.

In the treatment and/or prophylaxis of hyperglycaemic non human mammals, especially dogs, the active ingredient may be adminstered by mouth usually once or twice a day and in an amount in the range of from about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg. Similar dosage regimens are suitable for the treatment and/or prophylaxis of hyperlipidaemic in non-human mammals.

The dosages regimens for the treatment or hypertension cardiovascular disease and eating disorders will generally be those mentioned above in relation to hyperglycaemia.

In a further aspect the present invention provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia.

The present invention also provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and or prophylaxis of hyperlipidaemia hypertension, cardiovascular disease or certain eating disorders.

The following Example illustrates the invention but does not limit it in any way.

EXAMPLE 1

5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione, maleic acid salt

5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4 dione (470 g) and maleic acid (137 g) were dissolved via ethanol (41) at boiling. The hot solution was filtered via diatomaceous earth and was then allowed to cool slowly with gentle agitation. After leaving in a refrigerator at 0–5° C. for several hours, the maleate salt was filtered off, washed with ethanol and dried in vacuo at 50° C. to give 446 g (73%) of product, m.p 120–121° C.

1H NMR δ (d_6-DMSO): 3.0–3.35 (2H, complex); 3.10 (3H, s); 3.95 (2H, t); 4.15 (2H, t); 4.85 (1H, complex): 6.20 (2H, s); 6.65 (1H, t); 6.85 (3H, complex); 7.15 (2H, d) 7.65 (1H, t); 8.05 (1H, complex); 11.85–12.1 (1H, broad, exchanges with D_2O)

A very broad signal was observed in the range 2–5 ppm which is thought to be due to residual water from the solvent and the exchangeable carboxylic acid protons.

EXAMPLE2

5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione, maleic acid salt

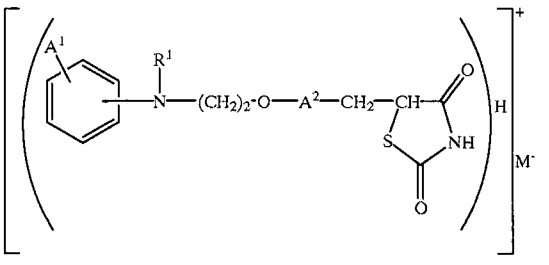
5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl] thiazolidine-2,4-dione, maleic acid salt (294.6 g, 0.825M) and maleic (95.8 g 0.825 m) were stirred in refluxing ethanol (2.71) until all the solid had dissolved. Decolourising charcoal was added and the hot solution filtered through celite, allowed to cool to room temperature with stirring. After cooling in a refrigerator at 0–5° C. for several hours, the title compound was filtered, collected and dried at 50° C. under vacuum overnight to give 364.1 g (87%) of product, m.p. 119–119.5° C.

The 1H NMR spectra was as for Example 1.

We claim:

1. A compound of formula (I):

(I)



or a tautomeric form thereof,wherein:

R^1 represents a hydrogen atom, C_{1-12} alkyl, C_{1-12} alkoxy, C_{1-12} alkylcarbonyl or arylC_{1-12}alkyl;

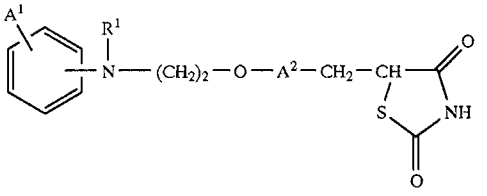
A^1 represents hydrogen or 1 to 4 optional substituents selected from the group consisting of: C_{1-12} alkyl, C_{1-12} alkoxy, aryl and halogen;

aryl represents phenyl or naphthyl optionally substituted with up to five groups selected from halogen, C_{1-12} alkyl, phenyl, C_{1-12} alkoxy, haloC_{1-12} alkyl, hydroxy, nitro, C_{1-12} alkoxycarbonyl, C_{1-12} alkoxycarbonyl C_{1-12} alkoxycarbonyloxy, or C_{1-12} alkylcarbonyl;

A^2 represents a benzene ring having 1 to 3 optional substituents selected from hydrogen, halogen, C_{1-12} alkyl, C_{1-12} alkoxy; and

M^- represents a counter-ion other than the maleate ion.

2. A process for the preparation of a compound of formula (I) according to claim **1**, or a tautomeric form thereof, which process comprises reacting a compound of formula (II):



(II)

wherein R^1, A^1 and A^2 are as defined in relation to formula (I) in claim **1**, with a source of counter-ion M- which is defined in relation to formula (I), as defined in claim **1**.

* * * * *

LEA & FEBIGER
Box 3024
200 Chester Field Parkway
Malvern, PA 19355-9725
(215)251-2230

Executive Editor: George H. Mundorff
Production Manager: Thomas J. Colaiezzi
Project Editor: Denise Wilson

Library of Congress Cataloging-in-Publication Data

Martin, Alfred N.
Physical pharmacy : physical chemical principles in the pharmaceutical sciences / Alfred Martin ; with the participation of Pilar Bustamante and with illustrations by A.H.C. Chun.—4th ed.
p. cm.
Includes index.
ISBN 0-8121-1438-8
1. Pharmaceutical chemistry. 2. Chemistry, Physical and theoretical. I. Bustamante, Pilar. II. Title.
[DNLM: 1. Chemistry, Pharmaceutical. 2. Chemistry, Physical. QD 453.2 M379p]
RS403.M34 1993
541.3'024'615—dc20
DNLM/DLC 92-49751
for Library of Congress CIP

PRINTED IN THE UNITED STATES OF AMERICA

Print No. 5 4 3 2

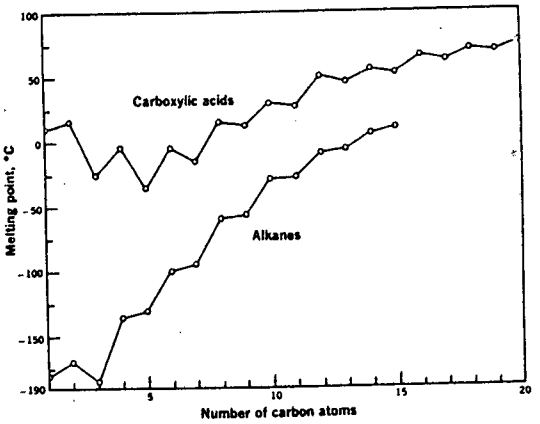


Fig. 2–6. The melting points of alkanes and carboxylic acids as a function of carbon chain length. (Modified from C. R. Noller, *Chemistry of Organic Compounds*, 2nd Ed., Saunders, Philadelphia, 1957, pp. 40, 149).

The melting points of normal carboxylic acids also show this alternation, as seen in Figure 2–6. This can be explained as follows. Fatty acids crystallize in molecular chains, one segment of which is shown in Figure 2–7. The even carbon acids are arranged in the crystal as seen in the more symmetric structure I, whereas the odd numbered acids are arranged according to structure II. The carboxyl groups are joined at two points in the even carbon compound; hence, the crystal lattice is more stable and the melting point is higher.

The melting points and solubilities of the xanthines of pharmaceutical interest, determined by Guttman and Higuchi,[9] further exemplify the relationship between melting point and molecular structure. Solubilities, like melting points, are strongly influenced by intermolecular forces, as will be discussed later in Chapter 10. It will be observed by reference to Table 2–6 that methylation of theophylline to form caffeine, and lengthening of the side chain from methyl (caffeine) to propyl in the 7 position results in a decrease of the melting points and an increase in solubilities. These effects presumably are due to a progressive weakening of intermolecular forces.

Polymorphism. Some elemental substances, such as carbon and sulfur, may exist in more than one crystalline form and are said to be *polymorphic*. Polymorphs generally have different melting points, x-ray diffraction patterns, and solubilities, even though they are chemically identical.

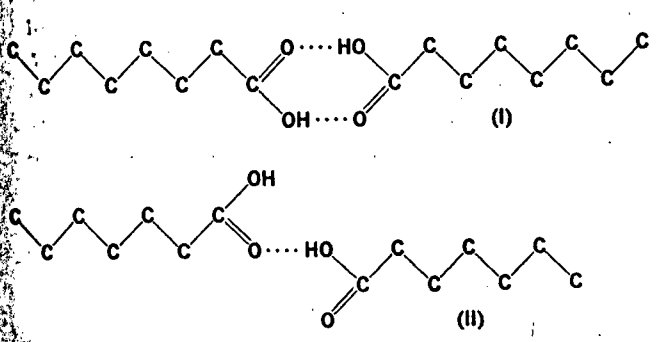
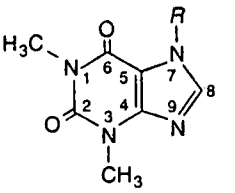


Fig. 2–7. Configuration of fatty acid molecules in the crystalline state. (Modified from A. E. Bailey, *Melting and Solidification of Fats*, Interscience Publishers, New York, 1950, p. 120.)

TABLE 2–6. ***Melting Points and Solubilities of Some Xanthines****



Basic structure

Compound	Melting Point (°C uncorrected)	Solubility in Water at 30° C (mole/liter × 10^2)
Theophylline (R = H)	270–274	4.5
Caffeine (R = CH_3)	238	13.3
7-Ethyltheophylline (R = CH_2CH_3)	156–157	17.6
7-Propyltheophylline (R = $CH_2CH_2CH_3$)	99–100	104.0

*From D. Guttman and T. Higuchi, J. Am. Pharm. Assoc., Sci. Ed. **46**, 4, 1957.

Nearly all long-chain organic compounds exhibit polymorphism. In fatty acids, this results from different types of attachment between the carboxyl groups of adjacent molecules, which in turn modify the angle of tilt of the chains in the crystal. The triglyceride, tristearin, proceeds from the low-melting metastable alpha (α) form through the beta prime (β′) form and finally to the stable beta (β) form, having a high melting point. The transition cannot occur in the opposite direction.

Theobroma oil or cacao butter is a polymorphous natural fat. Since it consists mainly of a single glyceride, it melts to a large degree over a narrow temperature range (34°–36° C). Theobroma oil is capable of existing in four polymorphic forms, the unstable gamma form melting at 18°, the alpha form melting at 22°, the beta prime form melting at 28°, and the stable beta form melting at 34.5° C. Riegelman[10] has pointed out the relationship between polymorphism and the preparation of cacao butter suppositories. If theobroma oil is heated to the point at which it is completely liquefied (about 35° C), the nuclei of the stable beta crystals are destroyed and the mass does not crystallize until it is supercooled to about 15° C. The crystals that form are the metastable gamma, alpha, and beta-prime forms, and the suppositories melt at 23° to 24° C or at ordinary room temperature. The proper method of preparation involves melting cacao butter at the lowest possible temperature, about 33° C. The mass is sufficiently fluid to pour, yet the crystal nuclei of the stable beta form are not lost. When the mass is chilled in the mold, a

stable suppository, consisting of beta crystals and melting at 34.5° C, is produced.

Polymorphism has achieved significance in recent years owing to the fact that different polymorphs exhibit different solubilities. In the case of slightly soluble drugs, this may afffect the rate of dissolution. As a result, one polymorph may be more active therapeutically than another polymorph of the same drug. Aguiar et al.[11] have shown the polymorphic state of chloramphenicol palmitate to have a significant influence on the biologic availability of the drug. Khalil et al.[12] reported that form II of sulfameter, an antibacterial agent, was more active orally in humans than form III, although marketed pharmaceutical preparations were found to contain mainly form III.

Polymorphism can also be a factor in suspension technology. Cortisone acetate has been found to exist in at least five different forms, four of which were found to be unstable in the presence of water and which change to a stable form.[13] Since this transformation is usually accompanied by appreciable caking of the crystals, these should all be in the form of the stable polymorph before the suspension is prepared. Heating, grinding under water, and suspension in water are all factors that affect the interconversion of the different cortisone acetate forms.[14]

It is difficult to determine the crystal structure and molecular conformations of different polymorphs of a single drug, and the reports of such work are not common. Azibi et al.[15] studied two polymorphs of spiperone, a potent antipsychotic agent used mainly in the treatment of schizophrenia. The chemical structure of spiperone is shown in Figure 2–8a, and the molecular conformations* of the two polymorphs, I and II, are shown in Figure 2–8b. The difference between the two polymorphs is in the positioning of the atoms in the side chains, as seen in Figure 2–8b, together with the manner in which each molecule binds to neighboring spiperone molecules in the crystal. The results of the investigation showed that the crystal of polymorph II is made up of dimers (molecules in pairs), whereas polymorph crystal I is constructed of nondimerized molecules of spiperone. In a later study, Azibi et al.[16] examined the polymorphism of a number of drugs to ascertain what properties cause a compound to exist in more than one crystalline form. Differences in intermolecular van der Waals forces and hydrogen bonds were found to produce different crystal structures in antipsychotic compounds such as haloperidol (Fig. 2–9) and bromperidol. Variability in hydrogen bonding also contributes to polymorphism in the sulfonamides.[17]

Goldberg and Becker[18] studied the crystalline forms of tamoxifen citrate, an antiestrogenic and antineoplastic drug used in the treatment of breast cancer and postmenopausal symptoms. The structural formula of tamoxifen is shown in Figure 2–10. Of the two forms found, the stable polymorph, referred to as *form B*, is held in its molecular conformation in the solid state by hydrogen bonding. One carboxyl group of the citric acid moiety donates its proton to the nitrogen atom on an adjacent tamoxifen molecule to bring about the hydrogen bonding and to stabilize the molecular crystal of form B. The other polymorph, known as *form A*, is a metastable polymorph of tamoxifen citrate, its molecular structure being less organized than that of the stable B form. An ethanolic suspension of polymorph A spontaneously rearranges into polymorph B.

Lowes et al.[19] made physical, chemical, and x-ray studies of carbamazepine. Carbamazepine is used in the treatment of epilepsy and trigeminal neuralgia (severe pain in the face, lips, and tongue). The β polymorph of the drug can be crystallized from solvents of high dielectric constant, such as the aliphatic alcohols. The α polymorph is crystallized from solvents of low dielectric constant, such as carbon tetrachloride and cyclo-

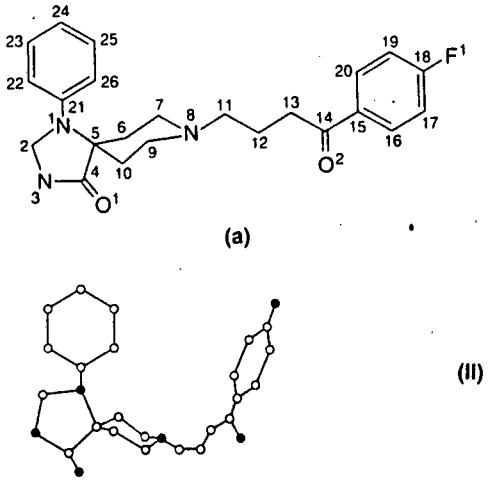


Fig. 2–8. *(a)* Structure and numbering of spiperone. *(b)* Molecular conformation of two polymorphs I and II of spiperone. (M. Azibi, et al., J. Pharm. Sci., 72:232, 1983. Reproduced with permission.)

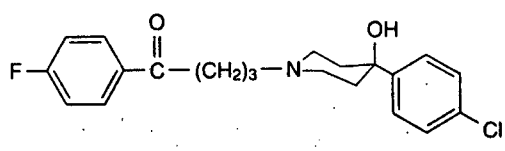


Fig. 2–9. Haloperidol.

*The arrangement of the atoms in a particular stereoisomer gives the *configuration* of a molecule. On the other hand, *conformation* refers to the different arrangements of atoms resulting from rotations about single bonds.

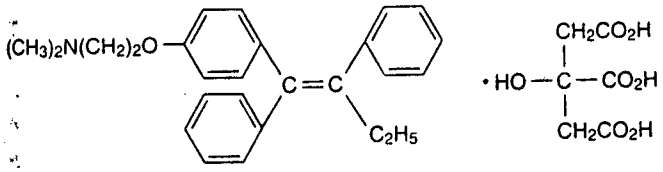
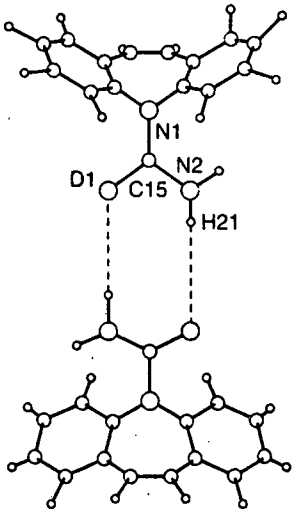


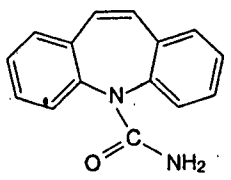
Fig. 2–10. Tamoxifen citrate.

hexane. A rather thorough study of the two polymorphic forms of carbamazepine was made using infrared spectroscopy (p. 89), thermogravimetric analysis (p. 49), hot-stage microscopy, dissolution rate (p. 330–332), and x-ray powder diffraction (p. 30). The hydrogen-bonded structure of the α polymorph of carbamazepine is shown in Figure 2–11a, together with its molecular formula (Fig. 2–11b).

Estrogens are essential hormones for the development of female sex characteristics. When the potent synthetic estrogen ethynylestradiol is crystallized from the solvents acetonitrile, methanol, and chloroform saturated with water, four different crystalline solvates are formed. Ethynylestradiol has been reported to exist in several polymorphic forms. However, Ishida et al.[20] have now shown from thermal analysis, infrared spectroscopy, and x-ray studies that these forms are crystals containing solvent molecules and thus should be classified as *solvates* rather than as polymorphs. Solvates are sometimes called *pseudopolymorphs*.[21]



(a)



(b)

Fig. 2–11. *(a)* Two molecules of the polymorph, α-carbamazepine, joined together by hydrogen bonds. (M. M. J. Lowes, et al., J. Pharm. Sci., 76:744, 1987. Reproduced with permission.) *(b)* Carbamazepine.

Other related estradiol compounds may exist in true polymeric forms.

Behme et al.[22] reviewed the principles of polymorphism with emphasis on the changes that the polymorphic forms may undergo. When the change from one form to another is reversible, it is said to be *enantiotropic*. When the transition takes place in one direction only—for example, from a metastable to a stable form—the change is said to be *monotropic*. Enantiotropism and monotropism are important properties of polymorphs, as described by Behme et al.[22]

The transition temperature in polymorphism is important because it helps to characterize the system and determine the more stable form at low temperatures. At their transition temperatures, polymorphs have the same free energy, identical solubilities in a particular solvent, and identical vapor pressures. Accordingly, plots of logarithmic solubility of two polymorphic forms against $1/T$ provide the transition temperature at the intersection of the extrapolated curves. Often the plots are nonlinear and cannot be extrapolated with accuracy. For dilute solutions, in which Henry's law (p. 152) applies, the logarithm of the solubility ratios of two polymorphs can be plotted against $1/T$, and the intersection at a ratio equal to unity gives the transition temperature.[23] This temperature can also be obtained from the phase diagram of pressure versus temperature and by using differential scanning calorimetry.[24] An example of the solubility method is given as *Problem 2–20*.

Biles,[25] as well as Haleblian and McCrone,[26] have discussed in some detail the significance of polymorphism and solvation in pharmaceutical practice.

Amorphous Solids. Amorphous solids may be considered as supercooled liquids in which the molecules are arranged in a random manner somewhat as in the liquid state. Substances such as glass, pitch, and many synthetic plastics are amorphous solids. They differ from crystalline solids in that they tend to flow when subjected to sufficient pressure over a period of time, and they do not have definite melting points. In Chapter 17, it will be learned that the rheologist classifies as a solid any substance that must be subjected to a definite shearing force before it fractures or begins to flow. This force, below which the body shows elastic properties, is known as the *yield value*.

Amorphous substances, as well as cubic crystals, are usually *isotropic*, that is, they exhibit similar properties in all directions. Crystals other than cubic are *anisotropic*, showing different characteristics (electric conductance, refractive index, rate of solubility) in various directions along the crystal.

It is not always possible to determine by casual observation whether a substance is crystalline or amorphous. Beeswax and paraffin, although they appear to be amorphous, assume crystalline arrangements when heated and then allowed to cool slowly. Petrolatum, as already mentioned, contains both crys-

talline and amorphous constituents. Some amorphous materials, such as glass, may crystallize after long standing.

Whether or not a drug is amorphous or crystalline has been shown to affect its therapeutic activity. Thus, the crystalline form of the antibiotic novobiocin acid is poorly absorbed and has no activity, whereas the amorphous form is readily absorbed and therapeutically active.[27]

THE LIQUID CRYSTALLINE STATE

Three states of matter have been discussed thus far in this chapter: gas, liquid, and solid. A fourth state of matter is the *liquid crystalline* state or *mesophase*. The term *liquid crystal* is an apparent contradiction, but it is useful in a descriptive sense since materials in this state are in many ways intermediate between the liquid and solid states.

Structure of Liquid Crystals. As seen earlier, molecules in the liquid state are mobile in three directions and can also rotate about three axes perpendicular to one another. In the solid state, on the other hand, the molecules are immobile, and rotations are not possible.

It is not unreasonable to suppose, therefore, that intermediate states of mobility and rotation should exist, as in fact they do. It is these intermediate states that constitute the liquid crystalline phase, or mesophase, as the liquid crystalline phase is called.

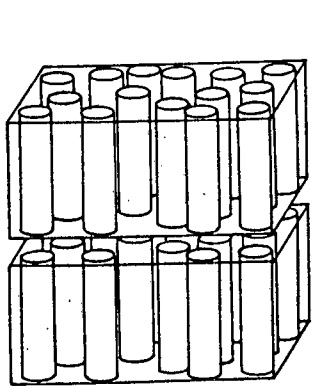
The two main types of liquid crystals are termed *smectic* (soap- or grease-like) and *nematic* (thread-like). In the smectic state, molecules are mobile in two directions and can rotate about one axis (Fig. 2–12*a*). In the nematic state, the molecules again rotate only about one axis but are mobile in three dimensions (Fig. 2–12*b*). A third type (cholesteric crystals) exist but may be considered as a special case of the nematic type.

The smectic mesophase is probably of most pharmaceutical significance since it is this phase that usually forms in ternary (or more complex) mixtures containing a surfactant, water, and a weakly amphiphilic or nonpolar additive (see Chapter 18).

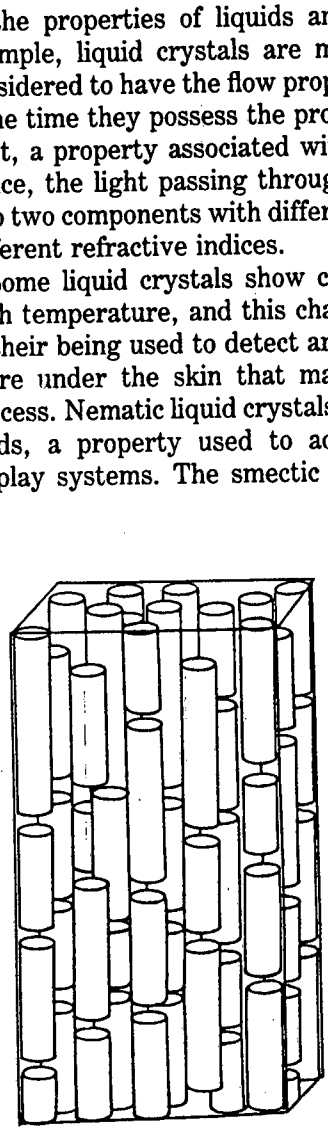
In general, molecules that form mesophases (1) are organic, (2) are elongated and rectilinear in shape, (3) are rigid, and (4) possess strong dipoles and easily polarizable groups. The liquid crystalline state may result either from the heating of solids (thermotropic liquid crystals) or from the action of certain solvents on solids (lyotropic liquid crystals). The first recorded observation of a thermotropic liquid crystal was made by Reinitzer in 1888 when he heated cholesteryl benzoate. At 145° C, the solid formed a turbid liquid (the thermotropic liquid crystal), which only became clear, to give the conventional liquid state, at 179° C.

Properties and Significance of Liquid Crystals. Because of their intermediate nature, liquid crystals have some of the properties of liquids and some of solids. For example, liquid crystals are mobile and thus can be considered to have the flow properties of liquids. At the same time they possess the property of being birefringent, a property associated with crystals. In birefringence, the light passing through a material is divided into two components with different velocities and hence different refractive indices.

Some liquid crystals show consistent color changes with temperature, and this characteristic has resulted in their being used to detect areas of elevated temperature under the skin that may be due to a disease process. Nematic liquid crystals are sensitive to electric fields, a property used to advantage in developing display systems. The smectic mesophase has applica-



(a) Smectic mesophase



(b) Nematic mesophase

Fig. 2–12. Liquid crystalline state. *(a)* Smectic structure; *(b)* nematic structure.

QUIMICA FUNDAMENTAL

99

Si algunos de los átomos de carbono asimétricos son similares, hay menos de 2^n isómeros ópticos diferentes. Cada uno de los átomos de carbono asimétricos (con asteriscos) tienen unidos los mismos cuatro grupos —H, —OH, —COOH y —CHOH—COOH. Si se escriben todas las fórmulas posibles resultan las cuatro configuraciones siguientes:

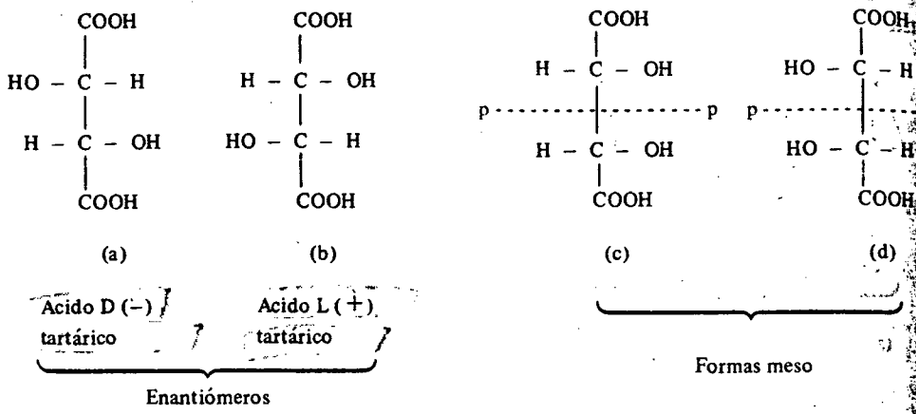


Figura 10.12 Estereoisómeros del ácido tartárico

Las configuraciones (c) y (d) son idénticas, para verificarlo se puede rotar la fórmula proyectada de Fischer (d), 180° en el plano del papel y se observa que es idéntica a la fórmula (c). Estas fórmulas son imágenes especulares superponibles. Cualquiera de estas fórmulas tiene un plano de simetría (p----- p). Debido a esta simetría la molécula es idéntica con su imagen especular y es ópticamente inactiva. *Una molécula que es un estereoisómero ópticamente inactivo,* de compuestos que pueden existir en otras formas ópticamente activas, se designa como la *forma meso.* En la forma meso la mitad de la molécula es la imagen especular de la otra mitad.

Tabla 10.1. Propiedades físicas de los ácidos tartáricos

Acido tartárico	P. F. (°C)	Peso específico	Solubilidad g/100 g H_2O a 20°C	$[\alpha]_D^{20}$ en agua
Dextro	170	1,76	139	+12°
Levo	170	1,76	139	−12°
Meso	140	1,67	125	0

Los otros dos isómeros del ácido tartárico son ópticamente activos, las imágenes especulares de (a y b) no son superponibles. Si se comparan las configuraciones con las del gliceraldehído, resulta que la configuración (a) es el ácido D(—)-tartárico y la configuración (b) es el ácido L(+)-tartárico. Por lo tanto, solo existen tres (y no cuatro) isómeros ácidos tartáricos. Algunas de las propiedades de los tres ácidos tartáricos se dan en la tabla 10.1.

10.11 RESOLUCION DE MEZCLAS RACEMICAS

Se llama resolución el proceso de separar una mezcla racémica en sus componentes (+) y (—). Como en la síntesis de sustancias con carbonos asimétricos usualmente se producen mezclas racémicas, es necesario *resolverlas* para separar los componentes dextrógiros de los levógiros.

1. Resolución química

Como las propiedades físicas de los enantiómeros son idénticas, no se pueden separar por métodos físicos, como la destilación o cristalización fraccionadas. Solamente cuando reaccionan con otro compuesto ópticamente activo (separación química) los productos formados se comportan en forma diferente, esto es, se forman *diastereómeros* que tienen propiedades físicas diferentes: solubilidad, punto de fusión, etc., de tal manera que se pueden separar. Después de separar los enantiómeros se pueden recuperar por otra reacción química.

Ejemplo, separar un racemato (mezcla racémica de un ácido). Si la mezcla racémica se hace reaccionar con una base ópticamente activa, (una dextrógira (d) para nuestro ejemplo) se forma una sal, como se indica a continuación:

$$\underbrace{\begin{matrix}\text{(d) ácido}\\ \text{(l) ácido}\end{matrix}}_{\text{Mezcla racémica}} + \text{(d) base} \rightarrow \underbrace{\begin{matrix}\text{(d) ácido (d) base}\\ \text{(l) ácido (d) base}\end{matrix}}_{\text{Sales diastereoisómeras}}$$

Aunque los ácidos (d) y (l) son imágenes especulares, no se pueden separar por medios físicos, las sales no son imágenes especulares sino diastereoisómeros. Estas se pueden separar por cristalización fraccionada, de un solvente adecuado. Luego cada sal se puede convertir nuevamente en el ácido original ópticamente activo:

Diastereómeros

(d) ácido (d) base $\xrightarrow{HCl}$ (d) ácido + (d) base clorhidrato

Separadas por cristalización

(l) ácido (d) base $\xrightarrow{HCl}$ (l) ácido + (d) base clorhidrato